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Familial Predisposition of Left Ventricular Hypertrophy

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OBJECTIVES The study evaluated the contribution of familial predisposition to the risk of left ventricular hypertrophy (LVH).

BACKGROUND Left ventricular hypertrophy is a multifactorial condition that serves as an important predictor of cardiovascular mortality. At present it is unclear whether familial predisposition contributes to the manifestation of LVH. Thus, we determined whether siblings of subjects with LVH are at increased risk to present with an elevation of LV mass or an abnormal LV geometry.

METHODS Echocardiographic and anthropometric measurements were performed in 2,293 individuals who participated in the echocardiographic substudies of population-based MONICA Augsburg surveys. In addition, a total of 319 siblings of survey participants with echocardiographic evidence of LVH were evaluated. The risk of these siblings to present with LVH or abnormal LV geometry was estimated by comparison with 636 subjects matched for gender and age that were selected from the entire echocardiography study base.

RESULTS Blood pressure, body mass index, age, and gender (i.e., known determinants of LV mass) were comparable in LVH-siblings and the matched comparison group. However, septal and posterior wall thicknesses, relative wall thickness as well as LV mass index were significantly elevated in LVH-siblings ($p < 0.001$, each) whereas LV dimensions did not differ. Likewise, the prevalence of LVH was raised in LVH-siblings, as was the relative risk of LVH after adjustment for confounders ($p < 0.05$). More specifically, LVH-siblings displayed increased prevalences of concentric remodeling and concentric LVH ($p < 0.05$) but not of eccentric LVH.

CONCLUSIONS Familial predisposition appears to contribute to increased LV wall thickness, to the development of LV hypertrophy and abnormal LV geometry. (J Am Coll Cardiol 1999;33: 1685–91) © 1999 by the American College of Cardiology

Left ventricular hypertrophy (LVH) is of heterogeneous etiology, with hypertension and obesity being principal determinants of this major cardiovascular risk factor (1,2). Interestingly, the manifestation of both arterial hypertension and morbid obesity is partially related to a genetic predisposition (3,4). In particular, studies on twins indicated that up to 50% of blood pressure variability and 70% of body mass index variability may be determined by inherited factors (3,4). Likewise, there is growing evidence from studies on juvenile twins that left ventricular wall thickness or left ventricular mass (LVM) displays only minimal variance in subjects with identical genetic background (3,5–8). Furthermore, recent analyses of the Framingham Heart Study document significant intraclass correlations of LVM in first-degree relatives and identified a small but discernible proportion of its variance as being due to heredity (9). However, the impact of a familial predisposition on the manifestation of LVH has never been examined specifically. We thus investigated the hypothesis that siblings of subjects with LVH have an increased LV mass and a higher risk to develop LVH.

SUBJECTS AND METHODS

Study population. The study was set up as a part of the World Health Organization MONICA project (10) to monitor trends and determinants of cardiovascular morbidity and mortality in the city of Augsburg and two adjacent counties in southern Germany. In 1984 to 1985, 1989 to 1990 and 1994 to 1995, three surveys were conducted selecting independent, age-stratified random samples of the population for assessment of the risk factor profile (11). All

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Abbreviations and Acronyms

BMI	= body mass index
EDD	= end-diastolic diameter
LVH	= left ventricular hypertrophy
LVM(I)	= left ventricular mass (index)
PWT	= posterior wall thickness
RWT	= relative wall thickness
SWT	= septal wall thickness

individuals who participated in this study gave written informed consent.

Echocardiographic substudies were performed to further evaluate electrocardiographic data suggesting that inheritable factors are involved in the pathogenesis of LVH (12). In 1994, participants of the 1984 to 1985 survey were reinvited for an echocardiographic examination. The invitation was restricted to subjects 52 to 67 years of age, and 646 men and women (response 64%) could be examined (13–15). In addition, echocardiographic examinations were offered to all participants of the 1994/1995 survey attending the Augsburg study center. Thereby, another 1,678 men and women in the age range from 25 to 74 years (response 70.6%) could be examined (16).

All participants of the two echocardiographic substudies who displayed LVH by echocardiography (LVM indexed to body height >143 g/m in men and >102 g/m in women; n = 427) were interviewed about the number and gender of their living siblings. Whenever study participants and their siblings agreed, siblings were invited to participate in the examinations applying the same study protocol. A total of 373 male and female siblings were subsequently examined.

From all 2,293 participants of the echocardiographic substudies and all LVH-siblings, data on medical history, medication, and smoking or drinking behavior were obtained by interviews. Subjects' body height and weight were measured in light clothing and without wearing shoes, and the body mass index (BMI) was computed as weight in kilograms divided by height in meters squared (kg/m^2). Resting blood pressure was measured before and after echocardiography using a standard mercury sphygmomanometer. Blood pressure was read three times at the right arm, and the mean of all three measurements was used in this study. Hypertension was defined as blood pressure values equal or above systolic 160 mm Hg and/or diastolic 95 mm Hg, or as present in subjects chronically taking antihypertensive medication.

Echocardiographic measurements. Two-dimensional guided M-mode echocardiograms were obtained from each subject by one of three expert sonographers with a Sonos 1500 (Hewlett-Packard, Andover, Massachusetts). The M-mode tracings were recorded on strip chart paper at 50 mm/s, given a code number and analyzed without knowledge on whether the echocardiogram was from a LVH-sibling or a control subject. Only tracings that demonstrated optimal visualization of left ventricular interferences were used. Measurements of wall thicknesses and ventricular diameters for the calculation of LVM were made in random order on coded strip charts without knowledge of whether the recording was from a sibling or a matched subject. Left ventricular internal end-diastolic diameter (EDD), septal wall thickness (SWT), and posterior wall thickness (PWT) were measured according to the Penn convention just below the tip of the mitral valve as recommended by the American Society of Echocardiography (17). Left ventricular mass (LVM) was calculated according to the formula of Devereux et al. (18):

$$\text{LVM (in grams)} = (1.04\,[\text{EDD} + \text{SWT} + \text{PWT}]^3 - \text{EDD}^3) - 13.6\ \text{g}.$$

The LVM indexed to body size (LVMI) was obtained in three different ways: it was either divided by body height in meters (19), by the allometric signal $\text{height}^{2.7}$ (20), or by body surface area in meters squared (19). The following LVH criteria for each indexation method were used: LVM indexed to height: >143 g/m in men, >102 g/m in women (19); LVM indexed to body surface area: >131 g/m^2 in men, >100 g/m^2 in women (19); LVM indexed to $\text{height}^{2.7}$: >50 $g/m^{2.7}$ in men, >47 $g/m^{2.7}$ in women (20). Patterns of left ventricular geometry were defined as proposed by Ganau et al. (21)—that is, as normal geometry when LVMI was normal and relative wall thickness (RWT = 2 PWT/EDD) <0.45; as left ventricular remodeling when normal LVMI was combined with RWT >0.45; as concentric LVH when left ventricular hypertrophy occurred with a RWT >0.45; and as eccentric LVH when left ventricular hypertrophy and a RWT <0.45 were combined.

Statistical analyses. To investigate the influence of familial predisposition on risk of LVH we used a method proposed by Weis et al. (22,23). We compared each sibling with two control subjects from the population-based echocardiographic substudies of the MONICA Augsburg project. For this purpose, each LVH-sibling was randomly matched with two individuals of the same gender and five-years' age group. We thus avoided a direct comparison of sibling pairs (i.e., correlation analysis), which might be criticized for the fact that various factors can introduce high correlations between siblings rather indirectly (with respect to the heart—e.g., body size) or may be explained by factors beyond inheritance ("shared environment" in a large sense). By distinction, we examined in our study design how the "exposure" of individuals to familial predisposition, defined as having a sibling diagnosed with LVH, may relate to left ventricular mass and hypertrophy aside from the amount contributed by age, gender, body mass, and blood pressure. The latter factors were controlled by design either through appropriate matching (age, gender) or through statistical adjustment (BMI and systolic blood pressure).

Table 1. Mean Values (and Standard Errors) and Percentages of Baseline Characteristics in LVH-Siblings and a Comparison Group Matched by Age and Gender

	Survey Participants (n = 1,923)	LVH-Siblings (n = 319)	Comparison Group (n = 636)	LVH-Siblings vs. Comparison Group p-Value
Male (%)	48.7	45.2	45.2	0.98
Age (yrs)	51.5 (0.2)	55.2 (0.6)	55.5 (0.4)	0.68
Body height (cm)	167.0 (0.2)	167.1 (0.5)	166.8 (0.4)	0.60
Body surface area (m^2)	1.83 (0.01)	1.86 (0.01)	1.84 (0.01)	0.20
Body mass index (kg/m^2)	26.7 (0.09)	27.5 (0.3)	27.1 (0.2)	0.16
Systolic BP (mm Hg)	144.4 (0.5)	148.1 (1.3)	149.3 (0.9)	0.45
Diastolic BP (mm Hg)	87.1 (0.3)	90.9 (0.8)	89.9 (0.5)	0.24
Antihypertensive medication (%)	14	19	22	0.22

Values are expressed as mean ± SEM; systolic and diastolic BP represent respective blood pressures.

Echocardiographic tracings that demonstrated optimal visualization of left ventricular inferences and a complete set of analytic variables were obtained from 319 LVH-siblings (85% of the total of 373 examined) and from 1,923 individuals from the survey samples (84% of the total of 2,293). Excluded subjects were significantly older, more obese and more often men (each $p < 0.01$). The analyses in this report are based on a comparison 319 LVH-siblings with 636 subjects who were randomly selected after successful matching by gender and age group.

The description of baseline data compares the mean values of age, blood pressure, and body size between LVH-siblings and the comparison group. The statistical significance of differences in continuous variables was assessed by two-sided *t* tests for unpaired groups and for categorized variables by chi-square tests. Mean values of echocardiographic measurements were compared after adjustment for age, gender, systolic blood pressure, and BMI by means of multiple linear regression modeling (PROC GLM of the SAS statistical software, Version 6.11). Furthermore, the prevalences of LVH using indexations for body height, $height^{2.7}$, and body surface area were assessed. Multiple logistic regression was applied to estimate the ratio of the LVH odds in LVH-siblings and their comparisons controlling for age, gender, systolic blood pressure, and BMI. The 95% confidence intervals are reported as a measure of the precision of the odds ratio estimates. Finally, the geometric patterns of LVH were analyzed in both siblings and controls. The odds ratio for the occurrence of a concentric pattern (relative wall thickness >0.45) was estimated by logistic regression controlling for covariates.

RESULTS

Baseline characteristics. Table 1 displays the mean values of body size, blood pressure as well as the proportion of individuals taking antihypertensive medication in the survey population as well as in LVH-siblings and the matched comparison group. Statistical analysis, carried out between LVH-siblings and the matched comparison group, did not display any significant differences with respect to any of these variables, which are known determinants of LV mass and hypertrophy.

Echocardiographic measurements. There were marked differences in cardiac structure and geometry of LVH-siblings and matched controls (Table 2). After adjustment for age, gender, systolic blood pressure and BMI, the interventricular septum and the posterior ventricle wall were significantly thicker in LVH-siblings ($p < 0.001$). This contrasted with the lack of any discernible differences in the internal end-diastolic dimensions. Consequently, the relative wall thickness was significantly raised in siblings ($p <$

Table 2. Adjusted Mean Values (and Standard Errors) of Echocardiographic Measurements in LVH-Siblings and a Comparison Group Matched by Age and Gender

	Survey Participants (n = 1,923)	LVH-Siblings (n = 319)	Comparison Group (n = 636)	LVH-Siblings vs. Comparison Group p-Value
Septal wall thickness (mm)	10.6 (0.05)	11.6 (0.11)	10.9 (0.08)	< 0.001
Posterior wall thickness (mm)	8.7 (0.04)	9.5 (0.07)	8.9 (0.05)	< 0.001
End-diastolic diameter (mm)	48.0 (0.11)	47.7 (0.25)	48.1 (0.18)	0.18
Relative wall thickness (%)	38.1	40.2	37.7	< 0.001
LVM/height (g/m)	104.3 (0.83)	114.6 (1.6)	109.1 (1.1)	0.0035
LVM/BSA (g/m^2)	94.4 (0.67)	103.0 (1.4)	98.1 (0.9)	0.0041
LVM/$height^{2.7}$ ($g/m^{2.7}$)	43.5 (0.34)	47.8 (0.7)	45.8 (0.5)	0.012

LVM represents left ventricular mass; BSA, body surface area.

Table 3. Prevalence (in %) and Adjusted Odds Ratio of LVH in LVH-Siblings and A Comparison Group Matched by Age and Gender, Applying Three Different Indexations of Left Ventricular Mass

LVH by Indexation type	LVH-Siblings (n = 319)	Matched Controls (n = 636)	p-Value
Prevalence (LVM/height: m >143 g/m, f >102 g/m)	37.9%	32.7%	
Adjusted odds ratio of LVH 95% confidence interval	1.4 (1.004–1.954)	–*	0.047
Prevalence (LVM/BSA: m >131 g/m^2, f >100 g/m^2)	30.4%	25.4%	
Adjusted odds ratio of LVH 95% confidence interval	1.4 (1.031–2.015)	–*	0.033
Prevalence (LVM/$height^{2.7}$: m >50 $g/m^{2.7}$, f >47 $g/m^{2.7}$)	44.5%	34.9%	
Adjusted odds ratio of LVH 95% confidence interval	1.7 (1.249–2.423)	–*	0.001

*Reference category.
m = male; f = female; LVM = left ventricular mass; LVMI = indexed LVM; BSA = body surface area. Adjusted by multiple logistic regression models containing gender, age, systolic blood pressure and body mass index.

0.001). Finally, the LV masses of LVH-siblings were elevated irrespective of the type of indexation used (p = 0.012 or less).

Prevalence of LVH. The LVH prevalence in siblings was between 5% and 10% higher than in the matched comparison group, and the odds ratios for LVH were significantly raised among siblings (Table 3). The odds ratio was most pronounced when LVM indexed to $height^{2.7}$ was used in the definition of LVH (OR = 1.7, 95% confidence interval 1.25–2.42, p = 0.001), whereas it was 1.4 with the other indexations (each $p < 0.05$). A more specific analysis revealed that the increased LVH prevalence of siblings was caused exclusively by increased rates of remodeling and concentric LVH (Fig. 1). The odds ratio for the joint presence of these two conditions, which is synonymous with the prevalence of a relative wall thickness >45%, was 1.98 (95% confidence interval 1.47–2.68; p = 0.001) among siblings relative to the matched comparison group. The LVH-siblings presented with a significantly elevated odds ratio for an increased relative wall thickness irrespective of substratification by normal or elevated blood pressure or normal or elevated body weight, respectively (Table 4).

DISCUSSION

Genetic analyses on juvenile twins have established that the interindividual variability of left ventricular mass is strongly determined by inherited factors (3,7,8). Furthermore, data from the Framingham Heart Study display better intraclass

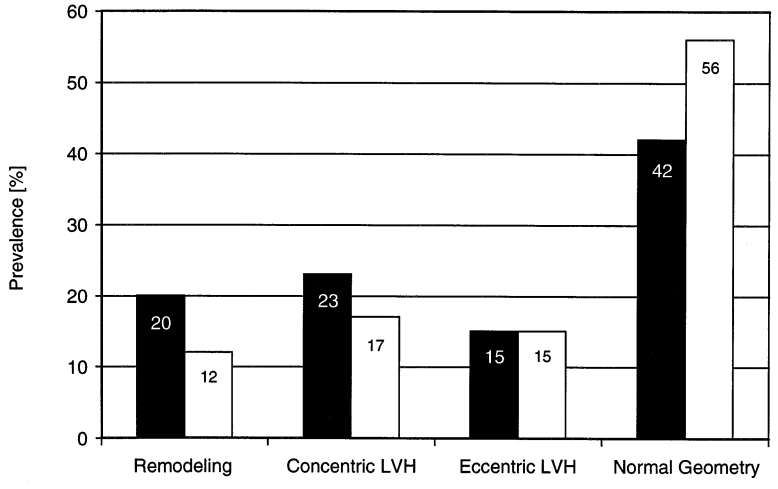

Figure 1. The bar graph displays the prevalence of various left ventricular geometries in siblings of subjects with LVH and matched controls. Remodeling and concentric LVH were significantly more prevalent in LVH-siblings, the opposite was true for normal LV geometry ($p < 0.05$, each). **Solid bars** = siblings; **open bars** = matched control groups.

Table 4. Prevalence (in %) and Adjusted Odds Ratio of Increased Relative Wall Thickness in LVH-Siblings and a Comparison Group Matched by Age and Gender, Stratifying by Hypertension and Overweight

	LVH-Sibling (n = 319)	Matched Controls (n = 636)	p-Value
Normotensives (n = 332)			
(SBP <140 mm Hg and DBP <90 mm Hg)			
Prevalence of RWT ≥45%	27.5%	14.7%	
Adjusted odds ratio of increased relative wall thickness	2.2	−*	0.0087
95% confidence interval	(1.2–4.0)		
Hypertensives (n = 624)			
(SBP ≥140 mm Hg or DBP ≥90 mm Hg)			
Prevalence of RWT ≥45%	49.8%	37.1%	
Adjusted odds ratio of increased relative wall thickness	1.9	−*	0.0003
95% confidence interval	(1.4–2.7)		
Normal weight (n = 273)			
(BMI <25 kg/m^2)			
Prevalence of RWT ≥45%	33.7%	18.4%	
Adjusted odds ratio of increased relative wall thickness	2.9	−*	0.0014
95% confidence interval	(1.5–5.7)		
Overweight (n = 683)			
(BMI <25 kg/m^2)			
Prevalence of RWT ≥45%	45.8%	33.6%	
Adjusted odds ratio of increased relative wall thickness	1.8	−*	0.0008
95% confidence interval	(1.3–2.5)		

*Reference category.

SBP = systolic blood pressure; DBP = diastolic blood pressure; RWT = relative wall thickness; BMI = body mass index. Adjusted by multiple logistic regression models containing gender, age, systolic blood pressure and body mass index.

correlations of left ventricular mass in first-degree relatives as compared to second-degree relatives or spouses (9). It is very intriguing to extrapolate these data to LVH, a highly recognized cardiovascular risk factor in middle-aged or elderly adults (24,25). However, long-term interaction of environmental factors might overcome genetic effects in the pathogenesis of LVH. Therefore, it is presently unclear whether familial predisposition is also a risk factor for the development of LVH. To study this question, we identified siblings of subjects with LVH and compared their odds to present with LVH with that of matched controls. Our principal finding is that the risk of LVH is substantially increased in siblings of affected individuals.

LVH a familial risk factor. After adjustment for age, blood pressure, and BMI, the risk elevation related to a familial disposition of LVH was 1.4 to 1.7. This proportion compares favorably to that calculated in recent twin studies for the genetic component of LVM variability (3,6–8). It needs to be pointed out, however, that the present data do not allow one to distinguish whether the elevated risk of LVH is related to the fact that the siblings shared genes, environment, or both (3,5–8,26). Nevertheless, the consideration of both—twin studies and the present investigation on siblings of subjects with LVH—allows the hypothesis that LVH is modulated, in part, by an inherited component. This view is strengthened by a small but significant effect of heredity on LVM observed in adult siblings of the Framingham Heart Study (9). Furthermore, the present analysis and two previous twin studies concur in the observation that wall thickness or LVM (I) rather than left ventricular dimension is affected by a familial (and presumably genetic) predisposition (7,8). Consequently, we observed a familial risk for the manifestation of concentric LVH and concentric left ventricular remodeling, both being characterized by increased wall thickness, but not eccentric LVH, which is

predominantly related to an increase in left ventricular dimension.

Interaction with other determinants of LVH. This study was carried out on population-based samples to avoid a preselection of LVH cases, which occurs in the clinical setting. It should be emphasized, therefore, that about one-third of the individuals with LVH were normotensive and with normal BMI and, thus, without traditional risk factors for LVH. This distribution resembles observations from other population-based surveys such as the Framingham Heart Study (12,27). We thus conducted subanalyses that revealed a familial component of increased RWT in LVH-siblings irrespective of blood pressure or body mass status. Although an observational study cannot entirely rule out secondary effects on LV mass, consistent findings after adjustment as well as stratification by blood pressure and weight status suggest that the familial risk of LVH, like the variability of left ventricular mass in twins (3), is not secondary to a familial predisposition for hypertension or obesity.

Implications for molecular genetics. Recent molecular genetic investigations suggested that the risk to present with LVH may be affected by alterations of specific candidate genes, such as the angiotensin-converting enzyme gene (12). Although a series of studies reproduced this observation, others were not able to confirm the hypothesis (28). Hence, current molecular genetic studies in humans do not definitively document a genetic component in the pathogenesis of LVH, whereas in experimental animals inherited susceptibility to LVH is well documented (29). Given the present data on human subjects, the overall familial contribution of LVH can be estimated and, thus, more realistic power estimations (to confirm or reject a null hypothesis of genetic association or linkage) for molecular genetic analyses can be made.

Conclusions. Although a familial and presumably a genetic component in the pathogenesis of LVH is suggested by this study, we do not wish to distract attention from measures that have been proven to regress LVH, including diet, physical activity, and, if indicated, antihypertensive medication. Furthermore, it remains to be shown that LVH derived from genetic predisposition confers an increased cardiovascular risk as has been documented for LVH in general (24,25). Nevertheless, the present data allow the reemphasis that several cardiovascular sequelae including LVH are potentially shared by family members of affected individuals, providing the opportunity for early recognition and, possibly, prevention of the associated risk.

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