Determinants of Left Ventricular Hypertrophy in Hypertensive Patients: Identification of High-Risk Patients by Metabolic, Vascular, and Inflammatory Risk Factors

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Abstract

Left ventricular hypertrophy (LVH) is recognized as an independent predictor of cardiovascular morbidity and mortality in hypertensive patients. Thus, it is critical to understand the mechanisms underlying the development of LVH for formulation screening and treatment strategies. This study was designed to determine the association between echographically determined LVH measures and markers of inflammation, neurohormonal activity, glomerular function, oxidative stress, insulin resistance, and vascular endothelial function. In this study, 129 hypertensive subjects were evaluated for lipids, glucose, HbA1C, insulin, homeostasis model assessment-insulin resistance, C-reactive protein (CRP), urinary microalbumin, homocysteine, aldosterone, renin, and endothelin. LVH parameters including interventricular septum thickness, posterior wall thickness (PWT), and left ventricular mass index (LVMI) were assessed echographically. Serum aldosterone levels were significantly positively associated with left ventricular mass (LVM) and marginally positively associated with LVMI and PWT. Both LVM and LVMI were significantly elevated in subjects with high versus normal serum aldosterone levels ($p = 0.018$ for LVM and $p = 0.050$ for LVMI). Serum endothelin was positively associated with LVM and LVMI. In multiple linear regression analysis, aldosterone remained a significant predictor of LVM (standardized $\beta = 0.229$, $p = 0.024$), and endothelin a marginally significant predictor of LVM (standardized $\beta = 0.178$, $p = 0.077$). Among serum lipids, high-density lipoprotein cholesterol only had a significant inverse association with LVM and PWT. Homocysteine as well as CRP were significantly positively associated with LVM and LVMI in females. This study found that aldosterone and endothelin levels are the most important independent determinants of LVH in hypertensive subjects. These markers may be useful to identify asymptomatic hypertensive subjects at risk for heart failure.

Keywords

- cardiovascular disease
- cardiovascular risk factors
- hypertension
- hypercholesterolemia
- creatinine
- high-sensitivity C-reactive protein

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Left ventricular hypertrophy (LVH), the most common cardiac abnormality associated with hypertension is recognized as an independent predictor of cardiovascular morbidity and mortality in hypertensive patients as well as in general population.[1] The pathogenesis of hypertensive LVH is multifactorial and includes hemodynamic as well as nonhemodynamic factors. It has been reported that a range of cardiovascular risk factors such as low high-density lipoprotein (HDL) cholesterol, insulin resistance, and increased adiposity are significantly correlated with left ventricular mass (LVM) in hypertensive patients.[2,3] However, previous studies were limited by their focus on individual markers representing single pathways. Thus, it is critical to understand the most important mechanisms underlying the development of LVH, as well as to formulate screening strategies that can reliably identify hypertensive individuals most likely to develop LVH.

This study was designed to determine the association between echographically determined LVH measures and markers of systemic inflammation (C-reactive protein, CRP), neurohormonal activity (aldosterone, renin), renal function and oxidant stress (homocysteine), renal glomerular function (urinary microalbumin), insulin resistance (homeostasis model assessment-insulin resistance, HOMA-IR), lipid metabolism (lipids), and vascular endothelial function (endothelin).

Methods

Study Subjects

In this study, 129 hypertensive subjects (54 women, 75 men, mean age 64.2 ± 11.6 years) were recruited from the outpatient hypertension clinic at the Wolfson Medical Center, Israel, and evaluated for this study. Patients suspected of secondary hypertension, with a history of major disease or surgery within 6 months preceding entrance to the study, were excluded. Patients with unbalanced endocrine disease were excluded, as were patients with plasma creatinine > 2 mg/dL, elevation of liver enzymes to more than twice the upper normal limit and electrolyte abnormalities. Patients included in the study were stabilized on their previous medical treatment in the outpatient clinic for up to 3 months before entrance to the study.

This study has approved by the local scientific committee and all participants gave informed consent before entering the study.

Biochemical Parameters

Blood sampling for full chemistry and metabolic parameters, including total cholesterol, HDL and low-density lipoprotein (LDL) cholesterol, triglycerides, fasting glucose, HbA1C, fasting insulin, and CRP was performed. Endothelin levels were determined by enzyme-linked immunosorbent assay (Biomedica Gruppe, Vienna, Austria). The intra-assay coefficients of variation for endothelin were 4.1%. Serum aldosterone and plasma renin activity were measured in a sitting position using commercially available radioimmunoassay. The lower limits of the serum aldosterone and plasma renin activity were 0.6 ng/dL and 0.1 ng/mL/h, respectively. The samples were measured in duplicate. Urinary microalbumin/creatinine ratio (milligrams per gram) was measured on a single-void morning urine specimen.

HOMA-IR was calculated by the following formula: fasting plasma insulin (mU/mL) × fasting plasma glucose (mg/dL)/405.

Echocardiographic Examination

Complete M-mode and two-dimensional Doppler echocardiographic analysis was performed with an HP SONOS 5500 (Hewlett–Packard Co, Palo Alto, CA) using a 2.5-MHz transducer. All measurements were made with the patient in the left lateral decubitus position. Two-dimensional M-mode–guided measurements were performed according to the recommendations of the American Society of Echocardiography.[4] The following parameters were assessed on the M-mode recordings: left ventricular end-diastolic diameter (LVEDD) and left ventricular end-systolic diameter (LVESD), left ventricular posterior wall thickness (PWT), and interventricular septum thickness (IVST). LVM was calculated by using the Penn convention, with the following regression-corrected cube formula:

$$\mathrm{LVM} = 1.04\,[(\mathrm{IVST} - \mathrm{LVEDD} - \mathrm{PWT})^3 - (\mathrm{LVEDD})^3] - 14\,\mathrm{g}$$

The LVM index (LVMI) was calculated by dividing LVM by the body surface area.

Data Analysis

Analysis of data was performed using SPSS 9.0 statistical analysis software (SPSS Inc., Chicago, IL, 1999). Distributions of continuous variables were assessed for normality using the Kolmogorov–Smirnov test (cutoff at $p < 0.01$). Normally distributed continuous variables were described using mean value ± standard deviation. Variables with distributions significantly deviating from normal were described using median (minimum–maximum). Categorical variables such as sex, comorbidities, and treatment prescriptions are described using frequency distributions and are presented as frequency (%). Univariate general linear modeling was used to assess associations between echocardiographic variables and hemodynamic/metabolic parameters. Multiple regression models were constructed to include age, sex, body mass index, smoking, mean arterial pressure, creatinine, HDL cholesterol, HOMA-IR, aldosterone, and endothelin. Backward elimination with probability of $F = 0.05$ for entry and 0.15 for removal from the model was performed to identify variables independently associated with LVM and LVMI. All tests are two-sided and considered significant at $p < 0.05$.

Results

Demographic and clinical characteristics of the study population are presented in ►**Table 1**. The study population included 129 hypertensive patients (mean age 64.2 ± 11.6 years) and was comprised 75 (58%) men.

As shown in ►**Table 2**, in univariate analysis, serum endothelin was significantly positively associated with LVM, LVMI and marginally positively associated with PWT. Serum aldosterone levels were significantly positively associated

Table 1 Demographic and clinical characteristics of total study population

Variables	
Male/female	75/54
Age (y), mean ± SD	64.2 ± 11.6
BMI (kg/m^2), mean ± SD	29.7 ± 13.5
Current smokers, *n* (%)	18 (14)
Diabetes, *n* (%)	39 (30)
Dyslipidemia, *n* (%)	82 (64)
Concomitant medication	
Aspirin, *n* (%)	68 (53)
Statin/bezafibrate, *n* (%)	69 (54)
β-blocker, *n* (%)	66 (51)
ACE/ARB, *n* (%)	97 (75)
Diuretic, *n* (%)	47 (36)
CC blocker, *n* (%)	66 (51)
Systolic blood pressure (mm Hg), mean ± SD	143.8 ± 14.8
Diastolic blood pressure (mm Hg), mean ± SD	76.9 ± 9.6
Mean arterial pressure (mm Hg), mean ± SD	101.3 ± 12.7
Fasting blood glucose (mg/dL), mean ± SD	115.8 ± 34.4
HbA1C (%), mean ± SD	6.4 ± 1.0
Total cholesterol (mg/dL), mean ± SD	182.6 ± 40.0
LDL cholesterol (mg/dL), mean ± SD	120.1 ± 61.7
HDL cholesterol (mg/dL), mean ± SD	46.3 ± 12.0
Triglycerides (mg/dL), mean ± SD	144.2 ± 80.1
Hs-CRP (mg/dL), mean ± SD	0.7 ± 1.6
Fasting insulin (IU/mL), mean ± SD	12.6 ± 6.3
HOMA-IR, mean ± SD	3.5 ± 1.9
Homocysteine (μmol/L), mean ± SD	13.5 ± 8.6
Plasma aldosterone (ng/mL), mean ± SD	8.3 ± 5.6
Plasma renin (ng/mL), mean ± SD	1.6 ± 2.1
Urinary MA/creatinine (mg/g), mean ± SD	58.1 ± 186.9
Endothelin (fmol/mL), mean ± SD	0.3 ± 0.6
Left ventricular mass (g), mean ± SD	245.5 ± 83.3
LVMI (g/m^2), mean ± SD	127.0 ± 39.1
IVST (cm), mean ± SD	1.43 ± 0.5
PWT (cm), mean ± SD	0.63 ± 0.17
LV end-diastolic diameter (cm), mean ± SD	4.8 ± 0.6
LV end-systolic diameter (cm), mean ± SD	2.9 ± 0.6

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CC, calcium channel; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment-insulin resistance; hs-CRP, high-sensitivity C-reactive protein; IVST, interventricular septum thickness; LDL, low-density lipoprotein; LV, left ventricular; LVMI, left ventricular mass index; MA, microalbumin; PWT, posterior wall thickness; SD, standard deviation.

with LVM, LVEDD and marginally positively associated with LVMI and PWT. Both LVM and LVMI were significantly elevated in subjects with high versus normal serum aldosterone levels (273.88 ± 87.33 vs. 234.99 ± 79.71, $p = 0.018$ for LVM and 138.06 ± 39.76 vs. 122.91 ± 38.27, $p = 0.050$ for LVMI).

Multiple linear regression analysis (►**Table 3**) was arrived at using a backward, stepwise approach with probability of $F = 0.05$ for entry and 0.15 for removal from the model. Backward elimination was performed to identify variables independently associated with LVM. In this model,

Table 2 Correlations

		LVM	LVMI	PWT	IVST	LVESD	LVEDD
Age	*r* value	0.092	0.166	0.105	0.156	0.001	−0.036
	p value	0.301	0.06	0.235	0.077	0.994	0.683
Systolic blood pressure	*r* value	0.103	0.119	0.163	0.164	−0.103	−0.035
	p value	0.244	0.179	0.064	0.063	0.25	0.694
Diastolic blood pressure	*r* value	0.03	−0.005	0.138	0.067	−0.046	−0.039
	p value	0.732	0.953	0.119	0.449	0.609	0.663
Mean blood pressure	*r* value	0.056	0.054	0.143	0.11	−0.136	−0.034
	p value	0.526	0.543	0.105	0.215	0.129	0.703
BMI	*r* value	0.12	−0.087	0.122	0.1	0.15	0.099
	p value	0.25	0.407	0.24	0.338	0.156	0.343
Fasting glucose	*r* value	0.111	0.178[a]	0.142	0.069	0.038	0.065
	p value	0.212	0.044	0.109	0.439	0.669	0.465
Creatinine	*r* value	0.123	0.09	0.194[a]	0.184[a]	−0.028	−0.018
	p value	0.165	0.31	0.028	0.037	0.755	0.839
HDL cholesterol	*r* value	−0.248[b]	−0.15	−0.173[a]	−0.067	−0.287[b]	−0.246[b]
	p value	0.005	0.089	0.05	0.452	0.001	0.005
LDL cholesterol	*r* value	−0.076	−0.051	0.009	−0.004	−0.129	−0.11
	p value	0.401	0.576	0.924	0.963	0.16	0.226
Triglycerides	*r* value	0.02	−0.029	0.005	0.039	0.051	0.022
	p value	0.826	0.746	0.953	0.664	0.574	0.802
Hs-CRP	*r* value	0.049	0.043	0.099	0.065	−0.009	−0.001
	p value	0.584	0.629	0.264	0.467	0.924	0.992
Homocysteine	*r* value	0.163	0.128	0.278[a]	0.206	0.013	−0.053
	p value	0.171	0.285	0.018	0.082	0.912	0.659
Urine MA	*r* value	0.092	0.093	0.200[a]	0.155	−0.003	−0.067
	p value	0.302	0.296	0.024	0.08	0.976	0.451
Endothelin	*r* value	0.267[a]	0.262[a]	0.211	0.056	0.019	0.174
	p value	0.017	0.019	0.061	0.625	0.867	0.123
HbA1C	*r* value	−0.086	−0.068	−0.005	−0.001	−0.146	−0.114
	p value	0.445	0.547	0.962	0.993	0.204	0.312
HOMA-IR	*r* value	0.052	−0.038	0.016	−0.068	0.0214	0.138
	p value	0.643	0.735	0.888	0.544	0.060	0.219
Aldosterone	*r* value	0.180[a]	0.159	0.158	0.065	0.028	0.181[a]
	p value	0.042	0.071	0.073	0.463	0.759	0.04
Renin	*r* value	−0.131	−0.13	−0.066	−0.032	−0.164	−0.144
	p value	0.138	0.142	0.458	0.723	0.066	0.104

Abbreviations: BMI, body mass index; CC, calcium channel; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment-insulin resistance; hs-CRP, high-sensitivity C-reactive protein; IVST, interventricular septum thickness; LDL, low-density lipoprotein; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVM, left ventricular mass; LVMI, left ventricular mass index; MA, microalbumin; PWT, posterior wall thickness.
[a]Correlation is significant at the 0.05 level (two-tailed).
[b]Correlation is significant at the 0.01 level (two-tailed).

aldosterone remained a significant predictor of LVM, and endothelin was a marginally significant predictor of LVM, even after controlling for age and sex. The overall model was significant ($p < 0.0001$) and explained 27.6% of the variability in LVM. HDL did not significantly contribute to the model so was removed.

Among serum lipids, HDL cholesterol only was significantly inversely associated with LVM as well as PWT, and

Table 3 Multiple linear regression analysis

Variables	LVM			
	Standard error	*t*	Standard beta	*p* value
Age	1.182	−0.255	−0.025	0.051
Sex	17.616	3.789	0.409	0.000
Aldosterone	1.753	2.297	0.229	0.024
Endothelin	11.977	1.795	0.178	0.077
HDL cholesterol	0.765	−0.105	−0.011	0.917

Abbreviations: HDL, high-density lipoprotein; LVM, left ventricular mass.

marginally inversely associated with LVMI. However, HDL cholesterol did not significantly contribute to multiple linear regression model of LVM.

No association between LVH parameters and HOMA-IR was observed.

Homocysteine levels were significantly positively associated with PWT and marginally positively associated with IVST. However, when the sample was stratified by gender, homocysteine was significantly positively associated with LVM as well as LVMI in females.

Although CRP levels were not associated with echographically determined LVH parameters in total study population, significant positive correlation between CRP and LVM as well as LVMI was found in females.

Urinary microalbumin levels were significantly positively associated with PWT and IVST.

No difference in LVM as well as LVMI by concomitant antihypertensive medications including β blockers, inhibitors of renin–angiotensin system, diuretic therapy, and statins was found. LVM and LVMI were significantly higher in subjects treated with α blockers as well as calcium channel blockers. Among metabolic parameters, insulin levels and aldosterone renin ratio were significantly higher while plasma renin activity was lower in subject treated with β blockers. Endothelin levels were significantly higher, CRP as well as urine microalbumin were marginally higher and insulin significantly lower in subjects treated with calcium channel blocker. Aldosterone levels were lower in patients treated with inhibitors of renin–angiotensin system and statin-treated subjects. HDL cholesterol was marginally lower, while the aldosterone renin ratio was significantly higher in subjects treated with diuretics.

Discussion

This study found that aldosterone and endothelin levels are the most important independent determinants of LVM in hypertensive population. The findings of this study are consistent with those of studies reporting a blood pressure independent effect of aldosterone as well as endothelin on left ventricular structure and function.[5,6] Moreover, previous studies have shown race- and sex-dependent differences in terms of relationship between aldosterone levels and LVM in adults as well as adolescents.[7] Altogether, these data suggest that these neurohormones may be important contributors to the pathophysiological changes occurring in heart failure.

The pathophysiology of neurohormone-induced vascular damage is not precisely known but may include smooth muscle cell proliferation, enhanced collagen synthesis, and structural changes of elastin in the ventricle as well as arterial wall.[8–10] In addition, angiotensin II, aldosterone, and endothelin-1 are vasoconstrictors and as such increase ventricular afterload.

Although endothelin-1 correlates directly with disease severity, and predicts hospitalization and mortality for heart failure,[11,12] several trials involving endothelin-1–receptor antagonists have failed to show beneficial effects on clinical outcomes.[13] The fact that aldosterone as well as endothelin is independent predictors of LVH in hypertensive subjects supports the concept that these markers are probably part of the direct underlying pathway for hypertensive heart failure. Therefore, we can speculate that favorable effect of renin–angiotensin–aldosterone system blockade may be more pronounced by lowering endothelin levels. However, advantage of this combination therapy will need to be confirmed by long-term follow-up studies.

Consistent with previous data, we observed associations between HDL cholesterol and LVM.[3] In addition, significant inverse association between HDL cholesterol and PWT as well as LVESD and LVEDD was found in this study.

The link between insulin sensitivity and LVH is still under debate. A significant positive relationship between insulin resistance measured indirectly using homeostasis model assessment method and LVH parameters has been showed in hypertensive patients.[14] However, no significant association between insulin sensitivity measured by the gold standard technique such as euglycemic hyperinsulinemic clamp and LVH was observed.[15] This study did not detect an association between HOMA-IR and LVH measures, whereas inverse association between fasting glucose and LVH was observed.

This study has several limitations. Since the study participants have had been treated with antihypertensive drugs, it is not possible to neutralize the effect of medications on LVH measures and biochemical markers. However, concomitant medications were kept stable for 3 months before entrance to the study to prevent possible influence on the study parameters. In addition, since this study focused on hypertensive

subjects, the application of our findings to other patient populations remains uncertain.

Conclusions

In conclusion, our findings suggest that measurements of endothelin and aldosterone appear to be useful to identify asymptomatic hypertensive subjects at risk for heart failure. However, the point of view that endothelin and aldosterone have an active role in the pathogenesis of LVH in hypertensive patients and blockade of aldosterone and endothelin has the potential to alleviate the cardiovascular damage in this population is still uncertain and deserves further investigation. Future research should focus on understanding the modifiable determinants of LVH as well as their overall clinical impact on cardiovascular outcomes in a large cohort of hypertensive patients with heart failure followed prospectively.

Note
The authors have no conflicts of interest or financial or other contractual agreements that might cause conflicts of interest.

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