REVIEW

Is left ventricular hypertrophy a risk factor in hypertensive patients?

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Abstract

Background: **Left ventricular hypertrophy (LVH) is supposed to be a risk factor of cardiovascular (CV) complications in hypertensive patients.**
Aim: **To compare clinical events in hypertensives with and without LVH.**
Patients and methods: **319 hypertensives with LVH (mean age 64.1±10.6 ys) and 177 hypertensives without LVH (mean age 62.5±11.3 ys). LVH defined by echo Penn convention as left ventricular mass index >134 g/m^2 in men and >110 g/m^2 in women. Clinical events — heart failure (EF<40 %), left ventricular diastolic dysfunction (echo-doppler: transmitral-flow where peak A>peak E), myocardial infarction (history, ECG, cardiac enzymes), chronic atrial fibrillation (more than 2 weeks duration), mitral regurgitation (echo) and renal involvement (creatininemia > 120 µmol/l). The two groups of hypertensives were matched by demographic criteria, duration and intensity of hypertension, obesity, diabetes mellitus, lipid serum levels and smoking habits.**
Results: **There were statistically significant at least p<0.05 more CV events (heart failure, left ventricular diastolic dysfunction, myocardial infarction, chronic atrial fibrillation, and mitral regurgitation cases) and renal involvement in LVH-positive patients than in LVH-negative patients.**
Conclusion: **LVH is a strong risk factor for clinical events in hypertensives, which necessitates their more intensive treatment, mainly with drugs producing also LVH regression.** ***(Tab. 5, Ref. 48.)***
Key words: hypertension, left ventricular hypertrophy, heart failure, left ventricular diastolic dysfunction.

Arterial hypertension (HTN) is a very common disease with multifactorial etiology, with serious long-term prognosis. It increases significantly morbidity and mortality. Arterial hypertension is also an important factor for the development of left ventricular hypertrophy (LVH) and ischaemic heart disease, heart failure and many other cardiovascular and non-cardiovascular diseases. In addition to arterial hypertension, there are also other metabolic diseases, which we categorize among risk factors for atherosclerosis development such as: diabetes mellitus (DM), overweight and obesity (body mass index BMI) >27 kg/m^2) and hyperlipidemia. These risk factors contribute to an increase in the incidence of cardiovascular changes such as left ventricular hypertrophy and other organs changes, including their dysfunction or failure, either through their direct effect or through increasing blood pressure itself (1, 2, 3, 4).

Alderman et al (1998) followed-up 8690 hypertensive patients for a mean time-period of 5.6 years. They demonstrated the importance of arterial hypertension by the appearance of their cardiovascular complications. They found out 468 cardiovascular events in these patients (morbidity: in 286 patients/mortality: in 182 patients), myocardial infarction (MI) in 282 patients (out of whom 99 patients died), stroke in 93 patients (out of whom 20 patients died), congestive heart failure in 30 patients and other fatal cardiovascular events in 63 cases. The presence of risk factors other than hypertension was also observed in those patients.

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Those who developed myocardial infarction were elderly, had diabetes mellitus and were smokers. Those who developed stroke had diabetes mellitus, obesity and were smokers. Diabetes mellitus, obesity and LVH were also risk factors for the development of heart failure too (5).

Left ventricular hypertrophy is also a prognostic risk factor and risk marker for hypertensive patients. Framingham study demonstrated that with the development and progression of left ventricular hypertrophy the incidence of cardiovascular morbidity and mortality increased (6).

In our work we intended to look at left ventricular hypertrophy as one of the significant prognostic risk factors of cardiac changes in hypertensives. We compared the clinical course of arterial hypertension in patients with and without LVH.

Our study aim was to compare the presence of serious clinical events and complications such as heart failure, chronic atrial fibrillation, mitral regurgitation and renal involvement in hypertensive patients with LVH and with those without it.

Patients and methods

We analysed hospital records of hospitalised patients in our department during the time-period between 1996—1999. All these patients were well examined also by echocardiography. Out of this group of patients we found 496 hypertensives (253 males, 243 females), out of whom 319 patients (64 %) (154 males, 165 females, average age 64.1±10.6 ys, range 31–83 ys) had left ventricular hypertrophy and 177 patients (36 %) (99 males, 78 females, average age 62.5±11.3 ys, range 36–85 ys) did not have it Table 1.

Most common reasons for hospitalisation were worsening of cardiac heart failure, myocardial infarction, arrhythmias, stroke, worsening of hypertension (such as hypertensive crisis) or uncontrolled diabetes mellitus. Some of admitted patients had more than one reason for the hospital admission.

Echocardiography

Patients were examined in supine position on their left side. Examination was performed by a 2-dimensional guided M-mode approach. Left ventricular hypertrophy was defined according to Penn convention while calculating LVH (7). The left ventricular size of these patients was within normal range. Patients with distorted shape of ventricles or with low quality views were excluded from our analysis. We judged the presence of left ventricular hypertrophy by echocardiography according to the following formula (7, 8:)

$$LVM_{(g)} = 1.04 \times [(IVSd + LVIDd + LVPWd)^3 - (LVIDd\ 3)^3] - 13.6$$

$LVM_{(g)}$ = left ventricular mass in grams, IVSd = thickness of interventricular septum in diastole, in cm, LVIDd = left ventricular internal diameter in diastole, in cm, LVPWd = left ventricular posterior wall in diastole, in cm. By adjusting LVM (left ventricular mass) to body surface area we calculated left ventricular mass index (LVMI) and so we could define the presence of LVH. If LVMI was >134 g/m^2 in men or >110 g/m^2 in women, LVH was considered as being present.

Risk factors

– Diabetes mellitus was defined from history taking, from medical documents and/or at least by measuring fasting blood glucose twice (≥7 mmol/l) or by oGTT (oral glucose tolerance test) with blood glucose level of ≥11.1 mmol/l in the second hour (120 min) after oral glucose intake of 75 g glucose load.

Tab. 1. Characteristics of hypertensives with and without left ventricular hypertrophy.

Hypertension	LVH+	LVH-	Statistical significance
Total number of patients	319	177	
Men	154 (48%)	99 (56 %)	NS
Women	165 (52%)	78 (44 %)	NS
Age (y)	64.1±10.6	62.5±11.3	
	(31-83 y)	(36-85 y)	NS
Duration of hypertension (y)	9.3±6.5	8.7±6.1	NS
Systolic blood pressure (mmHg)	151.5±13.8	151.1±14.0	NS
Diastolic blood pressure (mmHg)	88.6±9.1	90.2±10.8	NS
LVM (g)	299.0±63.9	203.2±42.3	p<0.001
LVMI (g/m^2)	158.0±28.1	105.5±16.5	p<0.001
BSA (m^2)	1.89±0.19	1.92±0.19	NS
IVSd (mm)	12.1±1.5	10.4±1.5	p<0.001
LVPWd (mm)	11.4±1.5	9.8±1.3	p<0.001
LVIDd (mm)	52.9±5.1	48.1±4.7	p<0.001
Left atrium (mm)	42.3±4.8	37.9±4.6	p<0.001
BMI (kg/m^2)	28.0±4.3	27.9±3.9	NS
EF (%)	49.7±10.9	56.0±7.4	p<0.001

LVM: left ventricular mass, LVMI: left ventricular mass index, IVSd: thickness of interventricular septum in diastole, LVIDd: left ventricular internal diameter in diastole, LVPWd: left ventricular posterior wall in diastole, BMI: body mass index, EF: ejection fraction, p<0.05: significant (S), p>0.05: nonsignificant (NS)

Tab. 2. Antihypertensive treatment in hypertensives with LVH and without LVH.

Antihypertensive treatment	Hypertension				Statistical significance
	LVH+		LVH-		
	n	%	n	%	
ACE inhibitors	219	68.7	93	52.5	p<0.001
Betablockers	122	38.2	64	36.2	NS
Calcium antagonists	138	43.3	70	39.5	NS
Diuretics	119	37.3	40	22.6	p<0.01

p<0.05: significant (S), p>0.05: nonsignificant (NS)

Tab. 3. Intensity of anti-hypertensive treatment in hypertensives with LVH and without LVH.

Antihypertensive treatment	Hypertension				Statistical significance
	LVH+		LVH-		
	n	%	n	%	
Without therapy	14	4.4	18	10.1	p<0.05
Monotherapy	92	28.8	67	37.9	NS
Combined therapy (2 drugs)	14	645.8	60	33.9	p<0.05
Combined therapy (3 drugs)	56	17.6	25	14.1	NS
Combined therapy (4 drugs)	11	3.4	7	4.0	NS

p<0.05: significant (S,) p>0.05: nonsignificant (NS)

Tab. 4. Occurrence of other atherosclerotic risk factors in hypertensives with LVH and without LVH.

Risk factors	Hypertension				Statistical significance
	LVH+		LVH-		
	n	%	n	%	
Overweight and obesity	112	35.1	77	43.5	NS
Diabetes mellitus	28	8.8	16	9.0	NS
Obesity+Diabetes mellitus	51	16.0	20	11.3	NS
Hypercholesterolemia	125	39.2	85	48.0	NS
Hypertriglyceridemia	68	21.3	56	31.6	p<0.05
Decreased level of HDL-C	88	27.6	48	27.1	NS
Increased level of LDL-C	86	27.0	50	28.2	NS
Smoking	75	23.5	47	26.6	NS

HDL-C: high density lipoprotein – cholesterol, LDL-C: low density lipoprotein – cholesterol p<0.05: significant (S), p>0.05: nonsignificant (NS)

– Overweight and obesity were defined according to BMI (body mass index). They were considered as positive, if BMI 27 kg/m^2.

– Hypercholesterolemia was defined according to total blood cholesterol. A levels 5.2 mmol/l was considered as abnormal. Hypertriglyceridemia, if the level of triglycerides in the blood was 2.1 mmol/l. Increased level of LDL-C was considered if it was 3.5 mmol/l and level of HDL-C lower than 0.9 mmol/l was considered as abnormal.

Tab. 5. Occurrence of cardiovascular events and diseases in hypertensives with LVH and without LVH.

Cardiovascular events and diseases	Hypertension				Statistical significance
	LVH+		LVH-		
	n	%	n	%	
Heart failure	124	38.9	19	10.7	p<0.001
LV diastolic dysfunction	155	48.6	65	36.7	p<0.05
Myocardial infarction	139	43.6	48	27.1	p<0.001
Chronic atrial fibrillation	82	25.7	23	13.0	p<0.01
Mitral regurgitation	137	42.9	24	13.6	p<0.001
Renal involvement	88	27.6	28	15.8	p<0.01

LV: left ventricular, p<0.05: significant (S), p>0.05: nonsignificant (NS)

– Smoking was judged by history taking.

We measured arterial blood pressure (systolic and diastolic) by standard sphygmomanometer method (first and fifth Korotkov sounds). We calculated the average of several readings along five consecutive days. These patients were on anti-hypertensive treatment.

Clinical events, diseases and findings

(a) The presence of systolic heart failure was defined by history taking, physical examination and X-ray findings in addition to ECHO results (ejection fraction (EF) ≤40 %), supported by the improvement noticed in the condition of a given patient after administrating the standard treatment of heart failure. Ejection fraction was defined by M-mode ECHO where examinations (at least three) were performed by an experienced cardiologist. Each results got were compared and adjusted to an experienced subjective visual evaluation. The ellipsoidal model by Teichholz was used to help in detecting EF with accuracy. So, the following formula was utilized: $V = [7.0 \div (2.4 + D)]D^3$, where V is the volume of left ventricle and D is left ventricular internal dimension determined by ECHO. In case of abnormal kinesis in the apical region or other regions of left ventricle, EF was corrected by visual examination of an experienced echocardiographer doctor.

(b) The presence of left ventricular diastolic dysfunction was judged as above but with normal EF (EF>45 %). The presence of sample volume was positioned at the level of tips of mitral leaflets. The mean of three revolutions was calculated. A typical picture of diastolic dysfunction (in case of sinus rhythm) was a transmitral dopplerogram with the A peak higher than E peak, "pseudonormal pattern" (peak E higher than peak A but with shortened deceleration time). We put attention also to a "restrictive pattern" (9).

(c) Occurrence of myocardial infarction was defined by typical ECG findings and/or positive medical documents.

(d) The presence of chronic atrial fibrillation was found out from medical documents and was supported by at least four ECGs performed during a period of two weeks.

(e) The presence of mitral regurgitation was judged by ECHO--doppler examination.

(f) Serum creatinine was considered as a parameter of renal involvement (serum creatinine was measured twice in a two weeks interval, the average of which was calculated). Level of serum creatinine 120 μmol/l was considered as abnormal.

Statistical analysis

Differences in the prevalence of individual cardiovascular events and diseases (heart failure, left ventricular diastolic dysfunction, myocardial infarction, chronic atrial fibrillation, mitral regurgitation and renal involvement) in hypertensives with LVH versus hypertensives without LVH were calculated by the help of contingent tables 2x2 with the use of testing character chi^2 (chi^2-square difference). Characteristics of groups (mean values and standard deviations) were compared by t-test (Student's test) on the basis of different values of significance. Calculations were done by statistical program "Primer of Biostatistics and Statographics Plus".

Results

Both compared groups of patients (hypertensives with and without LVH) did not have significant differences in demographic data. Even though males were more prevalent in the group of hypertensives without LVH and females were more common in the group of hypertensives with LVH, these differences did not reach statistical significance. The duration of hypertension was longer in the group of hypertensives with LVH, but this difference was again statistically not significant. Hypertensives (with and without LVH) did not have bigger differences in the mean values of treated blood pressure during hospitalisation. Hypertensives with LVH had in comparison with the group of hypertensives without LVH a bigger dimension of the left ventricle (in end-diastole) and a bigger dimension of the left atrium (both statistically significant). Ejection fraction was lower in the group of hypertensives with LVH than that in the group of hypertensives without LVH (statistically significant) (Tab. 1). Hypertensives with LVH used more (statistically significant) ACE inhibitors and diuretics (Tab. 2). A bigger percentage of hyperten-

sives without LVH was without antihypertensive treatment (statistically significant) and on the contrary hypertensives with LVH were more often treated with combined antihypertensive drugs (statistically significant) (Tab. 3). Both groups of hypertensives showed non-significant differences in the presence or absence of atherosclerotic risk factors such as overweight and obesity, diabetes mellitus, obesity + diabetes mellitus, hypercholesterolemia, increased level of LDL-C, decreased level of HDL-C and of smoking habits. Hypertriglyceridemia was more common in the group of hypertensives without LVH (Tab. 4).

The occurrence of clinical events such as heart failure, left ventricular diastolic dysfunction, myocardial infarction, chronic atrial fibrillation, mitral regurgitation and renal involvement was significantly more common in hypertensives with LVH than in hypertensives without LVH (Tab. 5). A 3.64-fold increase in the presence of heart failure was found in the group of hypertensives with LVH, 1.32-fold increase in the presence of left ventricular diastolic dysfunction, 1.61-fold increase in the presence of myocardial infarction, 1.98-fold increase in the presence of chronic atrial fibrillation, 3.15-fold increase in the presence of mitral regurgitation and 1.75-fold increase in the presence of renal involvement in comparison with the group of hypertensives without LVH (Tab. 5).

Discussion

Arterial hypertension is a very frequent cardiovascular disease, which significantly contributes to an increase in cardiovascular events and mortality. Arterial hypertension, if it is not adequately and correctly treated, contributes mostly to left ventricular diastolic dysfunction, despite the presence of normal left ventricular systolic function. This is frequently caused by the development of left ventricular hypertrophy. It also contributes to the development of atrial and ventricular arrhythmias, ischaemic heart disease, myocardial infarction, stroke, renal involvement and even to renal failure, and eventually contributes to left ventricular systolic dysfunction with the later development of chronic heart failure (10, 11, 12). STEPHY II study (13), and other studies (1, 4, 5, 14, 15) demonstrated that arterial hypertension is a significant risk factor for cardiovascular morbidity. In three years of follow-up of hypertensives and normotensives (mean age of 65 years), it was found that hypertensives had greater incidence of myocardial infarction, ischaemic heart disease and heart failure than normotensives (13).

At the beginning left ventricular hypertrophy is an adaptive heart mechanism to chronic pressure and volume overload. This mechanism of adaptation normalizes left ventricular stress of patient's heart, but after a prolonged period of time, it becomes malproductive. LVH then becames an independent risk factor for increased cardiovascular and non-cardiovascular events in hypertensives (16–24).

LVH even without the presence of hypertension is considered to be a risk factor for deterioration of left ventricular diastolic and systolic functions. Andrén et al (1999) found out in healthy normotensive people with LVH that their ejection fraction was significantly lower than that in healthy normotensive people without LVH. They also demonstrated that normotensives with LVH had a significantly greater prevalence of left ventricular diastolic dysfunction and greater prevalence of ischaemic ECG changes during stress testing than normotensives without LVH (25).

Both compared groups of our patients (hypertensives with and without LVH) were matched very well in demographic data. There were more females (non-significantly) in the group of hypertensives with LVH (Tab. 1). There was a higher prevalence of diabetes mellitus and obesity in females, which could contribute to the development of LVH in this group. The duration of hypertension (got from history) did not show a big difference when we compared hypertensives with LVH with those without LVH Table 1. We expected longer duration of arterial hypertension in hypertensives with LVH. We stress the fact here that development of LVH is not only dependent on the duration of HTN, but there are influences from other risk factors that could contribute to the development of LVH, such as obesity, diabetes, genetic predisposition and others (26).

More hypertensives with LVH (with a significant difference, when compared with the group without LVH) were on ACE inhibitors and diuretics. This could be partly a result of the presence of latent or symptomatic heart failure. The use of other antihypertensive drugs was the same in both groups (Tab. 2).

The use of antihypertensive monotherapy was on the contrary more common in hypertensives without LVH (Tab. 3).

The incidence of obesity and hyperlipidemia was slightly more common in hypertensives without LVH.

We found a greater occurrence of heart failure patients (with systolic and/or diastolic dysfunction) among hypertensives with LVH comparing them with hypertensives without LVH (Tab. 5). A lower mean ejection fraction was also noticed among hypertensives when LVH was present (Tab. 1). In this group of patients the size of left ventricle (in end-diastole) was also significantly bigger (Tab. 1). This represents a worse development of left ventricular remodelling during the course of hypertension.

Framingham study and other clinical experience proved that the occurrence of heart failure is about 2 times more common among hypertensives when LVH is present with the co-existence of ischaemic heart disease (IHD) in comparison with hypertensives with IHD but without LVH (27–30). Grodzicki et al (1998) also found statistically significant reduction in systolic function of the left ventricle in older hypertensives with LVH when compared with similar hypertensives but without LVH (31).

The development of left ventricular remodelling in hypertensives (later very often followed by LVH development) is associated with left ventricular dysfunction and/or (later) diastolic heart failure (32). This was also noticed in our group of LVH positive patients (Tab. 5).

Arterial hypertension however contributes also to the progression of coronary atherosclerosis and to the development of microvascular disease of coronary arteries. Both of them contribute to the development of myocardial ischaemia. Reduction of coronary reserve and myocardial ischaemia also lead to the development of abnormal relaxation of left ventricle (33, 34).

Hypertensives with LVH are shown to have significant larger dimension of left atrium than hypertensives without LVH (34).

Manolis et al (1997) investigated a group of hypertensives with LVH (a subgroup with a bigger degree of LVH and another subgroup with a smaller degree of LVH). They excluded those patients with ischaemic heart disease in these hypertensives by performing coronaro-angiography. They demonstrated by stress test that hypertensives with a bigger degree of LVH had more often and greater myocardial ischaemic changes on ECG during the stress testing than hypertensives with smaller degree of LVH (35). Also the occurrence of new coronary events (myocardial infarction or acute coronary syndromes) was more common in hypertensives with LVH than in hypertensives without LVH (36, 37). The same findings were seen in our patients (Tab. 5).

Aronow et al (1997, 1999) proved that the occurrence of atrial fibrillation was more common in patients when LVH accompanied hypertension than in hypertensives without LVH. After 44 months of follow-up there was also a greater incidence of strokes among patients with concomitant chronic atrial fibrillation and LVH than in patients with chronic atrial fibrillation but without LVH (36, 38). The incidence of chronic atrial fibrillation was also more common statistically significant in our group of hypertensives with LVH when compared with those without associated LVH (Tab. 5).

We found a greater incidence of mitral regurgitation in hypertensives with LVH when compared with patients without LVH. This 3.15-fold increase was statistically significant (Tab. 5).

We think that diabetes mellitus and obesity together with the presence of LVH (probably through the development of concomittant myocardial ischaemia, mainly of papillary muscles or as a part of heart failure syndrom) contributed to the development of mitral regurgitation (Tab. 5).

Kohara et al (1995) found a significant positive correlation between left ventricular mass index (LVMI) and creatinine serum levels in hypertensives with LVH but at the same time they showed also an inverse correlation between LVMI and glomerular filtration rate in these young hypertensives with LVH (39). Shigematsu et al (1997) showed the same positive correlation between LVMI and creatinine serum levels in hypertensives with LVH (40).

Left ventricular hypertrophy is nowadays considered also as a risk factor for renal dysfunction or disease (41–48). Our hypertensive patients with LVH had a greater renal involvement than those without LVH (Tab. 5). The relation (pathophysiology) between LVH and renal dysfunction is complex. The presence of LVH in hypertensive patients usually means the presence of a more severe form of hypertension, a more severe form of endothelial dysfunction and an apparent deterioration of microvascular circulation. These changes bring up slowly worsening in the blood supply to many vital organs (including kidneys) causing their structural changes and finally their failure (41, 42).

In many clinical studies it was found that hypertensive patients with chronic renal failure (before being put on regular haemodialysis) frequently have an inverse correlation between LVM and creatinine clearance and a positive correlation between LVM and average blood pressure (by 24 hour-Holter monitoring) (43, 44). Hypervolemia in patients with chronic renal failure contributes to a larger LVM and a larger left ventricular dimension (so called excentric hypertrophy of left ventricle). The presence of anaemia contributes also to the dilatation of the left ventricle with increased thickness of its walls (45–47).

Levin et al (1999) showed a significant increase in LVM and LVMI in patients with chronic renal failure after one year of follow-up. In their group of patients (n=446 patients) 34 % of those with LVH had a lower glomerular filtration, a lower haemoglobin level and higher readings of systolic blood pressure when compared with patients without LVH (48).

Left ventricular hypertrophy in our patients was not a result of chronic renal failure. We think that it was a result of long lasting hypertension. Anyway we found a statistically significant relation between renal involvement and LVH.

Study limitations

Arterial hypertension in the presence of LVH represents a more serious disease than that in patients without LVH. The presence of LVH represents at one side a useful adaptive reaction of the heart against hypertensive load, but on the other side it is also a risk factor for increased morbidity and mortality of hypertensive patients.

Many clinical studies, including our clinical follow-up, proved the unfavourable prognosis of hypertension with LVH.

It is expected that regression of LVH by appropriate and long-lasting antihypertensive treatment would improve the prognosis in these patients.

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