HOSPITAL CHRONICLES 2008, SUPPLEMENT: 210–214

The Impact of Reducing Hypertensive Left Ventricular Hypertrophy on Sudden Cardiac Death

Dimitris Tsilakis, MD, Nikolaos Parzakonis, MD,
George Andrikopoulos, MD, Ioannis Fouskarinis, MD,
Spyridon Koulouris, MD, Antonis S. Manolis, MD

First Department of Cardiology, "Evagelismos" General Hospital of Athens, Athens, Greece

ABSTRACT

It has been well recognized that the presence of left ventricular hypertrophy (LVH) is an adverse feature in hypertension, with such patients having a substantially higher risk of cardiovascular events, including mortality and morbidity from heart failure, ventricular arrhythmias, death from myocardial infarction, sudden cardiac death and cerebrovascular episodes. ECG may show findings suggestive of hypertrophy but echocardiography is the preferred test for the evaluation of the presence and extent of hypertrophy. The reduction of blood pressure via life style interventions and with the use of antihypertensive agents reduces cardiac mass in patients with LVH. This reduction is related both to the degree of antihypertensive response and to the specific therapy used. It appears that the degree of regression is more pronounced with angiotensin-converting enzyme inhibitors and calcium channel blockers, especially non-dihydropyridines. The regression of LVH is accompanied by a reduction in sudden death, acute myocardial infarction and heart failure.

KEY WORDS: *left ventricular hypertrophy; hypertension; sudden cardiac death*

ABBREVIATIONS:
LVH: left ventricular hypertrophy
ECG: electrocardiography
LV: left ventricular
BP: blood pressure
VPBs: ventricular premature beats
SCD: sudden cardiac death
VT: ventricular tachycardia
VF: ventricular fibrillation

Address for correspondence:
Professor Antonis S. Manolis, MD
Director of Cardiology
A΄ Department of Cardiology
Evagelismos General Hospital
Athens, Greece
Tel.: +30-210 720 1493
E-mail: asm@otenet.gr

INCIDENCE AND DEFINITION OF HYPERTENSIVE LEFT VENTRICULAR HYPERTROPHY (LVH)

Left ventricular hypertrophy (LVH) is a common finding in patients with borderline or overt arterial hypertension and it can be diagnosed based on electrocardiographic (ECG) or echocardiographic criteria [1,2]. Even though the ECG may show findings suggestive of LVH, it is much less sensitive and therefore echocardiography is the preferred test for the evaluation of the presence and extent of hypertrophy. Echocardiography, usually with the M-mode technique, is the gold standard test, given the low sensitivity of the ECG criteria for LVH (only 7% to 35% in moderate hypertrophy and 10% to 50% in severe hypertrophy) [3].

LVH is defined as an increase in left ventricular (LV) mass due to myocardial wall thickening or LV cavity dilatation or both. This increase in LV mass is the result of the continued exposure to an increased afterload in arterial hypertension. The pathogenetic mechanism involves an increase in the number and/or size of the individual sarcomeres in each cardiac myocyte. The normal LV mass in men is 135 g and the mass index is 71 g/m^2; in women, the values are 99 g and 62 g/m^2, respectively. Hypertrophy is defined as two standard deviations above the normal limits [4,5]. Data from the

Framingham Heart Study have shown that normalization of the LV mass index to height may be more accurate, the normal values being 163 gr/m for men and 121 gr/m for women [6]. Nevertheless, in clinical practice the presence of LVH is determined from the M-mode values or 2D measurements in the parasternal view.

In addition to the increase in the absolute value of LV mass, the geometrical shape of the LV cavity is also important [7]. Patients without an increase in absolute mass, but with an increase in relative wall thickness or in the wall thickness-to-cavity diameter ratio (called concentric remodeling) have the same adverse risk as those with an increase in both mass and relative wall thickness (called concentric hypertrophy). In each case there is an increased risk not only for cardiovascular sequelae, but also for death, which is independent of the blood pressure level [8].

ETIOLOGY

The development of LVH is a relatively premature response to arterial hypertension, as is echocardiographically shown in children and adults with borderline hypertension [17]. Patients that develop transient but substantial increase in blood pressure values during mental or physical work may also tend to develop hypertrophy [18]. Ambulatory blood pressure (BP) monitoring has suggested the existence of two additional risk factors for the development of hypertrophy: the daily hypertensive load defined as the percentage of values above 140/90 mmHg in the daytime and above 120/80 mmHg in the night time, and nocturnal hypertension, where the expected fall in blood pressure during the night rest is not observed.

Other studies have suggested that the peak morning BP value, or the peak exercise value are more predictive of the development of LVH [19]. This may explain why ambulatory BP monitoring values are more closely related to the development of LVH than the usual office BP measurement.

There is also evidence showing an increase in LV mass before the development of overt hypertension [20]. Data from the Framingham Heart Study for example showed a direct and continuous relationship between LV mass and the subsequent development of hypertension in previously normotensive subjects [20]. The above observations may be explained by three mechanisms: the patients had higher mean BP values from the beginning; the same factors such as angiotensin II, epinephrine, norepinephrine, endothelin and increased sympathetic tone, in the heart and peripheral vessels, predispose to hypertension and hypertrophy alike, and finally, the tendency to hypertrophy may be a genetic trait predisposing to hypertension as well.

CLINICAL IMPORTANCE

As regards the clinical importance of LVH, it is accompanied by an increase in heart failure, ventricular arrhythmias, death from myocardial infarction, reduced ejection fraction, sudden cardiac death (SCD) and cerebrovascular episodes [13-16]. In a prospective study, 1033 hypertensive patients, free of cardiovascular incidents, were followed up for a median of three years [14]. The percentage of major cardiovascular events (fatal or non-fatal myocardial infarctions, SCD, severe heart failure or severe renal failure requiring dialysis) was significantly higher in the 29% of patients who had an increased LV mass. After adjustment for other risk factors, LVH was associated with an increase in cardiovascular events, showing a relative risk of 2.08. For each increase in LV mass by 39 gr/m^2 there was an increased risk for cardiovascular events of 40%.

A report from the Framingham Heart Study examined the relation of LV mass and hypertrophy with SCD in 3661 subjects over 40 years of age, who were followed-up for 14 years [17]. The incidence of LVH was 22% and the relative risk for SCD was 2.16 ($p=0.008$). For every 50 gr/m increase of LV mass the relative risk increased by 1.45 ($p=0.008$).

LVH is also related to an increased risk of cerebrovascular events, both stroke and transient ischemic attacks, may be because it is a marker of more severe or prolonged hypertension. This was shown in a study of 2363 hypertensive subjects without previous cardiovascular disease, who were followed-up for 14 years [15]. The presence of LVH either in the ECG (18% of the study population) or echocardiographically (24% of the subjects) increased the risk of cerebrovascular events, with a relative risk of 1.79 and 1.64 respectively. For every increase in LV mass by one standard deviation on echocardiography, the relative risk of an event was 1.31.

The increased cardiovascular risk of LVH may be in part due to myocardial ischemia that can be the result of several factors. The hypertrophied myocardium is characterized by a reduced density of capillaries. Moreover, the enlarged LV mass limits the coronary arterioles' ability to dilate in response to reduced perfusion or during vasodilation [18]. The endocardial capillaries may also be directly compressed. The above may result in reduced coronary flow reserve and have several clinical implications.

In case of coronary artery occlusion the presence of LVH results in bigger infarcts and higher mortality rates, compared to the absence of LVH [19]. The hypertrophied myocardium is more vulnerable to the ischemic insult. In a study of patients that had suffered SCD the patients with hypertension and LVH had less extensive coronary artery disease and were less likely to have thrombi in the coronary vessels, compared to the normotensive ones [20].

The development of heart failure in patients with LVH is

the result of reduced systolic and/or diastolic function of the left ventricle. The adverse impact of LV remodeling may be a crucial factor promoting the progression of heart failure [21].

LVH also causes electrophysiological changes and a type of electrical remodeling, including changes in the action potential altered repolarization and dispersion of recovery, and easily provocable early afterdepolarizations. The latter are associated with an increased susceptibility to ventricular arrhythmias, especially torsade de pointes and SCD [22].

Patients with ECG evidence of LVH have a higher incidence and greater complexity of ventricular premature beats and more serious arrhythmias than patients without LVH or normotensives [23-27]. This correlation is irrespective of the etiology of LVH. Ventricular arrhythmias are also increased in patients with LVH compared to normotensives or hypertensive patients without LVH [26,28-31]. In a study of patients over 70 years of age, the presence of LVH, even in the absence of a history of hypertension, resulted in an increased incidence of ventricular arrhythmias [32].

The frequency and complexity of ventricular premature beats (VPBs) is related to the severity of LVH [28,29]. For example, a study of 49 patients without coronary artery disease, showed that the frequency and complexity of ventricular arrhythmias was closely related to the presence of LVH, as defined by the thickness of interventricular septum or posterior LV wall more than 1.2 cm or the LV mass. For each mm increase in wall thickness there was a two- to three- fold increase in the occurrence and complexity of VPBs. In addition to the occurrence of spontaneous ventricular arrhythmias, LVH also results in an increased ability to induce sustained ventricular tachycardia (VT) in animals and humans [33,34], especially in the presence of coronary artery disease [35].

Little is known about the pathophysiologic mechanisms responsible for ventricular arrhythmias in the hypertrophied LV. Many theories have been proposed, but it seams that the genesis of arrhythmias in the hypertrophied LV is multifactorial, the main factors being ischemia, electrophysiologic disturbances, myocardial cell abnormalities, increased sympathetic activity, fluctuations in blood pressure levels and electrolyte abnormalities from diuretic therapy in patients with hypertension.

The fact that ventricular arrhythmias and SCD are frequent in patients with LVH [36], does not prove that these arrhythmias precede ventricular fibrillation (VF) or fatal electrical events. It seems logical but remains unproven that, in a population documented to be at increased risk of SCD, such as patients with LVH, those with the greatest degree of electric instability are likely to be at highest risk. It is still unanswered whether the presence of ventricular arrhythmias in patients with LVH is a prognostic factor of SCD although several studies have shown that it is true for the complex ventricular arrhythmias [37-39]. For example in the Framingham Heart Study 671 patients with echocardiographically proven LVH were studied. At the end of the 6 year period of follow-up, the all cause mortality was increased in those with complex or frequent ventricular arrhythmias compared to those without (38% versus 12% for men and 22% versus 11% for women) [35]. However, the increased mortality was only marginally significant after adjusting for clinical factors. In another study 554 elderly patients were followed up for an average period of 27 months [38]. Hypertensive patients with coronary artery disease and non-sustained VT on ambulatory Holter monitoring who had echocardiographically proven LVH were significantly more likely to experience VF or SCD, compared to those who did not have VT or who had VT without LVH (57% versus 20% and 20% respectively, $p<0.001$). According to these data, it would seem logical that the regression of LVH would result in a reduction of ventricular ectopy and SCD.

THERAPEUTIC INTERVENTIONS

In general, the reduction of blood pressure via life style interventions and with the use of antihypertensive agents reduces cardiac mass in patients with LVH [33-35,39]. This reduction is related both to the degree of antihypertensive response and to the specific therapy used [41]. It appears that the degree of regression is more pronounced with ACE inhibitors and calcium channel blockers, especially nondihydropyridines while it may not occur with direct vasodilators such as hydralazine and minoxidil [41,42].

The regression of LVH is accompanied by a reduction in ventricular arrhythmias. In animal models, the regression of LVH normalized the action potentials and suppressed the diversity of refractoriness, thereby decreasing the susceptibility to the induction of polymorphic VT and VF [34]. A series of observations in humans shows similar results for some antihypertensive agents. In one study, the regression of LVH, after three months of treatment with a calcium channel blocker, decreased ventricular arrhythmia and this was associated with a reduction in LV mass [43]. In contrast, the patients treated with a diuretic had no reduction in either the LV mass or ventricular ectopy. Another study randomized 46 hypertensive patients to enalapril, hydrochlorothiazide, atenolol or verapamil. All agents reduced blood pressure levels effectively. At six months, the LV mass index and ventricular ectopy were reduced in the subgroups of enalapril, atenolol, and verapamil. In contrast hydrochlorothiazide affected neither LV mass nor the impact of arrhythmias [44]. In another small study, hypertensive patients were randomized to captopril or placebo [45]. Captopril therapy was accompanied by a reduction of LVH and ventricular arrhythmias. Another study using cisapril and isradipine showed similar results [46]. Based on these data it seems safe to assume that the reduction in ventricular arrhythmias related to the regression of LVH is

not due to a direct antiarrhythmic action of antihypertensive agents but rather due to their actions at the hemodynamic and possibly neurohormonal level.

Not many studies exist for the impact of the regression of LVH on cardiovascular morbidity and mortality. In general, they support but do not prove a benefit beyond blood pressure reduction [47,48,51]. Reports from the Framingham Heart Study have shown that the regression of LVH, based on ECG criteria, is accompanied by a reduction in SCD, acute myocardial infarction and heart failure [49,51]. Among patients with LVH the likelihood of a cardiovascular event such as, cardiac death, myocardial infarction, stroke, angina or need for revascularization, over a 10-year period was significantly lower in those subjects that achieved LVH regression compared to those in whom LVH persisted (3% versus 25%, $p<0.01$). Moreover, patients with normal LV mass who did not develop LVH in the 10-year period had significantly less cardiac events compared to those who developed LVH (5.1% versus 31.6%, $p<0.01$). Similar benefits come from the LIFE trial, which compared atenolol with losartan [50]. Although a similar blood pressure reduction was achieved with both drugs, the regression of LVH was greater with losartan, especially in diabetics. A further analysis of the trial data found that the incidence of SCD was significantly lower in the diabetics group treated with losartan compared to the patients treated with atenolol.

REFERENCES

1. Elias, MF, Sullivan, LM, Elias, PK, et al. Left ventricular mass, blood pressure, and lowered cognitive performance in the Framingham offspring. *Hypertension* 2007; 49:439.
2. Devereux, RB. Is the electrocardiogram still useful for detection of left ventricular hypertrophy? *Circulation* 1990; 81:1144.
3. de Vries, SO, Heesen, WF, Beltman, FW, et al. Prediction of the left ventricular mass from the electrocardiogram in systemic hypertension. *Am J Cardiol* 1996; 77:974.
4. Gardin, JM, McClelland, R, Kitzman, D, et al. M-mode echocardiographic predictors of six- to seven-year incidence of coronary heart disease, stroke, congestive heart failure, and mortality in an elderly cohort (the Cardiovascular Health Study). *Am J Cardiol* 2001; 87:1051.
5. Haider, AW, Larson, MG, Benjamin, EJ, et al. Increased left ventricular mass and hypertrophy are associated with an increased risk for sudden death. *J Am Coll Cardiol* 1998; 32:1454.
6. Beache, GM, Herzka, DA, Boxerman, JL, et al. Attenuated myocardial vasodilator response in patients with hypertensive hypertrophy revealed by oxygenation-dependent magnetic resonance imaging. *Circulation* 2001; 104:1214.
7. Carluccio, E, Tommasi, S, Bentivoglio, M, et al. Prognostic value of left ventricular hypertrophy and geometry in patients with a first, uncomplicated myocardial infarction. *Int J Cardiol* 2000; 74:177.
8. Burke, AP, Fard, A, Liang, YH, et al. Effect of hypertension and cardiac hypertrophy on coronary artery morphology in sudden cardiac death. *Circulation* 1996; 94:3138.
9. Ciulla, MM, Paliotti, R, Esposito, A, et al. Different effects of antihypertensive therapies based on losartan or atenolol on ultrasound and biochemical markers of myocardial fibrosis: results of a randomized trial. *Circulation* 2004; 110:552.
10. Franz, IW, Tonnesmann, U, Muller, JF. Time course of complete normalization of left ventricular hypertrophy during long-term antihypertensive therapy with angiotensin converting enzyme inhibitors. *Am J Hypertens* 1998; 11:631.
11. Dzau, VJ. Tissue renin-angiotensin system in myocardial hypertrophy and failure. *Arch Intern Med* 1993; 153:937.
12. Devereux, RB, Palmieri, V, Sharpe, N, et al. Effects of once-daily angiotensin-converting enzyme inhibition and calcium channel blockade-based antihypertensive treatment regimens on left ventricular hypertrophy and diastolic filling in hypertension: the prospective randomized enalapril study evaluating regression of ventricular enlargement (PRESERVE) trial. *Circulation* 2001; 104:1248.
13. Lorell, BH, Carabello, BA. Left ventricular hypertrophy: pathogenesis, detection, and prognosis. *Circulation* 2000; 102:470.
14. Liebson, PR, Grandits, G, Prineas, R, et al. Echocardiographic correlates of left ventricular structure among 844 mildly hypertensive men and women in the *Treatment of Mild Hypertension Study (TOMHS). Circulation* 1993; 87:476.
15. De Vries, SO, Heesen, WF, Beltman, FW, et al. Prediction of the left ventricular mass from the electrocardiogram in systemic hypertension. *Am J Cardiol* 1996; 77:974.
16. Norman, JE Jr, Levy, D. Improved electrocardiographic detection of echocardiographic left ventricular hypertrophy: Results of a correlated data base approach. *J Am Coll Cardiol* 1995; 26:1022.
17. Devereux, RB, Lutas, EM, Casale, PN, et al. Standardization of M-mode echocardiographic left ventricular anatomic measurements. *J Am Coll Cardiol* 1984; 4:1222.
18. Levy, D, Savage, DD, Garrison, RJ, et al. Echocardiographic criteria for left ventricular hypertrophy: The Framingham Heart Study. *Am J Cardiol* 1987; 59:956.
19. Krumholz, HM, Larson, M, Levy, D. Prognosis of left ventricular geometric patterns in the Framingham Heart Study. *J Am Coll Cardiol* 1995; 25:879.
20. Verdecchia, P, Schillaci, G, Borgioni, C, et al. Adverse prognostic significance of concentric remodeling of the left ventricle in hypertensive subjects with normal left ventricular mass. *J Am Coll Cardiol* 1995; 25:871.
21. Van Hoeven, KH, Factor, SM. A comparison of the pathologic spectrum of hypertensive, diabetic and hypertensive-diabetic heart disease. *Circulation* 1990; 82:848.
22. Jain, A, Avendano, G, Dharamsey, S, et al. Left ventricular diastolic function in hypertension and role of plasma glucose and insulin. Comparison with diabetic heart. *Circulation* 1996; 93:1396.
23. Messerli, FH, Ventura, HO, Elizardi, DJ, et al. Hypertension and sudden death: Increased ventricular ectopic activity in left ventricular hypertrophy. *Am J Med* 1984; 77:18.
24. McLenachan, JM, Henderson, E, Morris, KI, Dargie, HJ. Ven-

tricular arrhythmias in patients with hypertensive left ventricular hypertrophy. *N Engl J Med* 1987; 317:787.
25. Aronow, WS, Epstein, S, Schwartz, KS, Koenigsberg, M. Correlation of complex ventricular arrhythmias detected by ambulatory electrocardiographic monitoring with echocardiographic left ventricular hypertrophy in persons older than 62 years in a long-term health care facility. *Am J Cardiol* 1987; 60:730.
26. Levy, D, Anderson, KM, Savage, DD, et al. Risk of ventricular arrhythmias in left ventricular hypertrophy: The Framingham Study. *Am J Cardiol* 1987; 60:560.
27. Siegel, D, Cheitlin, MD, Blaek, DM, et al. Risk of ventricular arrhythmias in hypertensive men with left ventricular hypertrophy. *Am J Cardiol* 1990; 65:742.
28. Ghali, JK, Kadakia, S, Cooper, RS, Liao, YL. Impact of left ventricular hypertrophy on ventricular arrhythmias in the absence of coronary artery disease. *J Am Coll Cardiol* 1991; 17:1277.
29. Schmieder, RE, Messerli, FH. Determinants of ventricular ectopy in hypertensive cardiac hypertrophy. *Am Heart J* 1992; 123:89.
30. Novo, S, Barbagallo, M, Abrignani, MG, et al. Increased prevalence of cardiac arrhythmias and transient episodes of myocardial ischemia in hypertensives with left ventricular hypertrophy but without clinical history of coronary heart disease. *Am J Hypertens* 1997; 10:843.
31. Mammarella, A, Paradiso, M, Basili, S, et al. Morphologic left ventricular patterns and prevalence of high-grade ventricular arrhythmias in the normotensive and hypertensive elderly. *Adv Ther* 2000; 17:222.
32. Andren, B, Lind, L, Hedenstierna, G, Lithell, H. Impaired systolic and diastolic function and ventricular arrhythmia are common in normotensive healthy elderly men with left ventricular hypertrophy. *Coron Artery Dis* 1999; 10:111.
33. Vester, EG, Kuhls, S, Ochiulet-Vester, J, et al. Electrophysiological and therapeutic implications of cardiac arrhythmias in hypertension. *Eur Heart J* 1992; 13 Suppl D:70.
34. Rials, SJ, Wu, Y, Ford, N, et al. Effect of left ventricular hypertrophy and its regression on ventricular electrophysiology and vulnerability to inducible arrhythmia in the feline heart. *Circulation* 1995; 91:426.
35. Martins, JB, Kim, W, Marcus, ML. Chronic hypertension and left ventricular hypertrophy facilitate induction of sustained ventricular tachycardia in dogs 3 hours after left circumflex coronary artery occlusion. *J Am Coll Cardiol* 1989; 14:1365.
36. Haider, AW, Larson, MG, Benjamin, EJ, et al. Increased left ventricular mass and hypertrophy are associated with an increased risk for sudden death. *J Am Coll Cardiol* 1998; 32:1454.
37. Bikkina, M, Larson, MG, Levy, D. Asymptomatic ventricular arrhythmias and mortality risk in subjects with left ventricular hypertrophy. *J Am Coll Cardiol* 1993; 22:1111.
38. Aronow, WS, Epstein, S, Koenigsberg, M, et al. Usefulness of echocardiographic left ventricular hypertrophy, ventricular tachycardia and complex ventricular arrhythmias in predicting ventricular fibrillation or sudden cardiac death in elderly patients. *Am J Cardiol* 1988; 62:1124.
39. Kannel, WB, Gordon, T, Offutt, D. Left ventricular hypertrophy by electrocardiogram. Prevalence, incidence, and mortality in the Framingham study. *Ann Intern Med* 1969; 71:89.
40. Saadehm Anm Joes, JV. Predictors of sudden cardiac death in never previously treated patients with essential hypertension: long-term follow up. *J Hum Hypertens* 2001; 15:667.
41. Cruickshank, JM, Lewis, J, Moore, V, Dodd, C. Reversibility of left ventricular hypertrophy by differing types of antihypertensive therapy. *J Hum Hypertens* 1992; 6:85.
42. Dahlof, B, Pennert, K, Hansson, L. Reversal of left ventricular hypertrophy in hypertensive patients. A metaanalysis of 109 treatment studies. *Am J Hypertens* 1992; 5:95.
43. Messerli, FH, Nunez, BD, Nunez, MM, et al. Hypertension and sudden death: disparate effects of calcium entry blocker and diuretic therapy on cardiac dysrhythmias. *Arch Intern Med* 1989; 149:1263.
44. Novo, S, Abrignani, MG, Novo, G, et al. Effects of drug therapy on cardiac arrhythmias and ischemia in hypertensives with LVH. *Am J Hypertens* 2001; 14:637.
45. Gonzalez-Fernandez, RA, Rivera, M, Rodriguez, PJ, et al. Prevalence of ectopic ventricular activity after left ventricular mass regression. *Am J Hypertens* 1993; 6:308.
46. Manolis, AJ, Beldekos, D, Handanis, S, et al. Comparison of spirapril, isradipine, or combination in hypertensive patients with left ventricular hypertrophy: Effects on LVH regression and arrhythmogenic propensity. *Am J Hypertens* 1998; 11:640.
47. Koren, MJ, Devereux, RB. Mechanism, effects, and reversal of left ventricular hypertrophy in hypertension. *Curr Opin Nephrol Hypertens* 1993; 2:87.
48. Yurenev, AP, Dyakonova, HG, Novikov, ID, et al. Management of essential hypertension in patients with different degrees of left ventricular hypertrophy. Multicenter trial. *Am J Hypertens* 1992; 5:182S.
49. Levy, D, Salomon, M, D´Agostino, RB, et al. Prognostic implications of baseline electrocardiographic features and their serial changes in subjects with left ventricular hypertrophy. *Circulation* 1994; 90:1786.
50. Dahlof, B, Devereux, RB, Kieldsen, SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention for Endpoint reduction in hypertension study (LIFE). A randomized trial against atenolol. *Lancet* 2002; 359:995.
51. Koren, MJ, Devereux, RB, Casale, PN, et al. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. *Ann Intern Med* 1991; 114:345.