Left Ventricular Mass and Geometry and the Risk of Ischemic Stroke

Marco R. Di Tullio, MD; Donna R. Zwas, MD; Ralph L. Sacco, MD; Robert R. Sciacca, EngScD; Shunichi Homma, MD

Background and Purpose—Left ventricular hypertrophy (LVH) is a risk factor for cardiovascular events, but its effect on ischemic stroke risk is established mainly in whites. The effect of LV geometry on stroke risk has not been defined. The aim of the present study was to evaluate whether LVH and LV geometry are independently associated with increased ischemic stroke risk in a multiethnic population.

Methods—A population-based case-control study was conducted on 394 patients with first ischemic stroke and 413 age-, sex-, and race-ethnicity–matched community control subjects. LV mass was measured by transthoracic echocardiography. LV geometric patterns (normal, concentric remodeling, concentric or eccentric hypertrophy) were identified. Stroke risk associated with LVH and different LV geometric patterns was assessed by conditional logistic regression analysis in the overall group and age, sex, and race-ethnic strata, with adjustment for established stroke risk factors.

Results—Concentric hypertrophy carried the greatest stroke risk (adjusted odds ratio [OR], 3.5; 95% confidence interval [CI], 2.0 to 6.2), followed by eccentric hypertrophy (adjusted OR, 2.4; 95% CI, 2.0 to 4.3). Concentric remodeling carried slightly increased stroke risk (adjusted OR, 1.7; 95% CI, 1.0 to 2.9). Increased LV relative wall thickness was independently associated with stroke after adjustment for LV mass (OR, 1.6; 95% CI, 1.1 to 2.3).

Conclusions—LVH and abnormal LV geometry are independently associated with increased stroke risk. LVH is strongly associated with ischemic stroke in all age, sex, and race-ethnic subgroups. Increased LV relative wall thickness imparts an increased stroke risk after adjustment for LV mass and is of additional value in stroke risk prediction. (Stroke. 2003; 34:2380-2386.)

Key Words: echocardiography • heart ventricle • hypertrophy, left ventricular • stroke

Left ventricular hypertrophy (LVH), or increased LV mass, is a risk factor for cardiovascular diseases.1–9 Echocardiographic LVH is associated with cardiovascular morbidity and mortality, as well as all-cause mortality.4–9 The risk increase is independent of other cardiovascular risk factors, including arterial hypertension.4–6,8,9 Recently, there have been reports of incremental risk associated with abnormal LV geometry beyond the simple LV mass increase. From LV mass and relative wall thickness (RWT), 3 abnormal geometric patterns—concentric hypertrophy, eccentric hypertrophy, and concentric remodeling10—are identified that appear to carry different risks for cardiovascular events. Concentric hypertrophy (increase in both LV mass and RWT) carries the highest risk,4,11 followed by eccentric hypertrophy (increased LV mass, normal RWT4,11). The independent risk of an isolated RWT increase (concentric remodeling) is controversial.11–14

LVH is also independently associated with risk of ischemic stroke.15–20 This association, identified in ECG studies,14–17 was confirmed with more sensitive echocardiographic techniques.19,20 Increased stroke risk was shown mainly in whites,15–19 with fewer data available in blacks13,20 and Hispanics.21 The role of abnormal LV geometry in stroke risk has received little attention. In hypertensive patients, concentric and eccentric hypertrophy was associated with an ~2-fold increase in stroke incidence, whereas concentric remodeling did not carry increased risk.4 However, the small number of strokes precluded definitive conclusions in this and similar studies.4,13

The aim of the present study was to evaluate the role of LVH and abnormal LV geometry as independent risk factors for ischemic stroke in the multiethnic population of the Northern Manhattan Stroke Study (NOMASS).

Methods

Study Population

Subjects were drawn from NOMASS, a community-based epidemiological study that evaluates stroke incidence, risk factors, and
prognosis in northern Manhattan. Recruitment modalities have been published previously.21,22 Briefly, patients >39 years of age residing in northern Manhattan who were admitted to the Presbyterian Hospital with a first ischemic stroke were eligible. The race-ethnic distribution in this community is ~20% black, 63% Caribbean Hispanic, and 15% white residents. Race-ethnicity was defined by self-identification in response to a questionnaire modeled after the US census. Stroke-free subjects were identified by random-digit dialing of northern Manhattan households. Control subjects were matched to cases by age (within 5 years), sex, and race-ethnicity.

From May 1993 through December 1998, 431 patients with first ischemic stroke and 434 stroke-free control subjects underwent 2-dimensional transthoracic echocardiography. All necessary echocardiographic measurements were obtainable in 394 stroke patients (91.4%) and in 413 control subjects (95.2%). Written informed consent was obtained from all subjects. The study was approved by the Institutional Review Board of Columbia-Presbyterian Medical Center.

Diagnostic Evaluation

Stroke risk factors were collected by direct interview or medical record review. Arterial hypertension was defined by history or antihypertensive treatment or by blood pressure >140/90 mm Hg (average of 2 measurements). Hypercholesterolemia was defined as total serum cholesterol >240 mg/dL or the presence of appropriate treatment. Diabetes mellitus was defined as abnormal fasting blood sugar, positive history, or presence of oral or insulin treatment. Coronary artery disease included history of myocardial infarction or typical angina, a positive diagnostic test (stress test, coronary angiography), or appropriate treatment. Atrial fibrillation was documented on a current or past ECG or Holter monitoring. Congestive heart failure was diagnosed on the basis of clinical signs, symptoms, and/or appropriate medical treatment.

Neurological workup in stroke patients included head CT or MRI, carotid and vertebral artery duplex Doppler ultrasonography, and transcranial Doppler examination of the middle and anterior cerebral arteries or basilar artery.

<table>
<thead>
<tr>
<th>TABLE 1. Demographics of the Study Group</th>
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<tr>
<td>Stroke Patients (n=394)</td>
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<tr>
<td>-------------------------</td>
</tr>
<tr>
<td>Age*</td>
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<tr>
<td>Overall group</td>
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<tr>
<td>Whites</td>
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<td>Blacks</td>
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<td>Hispanics</td>
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*Mean±SD.

Echocardiographic Evaluation

Transthoracic echocardiography was performed according to the guidelines of the American Society of Echocardiography23 with Hewlett-Packard Sonos 1000 and 2500 ultrasound equipment (Hewlett-Packard Imaging Systems Division). LV end-diastolic diameter (LVEDD), LV end-systolic diameter (LVSD), interventricular septum (IVS), and posterior wall (PW) thickness at end diastole were measured. LV mass (LVM) was calculated from the corrected American Society of Echocardiography method24: LVM=0.8(1.04[(IVS+LVEDD+PW)3−LVEDD3])+0.6.

LV mass (log transformed to increase normality) was then regressed on height and sex. LVH was defined as adjusted LV mass greater than the 90th percentile of the control subjects without conditions associated with LVH such as arterial hypertension, diabetes mellitus, obesity, and cardiovascular diseases. RWT was calculated according to this formula:

\[ \text{RWT} = \frac{\text{IVS}}{\text{LVDD}} \]

The 90th percentile of the control population described above (RWT: 0.60 for women, 0.54 for men) was used as the upper limit of normal. Four LV geometric patterns10 were identified on the basis of LV mass and RWT: normal (normal LV mass, normal RWT), concentric remodeling (normal LV mass, abnormal RWT), eccentric hypertrophy (abnormal LV mass, normal RWT), and concentric hypertrophy (abnormal LV mass, abnormal RWT).

Echocardiographic studies were interpreted by researchers blinded to case-control status and other clinical characteristics. Interobserver variability for the variables measured ranged between 8% and 10%.

Statistical Analysis

Data are reported as mean±SD for continuous variables and as frequency for categorical variables. Differences between proportions were assessed by \( \chi^2 \) test or Fisher’s exact test; differences between mean values, by unpaired Student’s \( t \) test. A 2-tailed value of \( P<0.05 \) was considered significant.

Univariate and multivariate conditional logistic regression analyses (PROC PHREG, SAS 8.2) were used to test the association between LVH/geometric patterns and ischemic stroke. Unadjusted odds ratios (ORs) were calculated for the entire study group and age, sex, and race-ethnic subgroups. Multivariate analysis was used to determine the adjusted OR for stroke of LVH and each LV geometric pattern after adjustment for variables significantly associated with ischemic stroke by univariate analysis (arterial hypertension, diabetes mellitus, atrial fibrillation, coronary artery disease, congestive heart failure). Adjusted ORs and 95% confidence intervals (CIs) were calculated.

To assess the effect of age (41 to 59, ≥60 years), sex, and race-ethnicity on the association between LVH/geometric patterns and ischemic stroke, separate variables were fit in the model to quantify the effect of LVH/geometric patterns independently for each strata. Differences between strata were tested with Wald’s \( \chi^2 \).

To assess the effect of RWT above that of LV mass on stroke risk, multivariate analysis was performed after adjustment for LV mass as a predictor of stroke risk.

<table>
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<tr>
<th>TABLE 2. Stroke Risk Factors Distribution in the Entire Study Group and by Race-Ethnicity</th>
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<tr>
<td>Cases, Controls,</td>
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<td>%</td>
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<tr>
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</tr>
<tr>
<td>Arterial hypertension</td>
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<td>Diabetes mellitus</td>
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<tr>
<td>Cigarette smoking</td>
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<td>Hypercholesterolemia</td>
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<td>Atrial fibrillation</td>
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<td>CAD</td>
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<td>CHF</td>
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*Mean±SD.

CAD indicates coronary artery disease; CHF, congestive heart failure.
LV geometric patterns in the study population. □ Indicates normal; ▪, concentric remodeling; □, concentric hypertrophy; and □, eccentric hypertrophy.

a continuous variable and for other stroke risk factors described above.

Results
Demographics of the study population are shown in Table 1. Interracial differences existed in traditional stroke risk factors (Table 2).

LVH, LV Geometry, and Risk of Ischemic Stroke
The distribution of LV geometric patterns is summarized in the Figure. Normal pattern was more frequent in control subjects than in stroke patients (65% versus 43%; P < 0.0001). Stroke patients had significantly higher frequencies of concentric hypertrophy (13% versus 6%; P = 0.0001) and eccentric hypertrophy (33% versus 20%; P = 0.0001). Arterial hypertension frequency and duration and blood pressure values are listed in Table 3. Blood pressure was significantly higher in abnormal geometry compared with normal geometry groups (P < 0.01). Hypertension duration was longest in the concentric hypertrophy group, but not significantly (P = 0.1). Of patients with LVH, 15% had no diagnosis of hypertension.

LVH was associated with increased stroke risk (adjusted OR, 2.5; 95% CI, 1.7 to 3.5; Table 4). This was observed in all age, sex, and race-ethnic strata. No significant interaction between LVH and arterial hypertension or other stroke risk factors on stroke risk was found.

Concentric hypertrophy carried the greatest stroke risk (Table 5), followed by eccentric hypertrophy. Concentric remodeling was associated with a modest risk increase. Increase in risk was independent of the presence of arterial hypertension and other risk factors.

Effect of Age, Sex, and Race-Ethnicity
Concentric and eccentric hypertrophy was associated with ischemic stroke across all sex and age strata, with adjusted ORs ranging from 2.3 to 6.0 (Table 5). Concentric remodeling was not associated with increased stroke risk in any subgroup.

The effect of concentric hypertrophy on stroke risk appeared stronger in Hispanics (adjusted OR, 4.3; 95% CI, 1.9 to 9.8), although differences were not statistically significant (Hispanics versus blacks, P = 0.37; Hispanics versus whites, P = 0.93). Eccentric hypertrophy was associated with stroke in whites and Hispanics but less so in blacks. Interracial differences were not statistically significant (whites versus blacks, P = 0.18; Hispanics versus blacks, P = 0.76). Concentric remodeling was not associated with an increased stroke risk in any race-ethnic subgroups.

RWT and Risk of Stroke
After adjustment for LV mass as a continuous variable, abnormal RWT was found to significantly increase stroke risk in both univariate (OR, 1.5; 95% CI, 1.03 to 2.2) and multivariate (OR, 1.6; 95% CI, 1.1 to 2.3) analyses. No interaction on stroke risk was detected between RWT and LV mass (P = 0.47 unadjusted, P = 0.68 adjusted).

Geometric Patterns and Stroke Subtype
Of 392 strokes, 65 (16.6%) were large-vessel disease, 91 (23.2%) were lacunar, 72 (18.4%) were cardioembolic, 13 (3.3%) were other mechanisms, and 151 (38.5%) were cryptogenic. Concentric LVH tended to have more lacunar (32.7%) and fewer cryptogenic (23.1%) strokes than other geometries. Eccentric hypertrophy was associated with a

| TABLE 3. Prevalence and Duration of Hypertension and Blood Pressure Values in Different Geometric Patterns |
|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                                  | Normal          | Concentric Hypertrophy | Eccentric Hypertrophy | Concentric Remodeling |
| Prevalence of hypertension, %                    | 68.5            | 59.3             | 86.5            | 75.0            | 84.1            | 86.3            | 85.7            | 76.9            |
| Hypertension duration, y*                        | 10.9±10.6       | 12.7±13.5        | 15.8±15.3       | 18.7±17.0       | 14.4±12.3       | 12.0±10.4       | 13.7±13.0       | 12.0±7.8        |
| SBP, mm Hg                                       | 139.6±16.7      | 138.6±20.7       | 150.9±22.7      | 153.2±28.7      | 144.8±20.1      | 153.4±22.8      | 148.9±22.4      | 144.2±21.8      |
| DBP, mm Hg                                       | 80.7±10.4       | 81.7±11.2        | 86.1±13.2       | 86.0±13.3       | 84.2±11.3       | 84.7±12.6       | 85.0±15.1       | 86.2±11.1       |

SBP indicates systolic blood pressure; DBP, diastolic blood pressure. *Mean ± SD.
s slight excess of cardioembolic strokes (26.5%), as was concentric remodeling for lacunar strokes (26.2%).

Discussion

LVH and Stroke Risk
LVH is an established risk factor for cardiovascular diseases\(^1\)\(^–\)\(^9\) and ischemic stroke, the latter demonstrated mainly in whites.\(^1\)\(^5\)\(^–\)\(^9\) Fewer data are available in black populations, mainly regarding the combined end point of cardiovascular events and stroke.\(^13\)\(^–\)\(^20\) Little information is available in Hispanics, especially of Caribbean origin.\(^21\) In our study, LVH was associated with a 2.5-fold increase in stroke risk after adjustment for other stroke risk factors. LVH was independently associated with stroke across all the race-ethnic subgroups studied, suggesting that its effect on stroke risk may be similar across races, even in the presence of different stroke risk factors profiles.

The mechanisms of the association between LVH and ischemic stroke are not clear. LVH might be a marker of subclinical disease\(^25\) or predispose to other conditions directly involved in stroke etiology. LV mass correlates with carotid wall thickness and luminal diameter\(^26\)\(^–\)\(^27\) and predicts carotid atherosclerosis.\(^28\)\(^–\)\(^29\) LVH has been linked to cerebrovascular disease in blacks\(^30\) and predisposes to developing hypertension\(^31\) and atrial fibrillation.\(^32\) Alternatively, LVH could represent a time-integrated indicator of exposure to other risk factors such as hypertension and obesity, which affect the risk of stroke and cardiovascular disease.

LV Geometry and Stroke Risk
The value of LV geometry in the prediction of cardiovascular risk is controversial.\(^11\)\(^,\)\(^12\)\(^,\)\(^14\) Moreover, its role as a risk factor for ischemic stroke has been minimally investigated. We demonstrate that abnormal LV geometry is associated with an increased ischemic stroke risk and that RWT adds information not contained in LV mass. Although RWT per se did not increase stroke risk to a significant extent, it did so after adjustment for LV mass. This suggests that LV geometry may contribute to stroke in ways not necessarily related to LV mass. Determination of RWT may be useful for further stroke risk stratification, especially among patients with LVH.

The observation that abnormal LV geometry may affect stroke risk has precedents in the literature. Asymptomatic lacunar lesions are more frequent in patients with abnormal LV geometry, and both LV mass and RWT predict them.\(^34\) Arterial structure and function are abnormal in patients with concentric LVH\(^15\) and may partly explain its excess morbidity. Neurohormonal changes such as aldosterone and atrial natriuretic peptide elevation are associated with abnormal LV geometry\(^36\) and might be involved in both its development and its adverse prognostic effect. In our study, increased RWT tended to be more frequently associated with lacunar infarcts, suggesting a possible role of RWT as a marker of small-vessel disease. Cryptogenic stroke was less frequent in patients with concentric hypertrophy, which may be a marker of more extensive cardiovascular disease, leading to development of identifiable sources for stroke. Eccentric hypertrophy tended to be associated with cardioembolism, suggesting a role for LV dilatation as a possible embolic source. Further studies are needed to elucidate the complex relationship between LV mass, LV geometry, and stroke and potential strategies for decreasing stroke risk.

Study Strengths and Limitations
This is the first study to address the effect of LV mass and geometry on ischemic stroke risk in a community-based multiethnic population and in age, sex, and race-ethnic subgroups. Furthermore, it provides data on Hispanics of Caribbean origin, information that is scarce in the literature.

The case-control design has limitations, including potential selection bias. This bias was minimized by recruitment of cases and controls from the same community, randomization of control subject selection, and individual case-control matching. However, differences between cases and controls may have existed in variables not measured. Moreover, the study did not have power to address the association between LV mass and geometry and different stroke subtypes, and its power for detecting interracial differences was suboptimal. Finally, definitions of race-ethnicity are problematic because ethnicity is heterogeneous and its categorization may lead to assumptions of biological differences while masking other differences, such as cultural and socioeconomic variables, which may affect disease.
Clinical Implications

Our data suggest that assessment of LV mass and RWT should be included in stroke risk evaluation. Treatment is available to promote regression of LVH, possibly associated with reduction in the incidence of cardiovascular events, including stroke. Angiotensin-converting enzyme inhibitors were shown to decrease RWT in hypertensive patients even in the absence of LVH. The possibility that pharmacological treatment affecting LV mass and geometry may also reduce the risk of ischemic stroke deserves further investigation.

Acknowledgments

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Left Ventricular Hypertrophy: An Unseemly Risk Factor for Stroke?

Left ventricular hypertrophy (LVH) has been increasingly recognized in the last decade as a risk factor for cardiovascular disease and stroke. However, at least in this guest editor’s experience, LVH is seldom or never mentioned, in everyday practice, among the risk factors considered relevant in a patient with cerebrovascular disease, whether because it is forgotten, neglected, or even despised. Why is this so?

LVH is usually considered a consequence of arterial hypertension: the left ventricle increases its mass and wall thickness to oppose a rise in the pressure load. Patients with LVH whose blood pressure is normal are thought to be “probably hypertensive,” albeit with “nonsustained hypertension.” In this line of reasoning, the relevant risk factor is hypertension and not the “secondary” consequence of LVH. In other instances, LVH is dismissed as a phenomenon linked to “aging,” akin to the “sclerosis” of the aortic valve or the “stiffness” of the arterial vessels often found in ultrasound studies of the elderly. Embolism is considered the necessary mechanism to ascribe a stroke to cardiac disease, and LVH is not regarded as a cardiac source of embolism. In myocardial diseases, it is dilated and not hypertrophic cardiomyopathy that is deemed liable to cause stroke.

However, after adjusting for hypertension and other recognized factors, LVH remains an independent risk factor for stroke. Different patterns of LVH have now been described, and a coherent picture seems to be slowly emerging. In the current issue of Stroke, Di Tullio and coworkers present further evidence relating LVH to stroke, and new evidence relating LV geometric patterns to stroke risk and stroke subtypes in a tri-ethnic population. The authors did not find statistically significant differences between the groups they studied. LVH appeared thus to be independently associated with stroke, across age, sex, and ethnicity.

Although 38.5% of the cases in their series were cryptogenic, concentric remodeling and concentric hypertrophy were associated more with lacunar than with other stroke subtypes, and eccentric hypertrophy with an excess of cardioembolic strokes (26.5%). Concentric remodeling, in which the LV mass index remains normal and only changes in relative wall thickness (RWT) occur, was associated with 26.2% of lacunar strokes. Overall, concentric remodeling carried only a slight increase in stroke risk, but RWT was independently associated with stroke after adjusting for LV mass. Lacunar strokes were more prevalent in the concentric hypertrophy group (32.7%), which carried the highest stroke risk. The increased risk was independent of the presence of hypertension. In a previous article, RWT was found to be a predictor for asymptomatic lacunar lesions. Therefore, concentric remodeling emerges as a marker for stroke risk, small-vessel disease, and lacunar stroke, and as a predictor of concentric hypertrophy and stroke recurrence. Recently, concentric hypertrophy has also been shown to be related to asymptomatic cerebrovascular disease. Concentric remodeling occurs in elderly nonhypertensive subjects. It has been linked to aging and shown to parallel age-related arterial stiffening and elevation of systolic blood pressure. These factors may be associated with lacunar strokes. Concentric remodeling is associated with carotid intima-media thickening in hypertensive patients. Patients with concentric hypertrophy also show an increase in arterial wall thickness, even in general population studies. Concentric remodeling has even mysteriously been linked to insulin resistance in elderly men, suggesting as yet unknown disease mechanisms connecting the myocardium to metabolic disturbances.

It is not yet entirely clear whether LVH represents “a marker, a limited adaptative process or a pathological process,” amenable to different therapeutic strategies. But it seems clear that it responds to treatment. The same group reporting the present data has found that physical activity decreases stroke risk in patients with increased left ventricular mass. Antihypertensive treatment reduces LV mass and RWT, and concentric remodeling often goes untreated. And if eccentric hypertrophy is confirmed as a risk factor for cardioembolism in future studies, a rationale for antithrombotic treatment would reasonably follow.

Perhaps we may now understand better why also normotensive patients showed a reduction in stroke risk in recent trials with antihypertensive agents: they may have decreased LVH. It looks as if physicians should now do well to think again before dismissing LVH as irrelevant for cerebrovascular disease.

References


