Original Article

Cardiovascular risk in relation to a new classification of hypertensive left ventricular geometric abnormalities

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See editorial comment on page 690

Objectives: In 2010, the Dallas Heart Study proposed an upgrade of the left ventricular geometric classification proposed in 1991, by using left ventricular mass combined with end diastolic volumes, and introducing the new categories of dilated left ventricular hypertrophy (LVH). We adopted the new method to test the prognostic impact of the left ventricular geometric patterns from the new classification.

Methods: We evaluated baseline anthropometric, laboratory and echocardiographic parameters of 8848 hypertensive patients from the Campania Salute Network (53 ± 12 years, 56% male), free of prevalent cardiovascular disease, valve disease and with ejection fraction $\geq$50%. Cut points for left ventricular mass index, relative wall thickness and left ventricular end-diastolic dimension (cm/m) were derived from our historical normal reference population. Composite cardiovascular end-points were cardiac death, fatal and nonfatal myocardial infarction and stroke.

Results: Independent of confounders, eccentric dilated LVH, concentric nondilated LVH and concentric dilated LVH were associated with higher cardiovascular risk (hazard ratios between 2 and 9, all $P < 0.01$), mostly depending on the magnitude of LVM index. A volume load was present especially in dilated forms of LVH, the extent of which was important in the determination of harmful types of left ventricular geometry.

Conclusion: Consideration of left ventricular dilatation in the evaluation of risk related to hypertensive left ventricular geometry reveals the importance of the extent of the volume load coexisting with the typical hypertensive pressure overload. At a given normal ejection fraction, the balance between the two hemodynamic components influences the shape of left ventricular geometric adaptation, the amount of left ventricular mass and the impact on prognosis.

Keywords: cardiovascular outcome, left ventricular geometry

Abbreviations: BP, blood pressure; GFR, glomerular filtration rate; LVH, left ventricular hypertrophy; LVIDd, LV end-diastolic dimension; LVM, LV mass; RWT, relative wall thickness

INTRODUCTION

In 1992, we proposed a four-element classification of left ventricular geometry in hypertensive heart disease [1], based on left ventricular mass index and relative wall thickness. This classification scheme was designed to explain the pathophysiologic basis for cardiac remodeling in this condition. In addition to the condition of normal left ventricular mass and geometry, this scheme comprised three abnormal left ventricular geometric patterns: concentric left ventricular remodeling, eccentric left ventricular hypertrophy (LVH) and concentric LVH. We demonstrated different hemodynamic and peripheral resistance properties of each subtype. Subsequent studies extended these observations by showing that these subtypes could be associated with different outcomes [2–8]. Although some uncertainty persists concerning the relation between cardiovascular outcome and some of our specific left ventricular geometric subtypes [9,10], there is uniformity of opinion that concentric LVH, connoting severe pressure overload, is associated with worse outcome than eccentric LVH or concentric remodeling.

More recently, the investigators of the Dallas Heart Study (DHS), a multiethnic population study in the Dallas County [11], refined our classification of hypertensive left ventricular geometric abnormalities [1], by introducing the concept that LVH could exist in dilated or nondilated forms, regardless of left ventricular geometry, that is adding concentric dilated and nondilated as well as eccentric dilated and nondilated subtypes [12]. Although this study characterized the subjects by troponin and brain natriuretic peptide (BNP) data for each of the left ventricular geometric

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subtypes, it was not an outcome study per se. We already tested the new DHS paradigm in the relatively small subpopulation of the LIFE echo-sub-study [13], using combination of left ventricular mass with estimated volumes, and suggesting that LVH without left ventricular dilatation or concentric geometry might carry a relatively low cardiovascular risk. In the present analysis, performed in a very large observational registry (Campania Salute Network, CSN) of hypertensive patients, all eligible for programs of primary cardiovascular prevention, we adapted the DHS paradigm to evaluate cardiovascular outcome associated with each of the left ventricular geometric phenotypes derived from the combination of left ventricular mass, and primary measures of chamber dimension and concentricity index, and to define their characteristic hemodynamic profile.

METHODS

Participants

The CSN is an open registry collecting information from general practitioners and community hospitals in the five districts of the Campania Region, in Southern Italy. General practitioners and community hospitals are networked with the Hypertension Research Center of the Federico II University Hospital in Naples. The database generation of CSN was approved by our Institutional Ethic Committee and signed informed consent was obtained from all participants. Detailed characteristics of CSN population have been previously reported [14–16].

For the present analysis, from the cohort of 10 367 subjects of the CSN who entered the system with the code 'arterial hypertension,' we excluded hypertensive patients with secondary hypertension ($n = 258$), preexisting coronary heart disease (CHD, $n = 907$, defined as history of previous myocardial infarction, or coronary revascularization), aortic and/or mitral regurgitation more than mild ($n = 128$), any degree of aortic stenosis ($n = 113$) and ejection fraction less than 50% ($n = 113$). Thus, the present analysis included 8848 hypertensive participants without history of CHD, valve disease and with normal ejection fraction.

Incident composite fatal and nonfatal cardiovascular or cerebrovascular events were used as end-point of the present analysis, including fatal or nonfatal myocardial infarction, fatal or nonfatal stroke and sudden death (International Classification of Disease 9 codes: 410, 436, 431 and 798.1). Prevalent and incident cardiovascular and cerebrovascular disease were adjudicated by the Committee for Event Adjudication in the Hypertension Research Center, and was based on patients' history, contact with the reference general practitioner and clinical records documenting the occurrence of disease [16,17].

All hypertensive patients of the network were referred for baseline echocardiograms to our Hypertension Center.

Measurements and definitions

Diabetes was defined according to 2007 American Diabetes Association criteria (fasting plasma glucose >125 mg/dl or antidiabetic treatment) [18]. Obesity was defined as a BMI 30 kg/m^2 or higher. Glomerular filtration rate (GFR) was estimated by simplified Modification of Diet in Renal Disease (MDRD) equation.

Systolic and diastolic blood pressure (BP) were measured by standard aneroid sphygmomanometer after 5-min resting in the supine position, according to current guidelines.

As previously reported [19], follow-up BP was evaluated at the last available visit before events, and considered uncontrolled when systolic BP was 140 mmHg or higher and/or diastolic BP was 90 mmHg or higher in nondiabetic participants or 130/80 mmHg or higher in diabetic patients, under a therapeutic plan that included counseling for lifestyle measures and prescription of at least two medications (any class).

Echocardiography

Echocardiograms were recorded in our Hypertension Center on videotapes, using commercial machines and a standardized protocol, were digitally mastered and read off line by one expert reader under the supervision of a senior faculty member, using dedicated work-stations (MediMatic, Genova, Italy).

Measurements were made according to the American Society of Echocardiography/European Association of Echocardiography recommendations [20]. Left ventricular mass was estimated from a necropsy-validated formula [21] and normalized for height in meters to the power of 2.7 (LVMi) [22]. Table 1 displays the cut-points used for the definitions, based on our historical reference normal population [23].

Left ventricular mass was also evaluated in relation to the estimated hemodynamic load and expressed in percentage of the value predicted from sex, stroke work (as the product of systolic BP $\times$ stroke volume $\times$ 0.0144, expressed in gram-meters/beat) and body size (height$^{2.7}$), as excess of left ventricular mass, as previously reported [24]. An excess of 128% or above was classified as inappropriate left ventricular mass [24].

Left ventricular volumes were estimated by the z-derived method, which has been shown to be the most accurate estimation of left ventricular volume measured from linear measurements of left ventricular diameters [25], and used to

TABLE 1. Sex-specific definitions of LVH, concentric left ventricular geometry and left ventricular chamber dilatation

Definitions	Variables	Cut-points (≥)	
		Women	Men
Left ventricular hypertrophy (LVH)	Left ventricular mass index (g/m$^{2.7}$)	47	50
Concentric left ventricular geometry	Relative wall thickness	0.43	0.43
Left ventricular chamber dilatation	Height-normalized left ventricular diameter	3.30	3.34

LVH, Left ventricular hypertrophy.

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estimate ejection fraction, stroke volume and cardiac output. Stroke index and cardiac index were computed by allometric normalization for body height [26]. Total peripheral resistance (in kdyne $\times$ s $\times$ cm^{-5}) was computed as the ratio of mean BP to cardiac index, times 80 to represent the steady component of arterial impedance. The pulsatile component of arterial impedance was estimated as the ratio of pulse pressure to stroke index (PP/SVi), and used as a raw indicator of arterial stiffness [27].

Statistical analysis

Data were analyzed using SPSS (version 20.0; SPSS Inc, Chicago, Illinois, USA) and expressed as mean $\pm$ 1stan-1standard deviation. Descriptive comparison among the left ventricular geometric patterns was carried out by analysis of variance, using a random-effect model and the Ryan, Einot, Gabriel, and Welsch (REGW)-F test as posthoc for multiple comparison. Analysis of covariance was used to assess the effect of therapy on differences in left ventricular chamber dimension. Categorical variables were compared using chi-square distribution, and MonteCarlo simulation to generate exact *P* values. The initial antihypertensive therapy at the time of the first visit in our outpatient clinic was taken into account. Cox regression analysis, controlling for age, sex, diabetes and BMI, was run to compare left ventricular geometric patterns. Left ventricular mass index was eventually forced into the Cox model. A two-tailed α-value of 0.05 rejected the null hypothesis.

RESULTS

The study population comprised 8848 hypertensive patients from the CSN (3885 or 44% women), aged 53 ± 12 years. Obesity was present in 42% and diabetes in 11%.

Left ventricular geometric abnormalities could be detected in 3030 subjects (34%) distributed as follows: 4.9% had left ventricular concentric remodeling, 20.4% eccentric nondilated LVH, 3.7% eccentric dilated LVH, 5.1% concentric nondilated LVH, 0.15% concentric dilated LVH, whereas 66% had no left ventricular geometric abnormalities.

Phenotypic characteristics

Table 2 shows the general characteristics of all left ventricular geometric patterns. Patients with left ventricular geometric abnormalities were older, exhibited longer duration of hypertension, have higher BP and lower GFR than those with normal left ventricular geometry. Differences were found among the abnormal left ventricular geometric patterns, including higher BMI in patients with any type of LVH, especially when associated with left ventricular dilatation, and progressively higher BP from the normal left ventricular geometry to the concentric dilated pattern. Heart rate was significantly higher in the presence of concentric left ventricular geometry, whereas tended to be lower in eccentric LVH in the presence of normal or dilated left ventricular chamber and in the concentric dilated LVH (all $P < 0.05$).

Figure 1 displays the prevalence of obesity and diabetes in the groups with normal left ventricular geometry and in the groups with left ventricular geometric abnormalities. As evident, all left ventricular geometric abnormalities were associated with greater prevalence of obesity and diabetes, with the highest proportion of obese individuals in both types of dilated LVH, and the overwhelming prevalence of diabetes among patients with concentric dilated LVH (near 30%).

At the time of the first visit in our outpatient clinic, we observed that the number of antihypertensive medications prescribed by general practitioners or community hospitals was progressively higher from normal left ventricular geometry (0.88 ± 0.93) to concentric left ventricular remodeling (1.00 ± 1.02), eccentric nondilated LVH (1.29 ± 1.13), eccentric dilated LVH (1.38 ± 1.20), concentric nondilated LVH (1.41 ± 1.16) and concentric dilated LVH (2.31 ± 1.33, $P < 0.0001$). Table 3 shows the initial distribution of classes of antihypertensive medications; almost all classes of medications tended to be more frequently used with progression of severity of left ventricular geometric abnormality.

Morphologic parameters and hemodynamic profile

Table 4 shows that left ventricular and left atrial dimension were greater in all types of LVH, whereas concentric left ventricular remodeling exhibited reduced left ventricular dimension and normal left atrial size. Differences in left ventricular dimensions also remained when controlling for the initial therapy with β-blockers. Left ventricular mass index was increased in all abnormal left ventricular geometric patterns, but it was progressively higher progressing from concentric remodeling to eccentric nondilated LVH, eccentric dilated or concentric nondilated LVH, achieving the greatest value in the presence of combined concentric dilated LVH (Fig. 2). Ejection fraction was slightly reduced in the presence of indeterminate or dilated LVH, but not when left ventricular geometry was concentric, whereas stroke index and cardiac index were clearly increased in all types of LVH, including also the eccentric nondilated type, but reduced in concentric left ventricular remodeling. Total peripheral resistance and PP/SVi ratio were higher in the presence of concentric left ventricular remodeling or concentric nondilated LVH, lower with eccentric LVH (either nondilated or dilated) and normal in the presence of concentric dilated LVH (all $P < 0.05$).

We evaluated whether the difference in left ventricular mass index among the left ventricular geometric patterns could be attributed to different magnitude of hemodynamic load (stroke work). Figure 3 shows that stroke work was significantly increased in all patterns of LVH, especially when left ventricle was dilated, whereas in concentric left ventricular remodeling, stroke work was significantly lower than in normal left ventricular geometry. In contrast, excess of left ventricular mass was greater in all patterns of abnormal left ventricular geometry, with the highest values in the presence of concentric LVH (both nondilated and dilated).

Clear-cut inappropriate left ventricular mass was observed in 22% of patients with normal left ventricular geometry, in

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TABLE 2. General baseline characteristics of 8848 hypertensive patients, according to type of left ventricular geometric abnormality

		N	M ± σ	Post hoc
Age, (years)	Normal left ventricular geometry	5818	50.42 ± 11.45	
	Concentric remodeling	434	53.82 ± 11.37	a
	Eccentric nondilated LVH	1805	57.21 ± 10.90	a,b
	Eccentric dilated LVH	326	57.84 ± 11.11	a,b
	Concentric nondilated LVH	452	56.86 ± 11.01	a,b
	Concentric dilated LVH	13	62.31 ± 8.94	a,b
BMI, (kg/m^2)	Normal left ventricular geometry		26.97 ± 3.74	
	Concentric remodeling		27.27 ± 3.84	
	Eccentric nondilated LVH		29.73 ± 4.38	a,b
	Eccentric dilated LVH		31.26 ± 5.70	a,b,c,d
	Concentric nondilated LVH		29.35 ± 4.17	a,b
	Concentric dilated LVH		31.21 ± 4.98	a,b
Duration of hypertension (years)	Normal left ventricular geometry		9.07 ± 7.22	
	Concentric remodeling		10.59 ± 8.54	a
	Eccentric nondilated LVH		11.91 ± 8.57	a,b
	Eccentric dilated LVH		12.09 ± 8.51	a,b
	Concentric nondilated LVH		12.99 ± 9.64	a,b
	Concentric dilated LVH		14.49 ± 12.25	a,b
Systolic BP (mmHg)	Normal left ventricular geometry		138.38 ± 18.22	
	Concentric remodeling		142.07 ± 19.93	a
	Eccentric nondilated LVH		146.61 ± 21.99	a,b
	Eccentric dilated LVH		149.22 ± 23.28	a,b
	Concentric nondilated LVH		153.11 ± 25.40	a,b,e
	Concentric dilated LVH		167.92 ± 24.53	a,b,c,d,e
Diastolic BP (mmHg)	Normal left ventricular geometry		78.83 ± 10.76	
	Concentric remodeling		80.75 ± 11.59	a
	Eccentric nondilated LVH		80.91 ± 12.13	a
	Eccentric dilated LVH		80.93 ± 13.09	a,b
	Concentric nondilated LVH		84.26 ± 12.98	a,b,d,e
	Concentric dilated LVH		88.92 ± 14.12	a,b,d,e
Heart rate (bpm)	Normal left ventricular geometry		72.52 ± 11.87	
	Concentric remodeling		74.41 ± 11.44	a
	Eccentric nondilated LVH		70.15 ± 11.05	a
	Eccentric dilated LVH		70.49 ± 12.15	a,b
	Concentric nondilated LVH		72.07 ± 12.06	d,e
	Concentric dilated LVH		67.67 ± 14.10	a,b,c
GFR (ml/min per 1.73 m^2)	Normal left ventricular geometry		80.55 ± 17.94	
	Concentric remodeling		77.15 ± 19.20	a
	Eccentric nondilated LVH		77.11 ± 19.96	a
	Eccentric dilated LVH		76.80 ± 19.99	a
	Concentric nondilated LVH		74.26 ± 18.99	a
	Concentric dilated LVH		73.98 ± 12.51	a

BP, blood pressure; GFR, glomerular filtration rate; LVH, left ventricular hypertrophy.
[a] $P < 0.05$ vs. normal left ventricular geometry.
[b] $P < 0.05$ vs. concentric left ventricular remodeling.
[c] $P < 0.05$ vs. concentric nondilated LVH.
[d] $P < 0.05$ vs. eccentric LVH.
[e] $P < 0.05$ vs. eccentric dilated LVH.

59% of those with concentric left ventricular remodeling, 65% with eccentric LVH (either nondilated or dilated), in 89% with concentric nondilated LVH and in all patients with concentric dilated LVH ($P < 0.0001$).

General outcome analysis

The follow-up period ranged between 6 and 180 months [median: 35 months (interquartile range: 9–70)]. During follow-up, 153 major fatal (19 acute myocardial infarction, 5 stroke, 5 sudden death) or nonfatal cardiovascular events (105 acute myocardial infarction, 19 stroke) occurred. Table 5 shows that, compared with normal left ventricular geometry, hazard ratio of composite fatal and nonfatal cardiovascular events, adjusted for age, sex, diabetes and BMI, progressively increased across the five left ventricular geometric patterns from the lowest in the condition of concentric left ventricular remodeling to the highest in the presence of concentric dilated LVH, through a rank order formed by eccentric nondilated LVH, concentric nondilated LVH and eccentric dilated LVH. However, hazard of composite fatal and nonfatal cardiovascular events was statistically significant only for concentric nondilated, eccentric dilated and concentric dilated LVH (Fig. 3). Concentric nondilated LVH, eccentric dilated LVH and concentric dilated LVH exhibited two-fold to nine-fold greater risk of major cardiovascular events than normal left ventricular geometry, whereas no significant risk was detected for concentric left ventricular remodeling and eccentric nondilated LVH.

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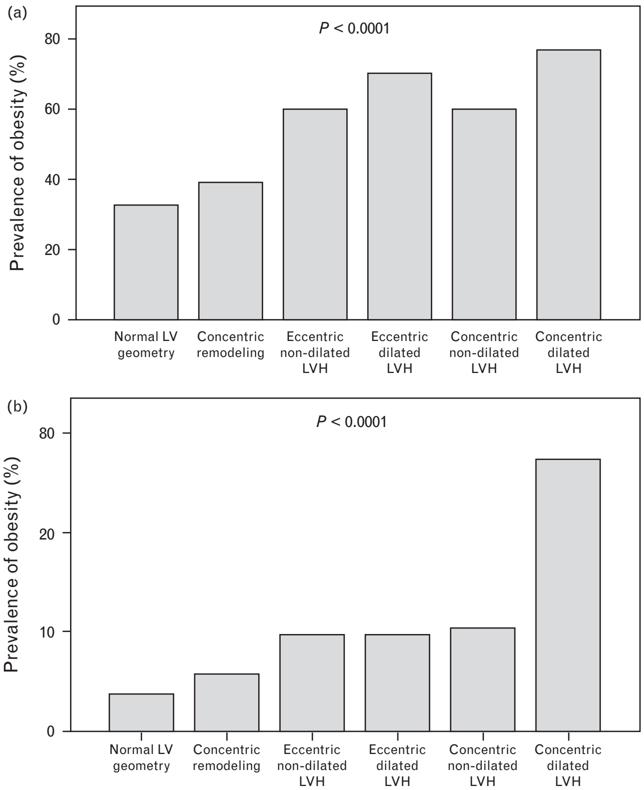

FIGURE 1 Proportion of obesity (panel A) and diabetes (panel B) in hypertensive left ventricular geometric abnormalities and in patients with normal left ventricular geometry. The *P* value for trend is given.

Owing to the documented relation between the magnitude of left ventricular mass index and patterns of left ventricular geometry, shown in Fig. 4, left ventricular mass index was forced into the Cox model shown in Table 4. The hazard ratios of all left ventricular geometric patterns fell down to a nonsignificant level, whereas age, sex, diabetes, BMI and left ventricular mass index held their statistical significance (all $P < 0.001$).

The Cox model presented above was also run using an allometric normalization of left ventricular mass proposed from an adult population (height in $m^{1.7}$) [28] and the above results were substantially confirmed (not shown).

DISCUSSION

Our study analyzes for the first time whether the new four-tiered classification of LVH adds value to our older, simpler scheme for the prediction of cardiovascular events, in a large registry of unselected, treated hypertensive patients participating to the CSN registry [14–16]. We could also demonstrate that there is a clear graduation of cardiovascular risk, based on the new classification of left ventricular geometry, but this graduation was not independent of the magnitude of left ventricular mass index.

In our analysis, compared with normal left ventricular geometry, concentric remodeling and eccentric nondilated LVH are associated with a nonsignificant increase in cardiovascular risk, whereas cardiovascular risk is definitely increased in concentric LVH, both nondilated and dilated, and eccentric dilated LVH. These results are similar to what has been shown in the 939 hypertensive patients with ECG LVH from the Losartan Intervention For Endpoint reduction in hypertension (LIFE) echo-sub-study [13], but also clarify that the risk is gradual according to the magnitude of left ventricular mass, suggesting that the value of left ventricular mass index is the key parameter to evaluate prospective cardiovascular risk in arterial hypertension, a concept already discussed in previous analyses [17].

Despite the substantial dependence of cardiovascular risk from the magnitude of left ventricular mass that parallels the severity of left ventricular geometric abnormality, the morphologic–hemodynamic patterns characterizing the different left ventricular geometric abnormalities provide interesting differences that might, at least on a theoretic ground, help decision-making.

In our analysis, we adapted the DHS scheme [12] for application with echocardiographic parameters, therefore using our traditional linear measurements with cut-points for concentric or dilated left ventricle derived from our historical reference adult population [22]. Combinations of the three parameters, left ventricular mass, left ventricular end-diastolic dimension (both normalized to geometrically consistent measures of body height) and relative wall thickness, resulted in the identification of 34% of abnormalities of left ventricular geometry, distributed across all possible combinations. The new proposed categories of dilated LVH (both eccentric and concentric) were present, though infrequently (about 4%), as has been previously observed in the DHS [12]. A major finding of our analysis is

TABLE 3. Distribution of initial antihypertensive medications according to the patterns of left ventricular geometry. Numbers are %

	Normal left ventricular geometry	Concentric left ventricular remodeling	Eccentric nondilated LVH	Eccentric dilated LVH	Concentric nondilated LVH	Concentric dilated LVH	*P*
Diuretics	28.5	33.3	40.7	43.4	41.2	76.9	<0.0001
β-blockers	15.5	13.7	18.0	19.0	21.2	38.5	<0.001
α-β-blockers	2.1	2.6	3.2	4.7	4.1	0	<0.007
ACE-inhibitors	21.7	27.9	32.5	32.9	30.5	46.2	<0.0001
ARB	17.6	21.0	20.1	18.4	21.4	33.8	<0.04
CCB	14.5	16.8	24.2	24.4	30.3	38.5	<0.0001
α-blockers	3.4	2.6	7.1	10.8	9.1	23.1	<0.0001
Other drugs	6.9	8.3	12.6	16.6	16.4	30.8	<0.0001

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; BP, blood pressure; CCB, Ca^{++}-channel blockers; LVH, left ventricular hypertrophy.

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TABLE 4. Cardiac geometry and function of 6499 hypertensive patients, according to type of harmful left ventricular geometric abnormality

		N	M ± σ	Posthoc
End-diastolic dimension index (cm/m)	Normal left ventricular geometry	5818	2.92 ± 0.15	
	Concentric remodeling	434	2.74 ± 0.12	a
	Eccentric nondilated LVH	1805	3.13 ± 0.11	a,b
	Eccentric dilated LVH	326	3.44 ± 0.12	a,b,c
	Concentric nondilated LVH	452	2.99 ± 0.13	a,b,c,d
	Concentric dilated LVH	13	3.42 ± 0.06	a,b,c,e
Left atrial dimension (cm)	Normal left ventricular geometry		3.70 ± 0.67	
	Concentric remodeling		3.69 ± 0.37	
	Eccentric nondilated LVH		3.93 ± 0.93	a,b
	Eccentric dilated LVH		4.03 ± 0.41	a,b
	Concentric nondilated LVH		3.94 ± 1.33	a,b
	Concentric dilated LVH		4.01 ± 0.31	a,b
left ventricular mass index (g/m$^{2.7}$)	Normal left ventricular geometry		43.1 ± 5.3	
	Concentric remodeling		45.4 ± 4.7	a
	Eccentric nondilated LVH		57.4 ± 4.7	a,b
	Eccentric dilated LVH		66.6 ± 9.5	a,b,c
	Concentric nondilated LVH		61.1 ± 8.2	a,b,c,d
	Concentric dilated LVH		86.3 ± 12.3	a,b,c,d,e
Relative wall thickness	Normal left ventricular geometry		0.37 ± 0.03	
	Concentric remodeling		0.45 ± 0.02	a
	Eccentric nondilated LVH		0.38 ± 0.03	a,b
	Eccentric dilated LVH		0.36 ± 0.03	a,b,c
	Concentric nondilated LVH		0.46 ± 0.03	a,b,c,d
	Concentric dilated LVH		0.46 ± 0.04	a,b,c,d
Ejection fraction (%)	Normal left ventricular geometry		66.7 ± 3.5	
	Concentric remodeling		66.6 ± 4.0	
	Eccentric nondilated LVH		65.2 ± 3.6	a,b
	Eccentric dilated LVH		63.4 ± 5.1	a,b,c
	Concentric nondilated LVH		64.9 ± 3.9	b,c,d
	Concentric dilated LVH		65.2 ± 5.1	b,d,e
Stroke index (ml/beat per m$^{2.04}$)	Normal left ventricular geometry		25.0 ± 2.8	
	Concentric remodeling		22.1 ± 2.2	a,b
	Eccentric nondilated LVH		28.2 ± 2.4	a,b
	Eccentric dilated LVH		33.1 ± 3.0	a,b,c
	Concentric nondilated LVH		25.6 ± 2.8	a,b,c,d
	Concentric dilated LVH		33.7 ± 2.6	a,b,c,e
Cardiac index (l/min per m$^{1.83}$)	Normal left ventricular geometry		2.02 ± 0.38	
	Concentric remodeling		1.83 ± 0.33	a
	Eccentric nondilated LVH		2.19 ± 0.39	a,b
	Eccentric dilated LVH		2.58 ± 0.49	a,b,c
	Concentric nondilated LVH		2.04 ± 0.39	b,c,d
	Concentric dilated LVH		2.51 ± 0.51	a,b,c,e
Total peripheral resistance index (dynes × s × cm^{-5} × m$^{1.83}$)	Normal left ventricular geometry		4024 ± 812	
	Concentric remodeling		4542 ± 938	a
	Eccentric nondilated LVH		3856 ± 804	a,b
	Eccentric dilated LVH		3330 ± 751	a,b,c
	Concentric nondilated LVH		4329 ± 985	a,b,c,d
	Concentric dilated LVH		3896 ± 1398	b,d,e
Pulse pressure/stroke index (mmHg × m$^{2.04}$/ml)	Normal left ventricular geometry		2.41 ± 0.64	
	Concentric remodeling		2.79 ± 0.71	a
	Eccentric nondilated LVH		2.35 ± 0.66	a,b
	Eccentric dilated LVH		2.08 ± 0.57	a,b,c
	Concentric nondilated LVH		2.72 ± 0.83	a,c,d
	Concentric dilated LVH		2.38 ± 0.60	b,d,e

LVH, left ventricular hypertrophy.
[a]$P < 0.05$ vs. normal left ventricular geometry.
[b]$P < 0.05$ vs. concentric left ventricular remodeling.
[c]$P < 0.05$ vs. eccentric nondilated LVH.
[d]$P < 0.05$ vs. eccentric dilated LVH.
[e]$P < 0.05$ vs. concentric nondilated LVH.

the evidence that left ventricular chamber dimension might be a key marker to explain LVH-associated cardiovascular risk. We believe that this consideration significantly augments the understanding of LVH-related cardiovascular risk, and has significant pathophysiological implications.

Concentric LVH and LVH with enlarged left ventricular chamber dimension, independently of the thickness of myocardial wall, emerge as the left ventricular geometric patterns carrying the highest cardiovascular risk, and are also associated with other markers of more severe

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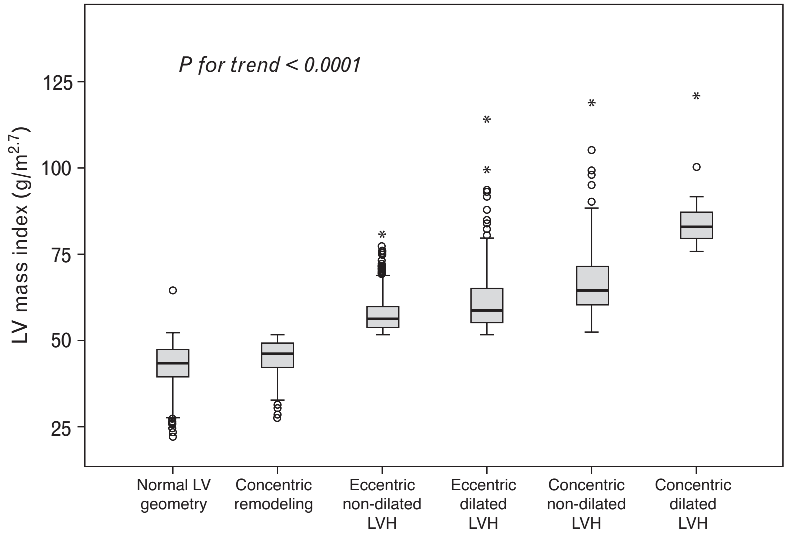

FIGURE 2 Box-plot of left ventricular mass index in the different left ventricular geometric patterns. The dark inner lines are medians; the boxes represent interquartile ranges; the T bars are the inner fences, corresponding to 95% of the subpopulations; the circles and the stars are outliers and extreme outliers.

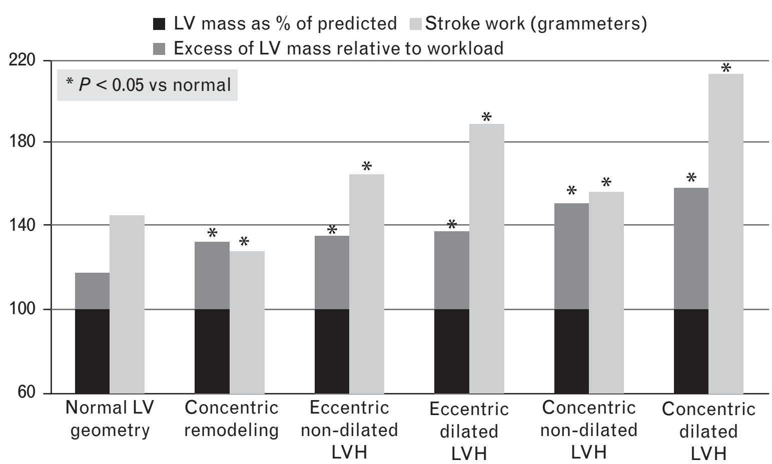

FIGURE 3 Stroke work (light grey bars), left ventricular mass as percentage of predicted from stroke work, sex and body size (black/dark grey bars) and excess of left ventricular mass (dark grey portion of bars) in hypertensive left ventricular geometric abnormalities and in patients with normal left ventricular geometry. The scale of the ordinate line represents percentage of predicted left ventricular mass or grammeters.

TABLE 5. Cox proportional hazard analysis of composite fatal and nonfatal cardiovascular events for five abnormal left ventricular geometric patterns found in treated arterial hypertension

			95% CI for hazard ratio	
	P	Hazard ratio	Lower	Upper
Concentric left ventricular remodeling (normal LVM; normal LVIDd; high RWT)	≤0.35	1.20	0.80	−1.60
Eccentric nondilated LVH (increased LVM; normal LVIDd; normal RWT)	≤0.23	1.23	0.87	−1.74
Eccentric dilated LVH (increased LVM; increased LVIDd; normal RWT)	≤0.006	1.95	1.22	−3.12
Concentric nondilated LVH (increased LVM; normal LVIDd; increased RWT)	≤0.008	2.16	1.23	−3.80
Concentric dilated LVH (increased LVM; increased LVIDd; increased RWT)	≤0.003	8.91	2.17	−36.59
Age (years)	≤0.0001	1.06	1.04	−1.07
Female sex	≤0.02	1.42	1.07	−1.88
Diabetes (n/y)	≤0.02	1.50	1.08	−2.09
BMI (kg/m^2)	≤0.09	0.97	0.93	−1.01

LVH, left ventricular hypertrophy; LVIDd, left ventricular end-diastolic dimension; LVM, left ventricular mass; RWT, relative wall thickness.

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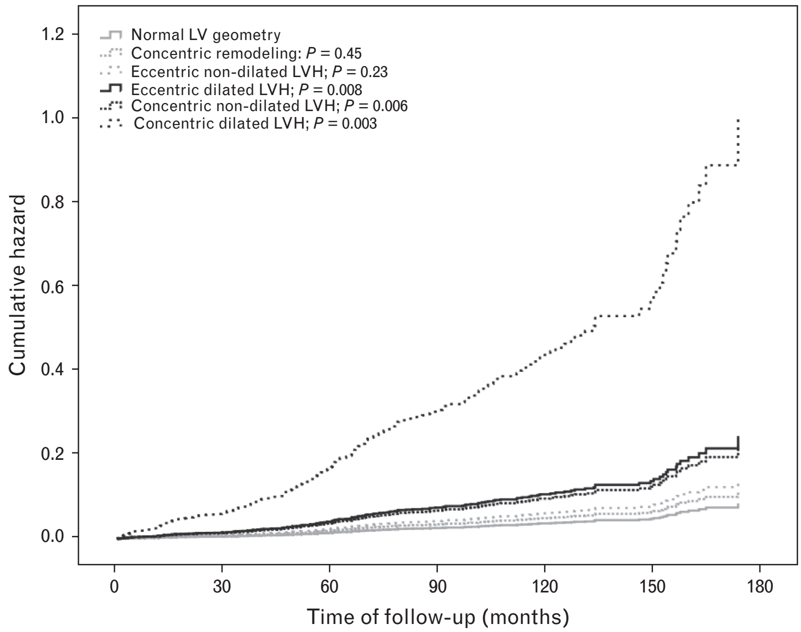

FIGURE 4 Cumulative hazard of hypertensive left ventricular geometric abnormalities adjusted for age, sex, diabetes and BMI.

cardiovascular impairment (lower GFR), as already reported in the LIFE study [29]. Left ventricular chamber dimension seems to be the hallmark of all three harmful left ventricular geometric abnormalities.

Concentric nondilated LVH was associated with normal left ventricular chamber size, and left ventricular systolic function and performance comparable with that found in patients with normal left ventricular geometry, but substantially higher level of peripheral resistance and arterial stiffness, indicating a predominant pressure overload. In contrast, patterns of dilated LVH were characterized by dilated left atrium, greater left ventricular mass, enhanced left ventricular pump performance and normal-to-reduced peripheral resistance and arterial stiffness, suggesting a more prominent volume load component. The only remarkable difference between the two dilated left ventricular geometric patterns was that eccentric dilated LVH was associated with lower peripheral resistance and more predominant signs of volume overload than the concentric dilated type of LVH.

The question emerging from these findings is whether the dilated left ventricular chamber is expression of the attempt to preserve left ventricular performance, therefore implying some degree of underlying myocardial dysfunction. The answer to this question is definitively negative. Ejection fraction and stroke index strongly indicate that both left ventricular systolic function and performance were preserved in these hearts; rather, at a given left ventricular systolic function, there was evidence of supranormal left ventricular performance, suggesting enhanced volume load.

Assuming that the pattern of left ventricular geometry represents the cardiac adaptation to type of hemodynamic overload, a most consolidated postulate [30,31], a second question is whether the usual prescription of antihypertensive therapy is fitting with the reported differences. Table 3 shows that there is no clearly visible difference among classes of prescribed antihypertensive medications. This would be expected because antihypertensive therapy is not driven by echocardiographic findings. What is clear in Table 3 is that therapy becomes more aggressive as left ventricular geometry worsens, following the difficulty in effectively controlling BP [19], as also shown in Table 2. Based on our findings, however, we might speculate that antihypertensive therapy better targeted on the emerging left ventricular geometric/hemodynamic pattern might be attempted. For instance, a dilated LVH might require even more diuretics than found in clinical practice, whereas a concentric LVH might better benefit from vasodilators than diuretics, given the increase in arterial impedance.

The reasons of the adverse effect on outcome of the three described left ventricular geometric patterns are clearly related to the severity of increase in left ventricular mass. The association of eccentric dilated, concentric nondilated and concentric dilated LVH with progressively greater excess of left ventricular mass (as shown in Fig. 4) strongly suggests that this sequence of left ventricular geometric abnormalities parallels more severe derangement of left ventricular structure, possibly with more severe fibrosis [32].

Limitations

This is an observational study derived from a registry, subjected to potential bias. However, the risk of bias is limited in the CSN because of the limited selection of patients referred to our Hypertension Center. Registry

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studies also offer the advantage of representing real world and common clinical behavior, as recently highlighted [33].

The DHS used MRI for assessment of left ventricular mass, whereas we could use 2D echocardiograms, a method that is less accurate in assessment of left ventricular geometry. However, in the DHS, the definition of left ventricular geometry (concentricity) was done using geometric assumptions, whereas we limited geometric assumptions by using direct measures of wall thickness and left ventricular internal dimension. The consistency of our findings with the Khouri's suggests that the pathophysiological consequences of the different left ventricular geometric patterns could be identified in our analysis.

Another limitation relies on the small cell size of the concentric dilated type of LVH. However, despite the small size, in addition to the result obtained in the Cox regression, the coefficients of variability of the examined variables in Tables 2 and 4 were not greater (or even smaller) than the other groups, suggesting homogeneity in the characteristics of this group; secondly, even more relevant, there was a clear consistency in the risk profile, with more severe impairment of kidney function, aortic root and left atrial dilatations, more aggressive antihypertensive therapy and greatest difficulty in achieving a good BP control. Accordingly, we believe that these patients, albeit rare, merit the highest possible attention.

Novelty and significance

1. What Is New? This is the first direct evidence that differences in left ventricular geometry might be relevant to define risk profile in large community-based registry of uncomplicated hypertensive patients. Consideration of left ventricular dilatation in the evaluation of risk related to left ventricular geometry reveals that LVH-related cardiovascular risk is also due to the extent of a volume load coexisting with the typical hypertensive pressure overload. At a given normal ejection fraction, the balance between the two hemodynamic components might determine the shape of left ventricular geometric adaptation and the magnitude of associated risk.
2. What Is Relevant? Our study suggests that there are geometric types and degrees of LVH that might be compensatory of the hemodynamic overload and, therefore, not at high risk, while demonstrating that the severity of increase in left ventricular mass parallels the severity of left ventricular geometric abnormality. Our results open to the speculation that a greater attention to the hemodynamic load associated with a given left ventricular geometric pattern might be conveniently paid to guide antihypertensive therapy, a hypothesis that needs to be tested in appropriate studies.

ACKNOWLEDGEMENTS

Conflicts of interest

No conflict of interest to disclose.

REFERENCES

1. Ganau A, Devereux RB, Roman MJ, de Simone G, Pickering TG, Saba PS, *et al*. Patterns of left ventricular hypertrophy and geometric remodeling in essential hypertension. *J Am Coll Cardiol* 1992; 19:1550–1558.
2. Muiesan ML, Salvetti M, Monteduro C, Bonzi B, Paini A, Viola S, *et al*. Left ventricular concentric geometry during treatment adversely affects cardiovascular prognosis in hypertensive patients. *Hypertension* 2004; 43:731–738.
3. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. *Ann Intern Med* 1991; 114:345–352.
4. Krumholz HM, Larson M, Levy D. Prognosis of left ventricular geometric patterns in the Framingham Heart Study [see comments]. *J Am Coll Cardiol* 1995; 25:879–884.
5. Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Gattobigio R, Zampi I, *et al*. Prognostic value of left ventricular mass and geometry in systemic hypertension with left ventricular hypertrophy. *Am J Cardiol* 1996; 78:197–202.
6. Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Battistelli M, Bartoccini C, *et al*. Adverse prognostic significance of concentric remodeling of the left ventricle in hypertensive patients with normal left ventricular mass. *J Am Coll Cardiol* 1995; 25:871–878.
7. Pierdomenico SD, Di NM, Pierdomenico AM, Lapenna D, Cuccurullo F. Cardiovascular risk in subjects with left ventricular concentric remodeling at baseline examination: a meta-analysis. *J Hum Hypertens* 2011; 25:585–591.
8. Gerdts E, Cramariuc D, de Simone G, Wachtell K, Dahlof B, Devereux RB. Impact of left ventricular geometry on prognosis in hypertensive patients with left ventricular hypertrophy (the LIFE study). *Eur J Echocardiogr* 2008; 9:809–815.
9. de Simone G. Concentric or eccentric hypertrophy: how clinically relevant is the difference? *Hypertension* 2004; 43:714–715.
10. de Simone G, De Marco M. Cardiovascular risk in subjects with left ventricular concentric remodeling: Does meta-analysis help reconcile inconsistent findings? *J Hum Hypertens* 2011; 25:575–577.
11. Victor RG, Haley RW, Willett DL, Peshock RM, Vaeth PC, Leonard D, *et al*. The Dallas Heart Study: a population-based probability sample for the multidisciplinary study of ethnic differences in cardiovascular health. *Am J Cardiol* 2004; 93:1473–1480.
12. Khouri MG, Peshock RM, Ayers CR, de Lemos JA, Drazner MH. A 4-tiered classification of left ventricular hypertrophy based on left ventricular geometry: the Dallas heart study. *Circ Cardiovasc Imaging* 2010; 3:164–171.
13. Bang CN, Gerdts E, Aurigemma GP, Boman K, de Simone G, Dahlof B, *et al*. Four group classification of left ventricular hypertrophy based on ventricular concentricity and dilatation identifies a low-risk subset of eccentric hypertrophy in hypertensive patients. *Circ Cardiovasc Imaging* 2014; 7:422–429.
14. Izzo R, de Simone G, Chinali M, Iaccarino G, Trimarco V, Rozza F, *et al*. Insufficient control of blood pressure and incident diabetes. *Diabetes Care* 2009; 32:845–850.
15. Izzo R, de Simone G, Trimarco V, Gerdts E, Giudice R, Vaccaro O, *et al*. Hypertensive target organ damage predicts incident diabetes mellitus. *Eur Heart J* 2013; 34:3419–3426.
16. De Luca N, Izzo R, Iaccarino G, Malini PL, Morisco C, Rozza F, *et al*. The use of a telematic connection for the follow-up of hypertensive patients improves the cardiovascular prognosis. *J Hypertens* 2005; 23:1417–1423.
17. de Simone G, Izzo R, Chinali M, De MM, Casalnuovo G, Rozza F, *et al*. Does information on systolic and diastolic function improve prediction of a cardiovascular event by left ventricular hypertrophy in arterial hypertension? *Hypertension* 2010; 56:99–104.
18. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2007; 30 (Suppl 1):S42–S47.
19. Izzo R, de Simone G, Devereux RB, Giudice R, De MM, Cimmino CS, *et al*. Initial left-ventricular mass predicts probability of uncontrolled blood pressure in arterial hypertension. *J Hypertens* 2011; 29:803–808.
20. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, *et al*. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed

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in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005; 18:1440–1463.
21. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, Reichek N. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol* 1986; 57:450–458.
22. de Simone G, Daniels SR, Devereux RB, Meyer RA, Roman MJ, de Divitiis O, Alderman MH. Left ventricular mass and body size in normotensive children and adults: assessment of allometric relations and impact of overweight. *J Am Coll Cardiol* 1992; 20:1251–1260.
23. de Simone G, Devereux RB, Daniels SR, Koren MJ, Meyer RA, Laragh JH. Effect of growth on variability of left ventricular mass: assessment of allometric signals in adults and children and their capacity to predict cardiovascular risk. *J Am Coll Cardiol* 1995; 25:1056–1062.
24. de Simone G, Verdecchia P, Pede S, Gorini M, Maggioni AP. Prognosis of inappropriate left ventricular mass in hypertension: the MAVI Study. *Hypertension* 2002; 40:470–476.
25. de Simone G, Devereux RB, Ganau A, Hahn RT, Saba PS, Mureddu GF, *et al.* Estimation of left ventricular chamber and stroke volume by limited M-mode echocardiography and validation by two-dimensional and Doppler echocardiography. *Am J Cardiol* 1996; 78:801–807.
26. de Simone G, Devereux RB, Daniels SR, Mureddu G, Roman MJ, Kimball TR, *et al.* Stroke volume and cardiac output in normotensive children and adults. Assessment of relations with body size and impact of overweight. *Circulation* 1997; 95:1837–1843.
27. de Simone G, Schillaci G, Chinali M, Angeli F, Reboldi GP, Verdecchia P. Estimate of white-coat effect and arterial stiffness. *J Hypertens* 2007; 25:827–831.
28. Chirinos JA, Segers P, de Buyzere ML, Kronmal RA, Raja MW, De BD, *et al.* Left ventricular mass: allometric scaling, normative values, effect of obesity, and prognostic performance. *Hypertension* 2010; 56:91–98.
29. Bang CN, Gerdts E, Aurigemma GP, Boman K, Dahlof B, Roman MJ, *et al.* Systolic left ventricular function according to left ventricular concentricity and dilatation in hypertensive patients: the Losartan Intervention For Endpoint reduction in hypertension study. *J Hypertens* 2013; 31:2060–2068.
30. Grossman W, Jones D, McLaurin LP. Wall stress and patterns of hypertrophy in the human left ventricle. *J Clin Invest* 1975; 56:56–64.
31. Carabello BA, Zile MR, Tanaka R, Cooper G. Left ventricular hypertrophy due to volume overload versus pressure overload. *Am J Physiol* 1992; 263:H1137–H1144.
32. de Simone G, Kitzman DW, Palmieri V, Liu JE, Oberman A, Hopkins PN, *et al.* Association of inappropriate left ventricular mass with systolic and diastolic dysfunction The HyperGEN study. *Am J Hypertens* 2004; 17:828–833.
33. de Simone G, Izzo R, Verdecchia P. Are observational studies more informative than randomized controlled trials in hypertension? Pro side of the argument. *Hypertension* 2013; 62:463–469.

Reviewers' Summary Evaluations

Reviewer 1

This study evaluates cardiovascular outcome according to left ventricular geometry, based on the combination of left ventricular mass, degree of dilatation, and concentricity, The authors conclude that the extent of volume load relates to future cardiovascular risk in addition to the coexisting pressure overload typically seen in hypertension. This significantly extends previous knowledge on the prognostic importance of hypertensive heart disease. Study limitations include that the results are based on observational data from a registry and relatively few events.

Reviewer 2

Despite numerous investigations the prognostic value of abnormal left ventricular geometric patterns remains controversial. In this study de Simone *et al.* demonstrated that hypertensive patients with concentric left ventricular hypertrophy and left ventricular hypertrophy with enlarged LV chamber dimension, according the Dallas Heart Study classification, have the highest cardiovascular risk. Notably, patients with normal left ventricular geometry, concentric remodeling and mild increase in left ventricular mass without either increased left ventricular diameter or concentricity have a similar risk of incident cardiovascular disease. In a practical perspective the use of this new classification may contribute to refine cardiovascular risk stratification and therapeutic strategies in the hypertensive setting.

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