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Continuous Relation Between Left Ventricular Mass and Cardiovascular Risk in Essential Hypertension

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Abstract—The detection of left ventricular (LV) hypertrophy on echocardiography is a powerful risk indicator in essential hypertension. However, the prognostic impact of LV mass values within the “normal” range and the shape of the relation between LV mass and prognosis remain unclear. Thus, 1925 white subjects with uncomplicated essential hypertension underwent off-therapy 24-hour blood pressure monitoring and M-mode echocardiography. During 4.0 ± 2 years of follow-up, there were 181 major cardiovascular events (2.4/100 patient-years) and 49 deaths from all causes. In the 5 gender-specific quintiles of LV mass distribution (partition values: 92, 105, 120, and 138 g/m² in men and 79, 91, 102, and 116 g/m² in women), cardiovascular event rates were 0.8, 1.7, 2.2, 2.9, and 4.3 per 100 patient-years. After adjustment for several risk factors, including 24-hour ambulatory blood pressure, the relative risk (RR) of developing a cardiovascular event increased progressively from the first quintile (RR 1) to the second (RR 1.6, 95% CI 0.8 to 3.1), third (RR 1.9, 95% CI 1.01 to 4.0), fourth (RR 3.0, 95% CI 1.5 to 5.8), and fifth (RR 3.5, 95% CI 1.8 to 6.8) quintile. For all-cause death, the RR in the fifth quintile compared with the first quintile was 4.3 (95% CI 1.2 to 13.4). In conclusion, the powerful relation between LV mass and risk of cardiovascular disease in subjects with uncomplicated essential hypertension is continuous over a wide range of LV mass values, even below the current “upper normal” limits. The relation remains significant after control for traditional risk factors, including ambulatory blood pressure. (*Hypertension*. 2000;35:580-586.)

Key Words: echocardiography ■ hypertension, arterial ■ hypertension, essential ■ hypertrophy ■ morbidity ■ mortality

Left ventricular (LV) hypertrophy detected on echocardiography is a powerful and independent predictor of cardiovascular complications and death in subjects with uncomplicated essential hypertension.¹⁻³ Furthermore, regression of LV hypertrophy appears to be a favorable prognostic marker independent of the treatment-induced reduction in blood pressure (BP).^{4,5}

LV mass shows a continuous distribution in the general population,⁶ whereas LV hypertrophy is an operational category that defines the upper end of LV mass distribution.¹⁻³ LV hypertrophy on echocardiography is generally found in 20% to 30% of relatively unselected subjects with mild-to-moderate hypertension,^{7,8} and its prevalence varies according to the selected cutoff value.⁹ The Framingham Heart Study showed an apparently continuous relation between LV mass and cardiovascular event rate in the general population.¹⁰ However, the important clinical issues regarding the shape of the relation between LV mass and cardiovascular risk in essential hypertension and the prognostic impact of LV mass values below the commonly agreed-on upper normal limits

have not been addressed. The present study was specifically designed to establish the link between LV mass and cardiovascular risk in subjects with essential hypertension over a wide range of LV mass distribution. The study was a collaborative project between 2 observational registries of subjects with essential hypertension.

Methods

Study Populations

The Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) study is a prospective registry of complications and death in white adult subjects with essential hypertension. The study design and procedures have been reported previously.^{3,5} Hypertensive subjects were referred to 1 of 3 participating centers (Perugia, Città della Pieve, and Castiglione del Lago) for baseline evaluation by a group of general practitioners practicing in Umbria, in central Italy. A total of 1686 subjects enrolled between 1988 and 1996, for whom good-quality echocardiographic recordings and complete follow-up data are available, were included in the present analysis.

A parallel cohort study was performed in a group of white adult hypertensive subjects at the University Hospital of Catanzaro, Catanzaro, Italy. A total of 239 subjects with good-quality echocar-

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TABLE 1. Selected Clinical Characteristics and Outcome Data by Center

Parameter	PIUMA Cohort (n=1686)	Catanzaro Cohort (n=239)
Age, y	50.3 (11)	48.7* (9)
Men, %	52	48
Body mass index, kg/m ²	26.7 (4)	27.7* (4)
Diabetes, %	6	9
Clinic BP, mm Hg	157/97 (18/10)	161*/99* (13/6)
24-h BP, mm Hg	138/87 (15/10)	145*/90* (9/5)
LV mass, g/m ²	108 (30)	109 (24)
Relative wall thickness	0.41 (0.09)	0.39* (0.07)
Follow-up, y	3.8 (2)	5.5 (2)
Cardiovascular events, n	150	31
Cardiovascular events, 100 patient-years ⁻¹	2.44	2.36

**P*<0.05.

diographic recordings and complete follow-up data, who were enrolled between 1990 and 1997, are included in the present analysis. Selected clinical characteristics of the 2 populations are reported in Table 1.

Inclusion Criteria

All study subjects fulfilled the following criteria: (1) clinic systolic BP of ≥ 140 mm Hg, diastolic BP of ≥ 90 mm Hg, or both on ≥ 3 visits at 1-week intervals; (2) no previous treatment for hypertension (70%) or withdrawal from antihypertensive drugs ≥ 4 weeks before the study; (3) no clinical or laboratory evidence of heart failure, coronary heart disease, previous stroke, valvular defects or secondary causes of hypertension, or important concomitant disease; (4) good-quality echocardiographic recordings (see later); and (5) ≥ 1 valid BP measurement per hour over the 24 hours. All subjects gave informed consent to participate in the study.

BP Measurement

Clinic BP was measured by a physician in the hospital clinic with a mercury sphygmomanometer, after the subject sat for ≥ 10 minutes. The average of ≥ 3 measurements on ≥ 2 sessions was considered for the analysis. Ambulatory BP was recorded with an oscillometric device (models 90202 and 90207; SpaceLabs) that was set to take a reading every 15 minutes throughout the 24 hours. Normal daily activities were allowed and encouraged, and patients were told to keep their nondominant arm still and relaxed to the side during measurements. Reading, editing, and analysis of data were performed as previously described.¹¹

Echocardiography

The M-mode echocardiographic study of the left ventricle was performed under 2-dimensional control. Measurements were taken according to the American Society of Echocardiography recommendations.¹² Only frames with optimal visualization of interfaces that simultaneously show the septum, LV internal diameter, and posterior wall were used for readings. Tracings were read by 2 observers in the PIUMA cohort and by 2 observers in the Catanzaro cohort, and the mean value from ≥ 5 measurements per observer was computed. All readers were unaware of patients' clinical data. The intraobserver and inter-observer variabilities in the PIUMA study laboratory have been reported elsewhere.⁶ Intraobserver coefficients of variation in the Catanzaro study laboratory were 4.6% for interventricular septum, 4.6% for posterior wall, 1.5% for internal diameter, and 6.3% for LV mass. LV mass was calculated according to Devereux et al¹³

and normalized by both body surface area and height^{2,7,14} to correct for the effect of overweight.

Follow-Up Procedures and End Point Evaluation

All subjects were followed by their family physicians in cooperation with the outpatient clinic of the referring hospital and treated with the aim of reducing clinic BP to $<140/90$ mm Hg through the use of standard lifestyle and pharmacological measures. Most patients continue to be periodically referred to our institutions for BP control and other diagnostic procedures. Diuretics, β -blockers, ACE inhibitors, Ca²⁺ channel blockers, and α_1 -blockers, alone or in various combinations, are the antihypertensive drugs that are most frequently prescribed. Contacts with family physicians and telephone interviews were periodically undertaken to determine the incidence of major cardiovascular complications of hypertension. For the subjects who developed a cardiovascular morbid event, hospital record forms and other available original source documents were reviewed in conference by the authors. Cardiovascular events included new-onset coronary artery disease (myocardial infarction, unstable angina with documentation of ischemic electrocardiographic changes, sudden cardiac death, or coronary revascularization procedure), stroke, transient cerebral ischemic attack, symptomatic aortoiliac occlusive disease verified with angiography, thrombotic occlusion of a retinal artery documented with fluoroangiography, progressive heart failure that required hospitalization, and renal failure that required dialysis. Transient ischemic attack was defined by the diagnosis by a physician of any sudden focal neurological deficit that cleared completely in <24 hours. Heart failure was defined by the presence of ≥ 2 major criteria or 1 major plus 2 minor criteria as reported in the Framingham Heart Study.¹⁵ The international standard criteria used to diagnose cardiovascular events in the PIUMA study have been described elsewhere.^{3,5,16}

Statistical Analysis

Because the 2 cohorts differed in some clinical characteristics (Table 1), analyses have been adjusted for the "center effect" as reported by de Simone et al.¹⁷ Briefly, BP and primary echocardiographic measurements (LV internal dimension and wall thickness) were related as dependent variables to a dummy variable indicating the center (0 or 1). The variables considered in this analysis were therefore adjusted with the linear coefficient of regression (*b*). Thus, the adjusted variable (adjV) was

$$\text{adjV} = V - b(\kappa - \mu)$$

where V is the observed value of the dependent variable, κ is the dummy variable representing the center, and μ is the average value of the variable representing the center.

Parametric data are reported as mean $\pm$ SD. Standard descriptive and comparative analyses were undertaken. The rates of events are presented as the number of events per 100 patient-years based on the ratio of the number of events observed to the total number of patient-years of exposure up to the terminating event or censor. For the patients without events, the date of censor was that of the last contact with the patient. For the subjects who experienced multiple events, survival analysis was restricted to the first event. For subjects who subsequently died, classification of the terminating event could differ from that of the previous nonfatal event. Survival curves were estimated with the use of the Kaplan-Meier product-limit method¹⁸ and compared with the use of the Mantel (logistic-rank) test.¹⁹ The effect of prognostic factors on survival was evaluated with use of the stepwise Cox semiparametric regression model.²⁰ The assumption of linearity for the Cox model was tested through visual inspection, and no violation of proportional hazards was found. We tested the variables of age (years), gender (women, men), serum cholesterol (in mmol/L), smoking habits (previous or never smokers, current smokers), body mass index (body weight [in kg] divided by the square of the height [in m]), clinic and 24-hour systolic and diastolic BP (in mm Hg), diabetes (no, yes), and antihypertensive drug treatment at the time of follow-up contact (no, yes). LV mass was considered both as a continuous variable and according to gender-

TABLE 2. Baseline Characteristics of Subjects by Quintile of LV Mass Index

Data	All (n=1925)	1st Quintile (n=385)	2nd Quintile (n=385)	3rd Quintile (n=385)	4th Quintile (n=385)	5th Quintile (n=385)	P (F test)
Age, y	50.1 (11)	46.4 (11)	48.6* (11)	50.7* (12)	51.8* (11)	53.2* (11)	<0.0001
Men, %	51	51	51	51	51	51	1.00
Body mass index, kg/m ²	26.8 (4)	26.2 (4)	26.4 (4)	26.8 (4)	27.2* (4)	27.5* (4)	<0.0001
Body surface area, m ²	1.83 (0.2)	1.83 (0.2)	1.82 (0.2)	1.83 (0.2)	1.83 (0.2)	1.84 (0.2)	0.65
Current smokers, %	24	24	21	25	24	25	0.73
Diabetes, %	6	5	7	5	6	10	0.09
Total cholesterol, mmol/L	5.51 (1.0)	5.54 (1.0)	5.45 (1.1)	5.55 (1.0)	5.59 (1.1)	5.42 (1.0)	0.14
Clinic systolic BP, mm Hg	157 (18)	149 (15)	153* (16)	155* (16)	162* (19)	167* (20)	<0.0001
Clinic diastolic BP, mm Hg	98 (10)	95 (8)	97 (8)	96 (9)	99* (11)	100* (10)	<0.0001
24-h systolic BP, mm Hg	139 (15)	132 (13)	135* (13)	137* (13)	142* (14)	149* (15)	<0.0001
24-h diastolic BP, mm Hg	87 (10)	85 (8)	85 (9)	86 (9)	89* (11)	92* (10)	<0.0001
Interventricular septum, mm	11.3 (2)	9.1 (2)	10.4* (2)	11.1* (2)	12.0* (2)	13.7* (2)	<0.0001
Posterior wall, mm	10.0 (2)	8.3 (1)	9.2* (1)	9.9* (1)	10.6* (1)	11.8* (2)	<0.0001
LV internal dimension, mm	49.6 (5)	47.3 (5)	48.4* (4)	49.5* (5)	50.3* (5)	52.6* (6)	<0.0001
LV mass/BSA, g/m ²	108 (29)	75 (10)	92* (8)	104* (9)	119* (11)	150* (27)	<0.0001
LV mass/height ^{2.7} , g/m ^{2.7}	49.8 (14)	34.0 (5)	42.0* (4)	48.0* (5)	55.2* (6)	70.3* (13)	<0.0001
Relative wall thickness	0.41 (0.09)	0.36 (0.08)	0.39* (0.07)	0.41* (0.08)	0.43* (0.08)	0.46* (0.10)	<0.0001

BSA indicates body surface area. Values are mean (SD).

* $P < 0.05$ vs 1st quintile (Tukey's honestly significant differences). Partition values for LV mass quintiles were 92.3, 105.4, 119.8, and 138.2 g/m² in men and 79.5, 91.2, 101.8, and 116.4 g/m² in women.

specific quintiles of LV mass adjusted for body surface area. The partition values between quintiles were 92.3, 105.4, 119.8, and 138.2 g/m² in men and 79.5, 91.2, 101.8, and 116.4 g/m² in women. We also tested the prognostic value of LV hypertrophy defined as a binary variable, after correction for body surface area (LV mass ≥ 125 g/m² in both genders¹⁻³ or LV mass ≥ 125 g/m² in men and ≥ 110 g/m² in women²¹) and for body height (LV mass ≥ 51.0 g/m^{2.7} in both genders¹⁴).

The extent to which the observed data were fitted by a particular model was tested with the use of the -2 log likelihood ($-2 \log L$) statistics.²² This procedure compares alternative models fitted to the same set of survival data, based on the consideration that the likelihood function summarizes the information that the data contain about unknown parameters in a given model. The likelihood function is expressed by a number between 0 and 1, and the inverse of its logarithm is commonly used for longitudinal statistics. Differences between the odds ratios were assessed with the χ^2 distribution of the difference between two $-2 \log L$ s. A significant difference between the $-2 \log L$ statistics provided through the use of different methods indicates a better prediction of risk estimate yielded by the method leading to the lowest $-2 \log L$ value. SPSS statistical package, release 7.5 (SPSS Inc), was used to perform the analyses. $P < 0.05$ was considered statistically significant.

Results

Clinical Characteristics

Table 2 reports the main clinical characteristics of the study population by quintiles of LV mass index. Compared with the first quintile, subjects with higher values of LV mass index were older and had a greater body mass index. In addition, BP values, both clinic and ambulatory, were higher than those for patients in the first quintile of LV mass. Serum cholesterol levels and prevalence of smokers and diabetic subjects did not differ between the groups. The prevalence of LV hypertrophy, defined as an LV mass of ≥ 125 g/m² in both genders, was 24.1% (n=463). The

prevalence increased to 30.5% (n=587) when LV hypertrophy was defined as an LV mass of ≥ 125 g/m² in men and ≥ 110 g/m² in women and to 40.3% (n=775) when LV mass was adjusted for body height (LV mass ≥ 51.0 g/m^{2.7} in both genders). By selection, subjects in the upper quintiles of the distribution of LV mass had a greater wall thickness, LV internal diameter, and LV mass than the subjects in the first quintile. In addition, relative wall thickness progressively increased with increasing LV mass.

Outcome Events

During a mean follow-up period of 4.0 ± 2 years (range 1.0 to 8.3 years), there were 181 new cardiovascular morbid events (2.42 events/100 patient-years) at the cardiac (n=96), cerebrovascular (n=64), or peripheral vascular (n=21) level. Specifically, there were 31 subjects with myocardial infarction, 4 with sudden cardiac death, 1 with cardiac death from other causes, 34 with unstable angina, 12 with coronary revascularization procedures, 14 with heart failure that required hospitalization, 46 with stroke, 18 with transient cerebral ischemia, 14 with new-onset aortoiliac occlusive disease, 3 with occlusion of the retinal artery verified with fluoroangiography, and 4 with renal failure that required dialysis.

During follow-up, we also registered 49 deaths from all causes (0.63 event/100 patient-years), of which 26 were from cardiovascular causes (6 fatal myocardial infarctions, 6 sudden cardiac deaths, 4 other cardiovascular deaths, and 10 fatal strokes), 14 were from neoplastic causes, and 9 were from other causes.

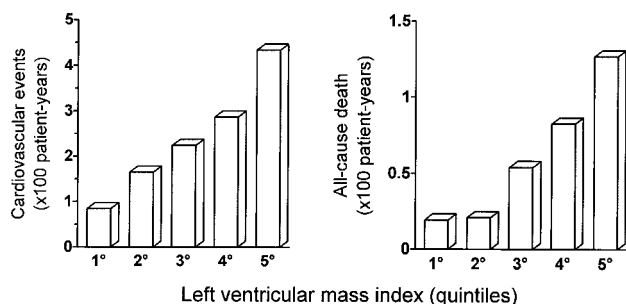


Figure 1. Progressive increase in cardiovascular morbidity (left) and all-cause mortality (right) rates from first to fifth quintile of distribution of LV mass index. See Table 2 for details.

Cardiovascular Morbidity Rates

As shown in Figure 1 (left), the rate of total (fatal plus nonfatal) cardiovascular events (per 100 patient-years) was 0.85, 1.66, 2.24, 2.86, and 4.34 in the first, second, third, fourth, and fifth quintile of LV mass, respectively, and this difference was highly significant (log-rank test, $P < 0.0001$). Event-free survival curves in the 5 quintiles of LV mass are shown in Figure 2. The cumulative cardiovascular event rate for the highest quintile was $\approx 35\%$ at 8 years compared with a cumulative rate of $< 10\%$ for the lowest quintile.

A significant risk gradient for adverse events was evident across the quintiles of LV mass after adjustment for age, gender, smoking, diabetes, cholesterol level, clinic and 24-hour ambulatory BP, treatment status, body mass index, family history, and LV relative wall thickness. As reported in Table 3, LV mass was independently associated with a progressive, linear increase in cardiovascular morbidity rates. In a multivariate analysis, the excess risk compared with the first quintile of LV mass was significant for the third, fourth, and fifth quintiles (LV mass > 91.2 g/m² in women and > 105.4 g/m² in men). When LV mass was indexed to height^{2.7} in the place of body surface area, the risk gradient across quintiles did not change substantially for the second (relative risk [RR] 1.27, 95% CI 0.64 to 2.51), third (1.85, 95% CI 1.01 to 3.41), fourth (2.49, 95% CI 1.38 to 4.49), and fifth (3.12, 95% CI 1.61 to 5.08) quintiles.

Death

All-cause mortality rates, expressed per 100 patient-years, were 0.19, 0.21, 0.54, 0.83, and 1.27 events per 100 patient-

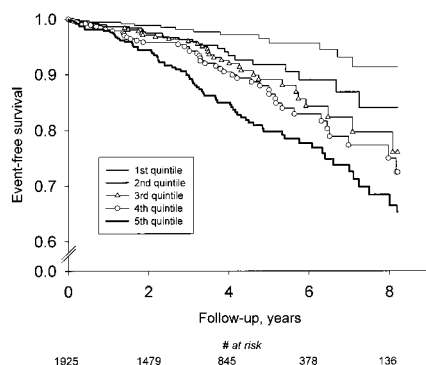


Figure 2. Cumulative cardiovascular event-free survival by quintile of LV mass index.

TABLE 3. Independent Predictors of Total Cardiovascular Morbid Events (Cox Model)

Variable	Adjusted Hazard Ratio (95% CI)	P
Age, y	1.06 (1.04–1.08)	<0.0001
Diabetes, yes vs no	1.50 (1.01–2.23)	<0.05
Cigarette smoking, yes vs no	1.62 (1.16–2.25)	<0.005
Gender, men vs women	1.77 (1.29–2.42)	<0.0004
24-h systolic BP, mm Hg	1.02 (1.01–1.03)	<0.006
Serum cholesterol, mmol/L	1.16 (1.01–1.33)	<0.03
LV mass index		
Quintile 2 vs quintile 1	1.55 (0.78–3.08)	0.18
Quintile 3 vs quintile 1	1.92 (1.01–3.98)	<0.05
Quintile 4 vs quintile 1	2.97 (1.51–5.84)	<0.002
Quintile 5 vs quintile 1	3.51 (1.82–6.78)	<0.0002

Family history for premature cardiovascular disease, clinic systolic and diastolic BP, 24-hour diastolic BP, body mass index, treatment status, and relative wall thickness failed to enter the equation. See Table 2 for details.

years in the 5 quintiles of LV mass (log-rank test, $P < 0.0001$) (Figure 1, right). Figure 3 shows survival curves in the 5 quintiles of LV mass. After control for the other independent covariates (age and male gender), we found that a greater LV mass was an independent predictor of all-cause death. As reported in Table 4, subjects in the fifth quintile of LV mass had a > 4 -fold RR for all-cause death compared with subjects in the first quintile. The excess risk bordered on significance for subjects in the fourth quintile.

Predictive Value of LV Hypertrophy Defined by Different Criteria

After adjustment for the other covariates in a multivariate model, LV hypertrophy was independently associated with risk for cardiovascular complications regardless of the use of height-based indexes (≥ 51 g/m^{2.7}; $P < 0.021$, $-2 \log L = 2320.1$), gender-specific indexes adjusted for body surface area (≥ 125 g/m² in men, ≥ 110 g/m² in women; $P < 0.004$, $-2 \log L = 2317.0$), or gender-independent indexes adjusted for body surface area (≥ 125 g/m²; $P < 0.016$, $-2 \log L = 2319.7$). When the classification of subjects into quintiles of LV mass replaced the categorical definition of LV hypertrophy in the equation, the resulting model provided a further improvement in the prediction of risk estimate,

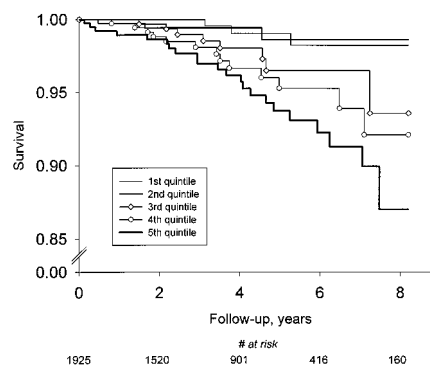


Figure 3. Cumulative survival by quintile of LV mass index.

TABLE 4. Independent Predictors of All-Cause Death (Cox Model)

Variable	Adjusted Hazard Ratio (95% CI)	P
Age, y	1.10 (1.06–1.13)	<0.0001
Gender, men vs women	2.98 (1.58–5.64)	<0.0008
LV mass index		
Quintile 2 vs quintile 1	0.94 (0.19–4.69)	0.94
Quintile 3 vs quintile 1	1.86 (0.48–7.19)	0.37
Quintile 4 vs quintile 1	2.90 (0.82–10.48)	0.09
Quintile 5 vs quintile 1	4.30 (1.16–13.40)	<0.048

Family history for premature cardiovascular disease, clinic and 24-hour BP, diabetes, serum cholesterol level, cigarette smoking, body mass index, treatment status, and LV geometric pattern failed to enter the equation.

See Table 2 for details.

expressed by a reduction in the $-2 \log L$ value (2305.9, $P<0.001$ versus all models based on binary partitions).

Men Versus Women

LV mass was significantly greater in men than in women, after adjustment for both body surface area (116.2 ± 31 versus 99.5 ± 25 g/m²) and height (52.0 ± 15 versus 47.6 ± 13 g/m^{2.7}, both $P<0.0001$). Event-free survival analysis was also performed separately in men and women. In a Cox regression model, LV hypertrophy (LV mass ≥ 125 g/m² in men, ≥ 110 g/m² in women) was an independent predictor of cardiovascular morbidity in women (hazard ratio 1.99, 95% confidence interval 1.17 to 3.37) as well as in men (hazard ratio 1.54, 95% confidence interval 1.05 to 2.25). The independent impact of increased LV mass on cardiovascular events was significantly greater in women than it was in men. For each 1-SD increment in LV mass (25 g/m² in women, 31 g/m² in men), the adjusted hazard ratio was 1.49 in women (95% CI 1.23 to 1.79) and 1.22 in men (95% CI 1.03 to 1.45; $P<0.02$ for gender/LV mass index interaction).

LV Geometry

Cardiovascular event rate was higher in subjects with LV concentric geometry ($n=523$), defined as a relative wall thickness of ≥ 0.45 , than in subjects with an eccentric geometry (3.53 versus 2.06 events/100 patient-years, $P<0.01$). However, the prognostic value of LV concentric geometry, defined either as a categorical or as a continuous variable, did not hold in a multivariate Cox model (Table 3). The hazard ratio for concentric geometry was 1.16 (95% CI 0.85 to 1.59) for cardiovascular events and 1.26 (95% CI 0.69 to 2.31) for all-cause deaths.

Discussion

This study showed a strong linear relation between LV mass on echocardiography and subsequent cardiovascular morbidity and all-cause mortality rates in initially untreated and uncomplicated subjects with essential hypertension. The relation was statistically significant, clinically consistent, and persisted after correction for the influence of several traditional risk factors, including age, gender, diabetes, cigarette smoking, serum cholesterol level, and clinic and 24-hour

ambulatory BP. An increased risk for cardiovascular disease was apparent for LV mass values of >105 g/m² in men and >91 g/m² in women, in large part below the traditional^{1–3,14,21} reference standards. The prevalence of subjects at increased risk ranged between 24% and 40%, depending on the criterion that was used, when binary definitions of LV hypertrophy were used, whereas it rose to 60% with the use of gender-specific LV mass quintiles. The use of quintiles significantly improved the goodness-of-fit of the multivariate model compared with the binary definitions, thus providing a better prediction of cardiovascular risk estimate.

Previous Studies

LV hypertrophy detected on echocardiography is a widely established risk factor for cardiovascular complications in hypertension^{1–3} and in the general population,^{4,5} as well as in a variety of clinical settings.^{23–25} It is unknown whether the association between LV mass and cardiovascular risk in hypertension is continuous over a wide range of values and whether this association holds also in the “normal” range of LV mass. Mensah et al²⁶ examined the prognostic value of LV mass in 193 subjects with essential hypertension stratified into 4 groups with progressively greater LV mass. The 12-year incidence of cardiovascular events was 64% in patients with pretreatment LV mass of >174 g/m² and 38% in patients with pretreatment LV mass between 125 and 174 g/m². However, the group at highest risk (LV mass >174 g/m²) included only 11 subjects, and the small number of events (50 total) did not allow a solid statistical adjustment for the effect of several potential confounders. A recent analysis of the Framingham Heart Study¹⁰ found an increased LV mass in 26% of subjects. LV mass showed a linear relationship with the rate of future cardiovascular events, but when the subjects with LV hypertrophy were stratified into 4 groups based on LV mass, the age- and risk factor-adjusted hazard ratio was only 1.27 in the majority of subjects (81% of the group) who had only a mild increase in LV mass. Hazard ratio increased up to 1.75, 2.05, and 3.10 in the other 3 subsets, which, however, represented only 19% of the subjects with LV hypertrophy.¹⁰ Because only one third of the studied population were hypertensive, these findings could not provide a definite answer to the question regarding the prognostic impact of a mild increase in LV mass in the specific setting of essential hypertension.

Present Study

Despite the considerable literature on the adverse prognostic value of LV hypertrophy in different clinical settings,^{1–5,23–25} only a few studies^{1–3,16,26,27} have been specifically conducted in uncomplicated subjects with essential hypertension. Other studies have been carried out with different populations of subjects, including the general population,^{10,28} subjects undergoing cardiac catheterization for presumed coronary artery disease,^{23,29} survivors of myocardial infarction,²⁴ and subjects with renal failure.²⁵ Thus, more data are needed for subjects with essential hypertension to better define the prognostic value of LV mass in this important setting.

The general acceptance in the clinical practice of LV hypertrophy as a binary variable is derived from its docu-

mented prognostic value^{1-5,23-26} and from the convenience and easy applicability of the classification of LV mass values into 2 categories: normal and abnormal. Nevertheless, the distribution of LV mass is continuous in the general population,⁶ therefore making any definition of a cutoff value arbitrary. In our study, LV hypertrophy defined according to 3 different binary criteria was a significant independent predictor of prognosis in men and women with essential hypertension. However, an important contribution of the present study was that the stratification of subjects into quintiles of LV mass added precision to the risk estimate, as demonstrated by the further reduction of the $-2 \log L$ value in comparison with models based on binary partitions. Thus, stratification of LV mass values into quintiles appears to be more rewarding and equally easy to use for cardiovascular risk stratification than the use of LV hypertrophy as a yes/no variable.

The basic pathophysiological mechanisms underlying the association between LV mass and cardiovascular risk remain elusive.³⁰ LV mass may be considered a time-integrated marker of exposure to high BP values and as a sensitive indicator of cardiac end-organ damage. It is well established³⁰ that LV mass (1) increases myocardial oxygen consumption while reducing coronary blood flow reserve, (2) is associated with an increase in atherosclerotic lesions at cardiac and extracardiac levels, and (3) is associated with enhanced arrhythmogenesis.

Some other points deserve comment. First, the use of different categorical definitions of LV hypertrophy did not yield different results in terms of cardiovascular risk stratification. This finding reflects the high degree of correlation between the different indexes of LV mass and is in agreement with a recent study by Liao et al.²⁹ Second, the adverse prognostic impact of increased LV mass was apparent in both genders but was significantly greater in women than in men. These data, which were obtained in uncomplicated subjects with essential hypertension, confirm and extend the results of another study by Liao et al, which was carried out in a hospital-based, predominantly black population of subjects with suspected coronary heart disease,³¹ in which the independent prognostic value of LV hypertrophy was considerably stronger in women than it was in men. The mechanisms underlying this gender difference remain unknown. Third, our study extends the existing literature^{2,16,27,31-33} by showing that the different LV geometric patterns seem to add little additional prognostic information to the overwhelming information provided by LV mass in hypertensive subjects.

Study Strengths and Limitations

The large number of cardiovascular events in the present study allowed adjustment for the confounding effect of several risk markers, including ambulatory BP. Our findings have been obtained in initially untreated white subjects, so results may not be extended to different racial groups or to subjects receiving antihypertensive treatment at the time of the qualifying echocardiographic study. Another limitation of the study was the lack of an assessment of the serial changes in office BP, ambulatory BP, and LV mass over time. In a previous study from our

group, the prognostic value of LV hypertrophy regression remained significant after control for baseline LV mass and serial changes in office and ambulatory BP.⁵

Clinical Implications

Our findings show a linear, powerful, and independent relation between LV mass and cardiovascular risk in initially untreated men and women with essential hypertension who were free from overt cardiovascular disease. The stratification of subjects into quintiles of LV mass provided a significant improvement of risk estimate compared with the binary definition of LV hypertrophy. An increased cardiovascular risk was already detectable at LV mass values ($>105 \text{ g/m}^2$ in men and $>91 \text{ g/m}^2$ in women) considerably lower than the traditional upper normal limits, thus allowing the identification of a substantially greater percentage of individuals at an increased cardiovascular risk. These findings may be of help in the clinical practice by allowing better interpretation of the results of quantitative echocardiography for cardiovascular risk stratification in subjects with essential hypertension.

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