Physical Activity Attenuates the Effect of Increased Left Ventricular Mass on the Risk of Ischemic Stroke

The Northern Manhattan Stroke Study

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OBJECTIVES
The goal of this study was to determine whether the risk of ischemic stroke associated with increased left ventricular mass (LVM) is modified by physical activity (PA).

BACKGROUND
Increased LVM is associated with an increased risk for stroke. Physical activity can decrease the risk of stroke and may have variable effects on LVM.

METHODS
We used a case-control study design in a multiethnic population in northern Manhattan, New York, to study 394 case subjects who had a first ischemic stroke and 413 stroke-free control subjects. All subjects were interviewed and two-dimensional echocardiograms obtained to determine LVM.

RESULTS
A sharp increase in risk of ischemic stroke was seen in the highest quartile of LVM (odds ratio [OR]: 6.14 [95% confidence interval [CI]: 3.04 to 12.38]). Thus, increased LVM was defined by the highest quartile of LVM. In multivariate analysis, the effect of increased LVM on the risk of stroke was significantly decreased by the presence of any level of PA versus no PA (OR: 1.59 [95% CI: 0.99 to 2.57]) p < 0.07 vs. 3.53 [95% CI: 1.94 to 6.42] p < 0.0001). Although PA decreased the risk of stroke in all patients, the effect was stronger in subjects with increased LVM than among those without increased LVM (p = 0.033).

CONCLUSIONS
Increased LVM is associated with an increased risk of stroke, especially among sedentary patients. Physical activity decreases the risk of stroke among patients with increased LVM to a level comparable to that of patients without increased LVM. Recommending PA may be a nonpharmacologic tool to reduce the stroke risk, especially among patients with increased LVM.

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Stroke has tremendous impact on public health. It continues to rank as the third leading cause of death in the U.S. and is also the leading cause of serious, long-term disability (1). Data show that over 700,000 people suffer a new or recurrent stroke each year (2). Because treatment options are relatively limited, the modification of risk factors and prevention of future events is especially important.

Echocardiographically determined left ventricular mass (LVM) has been shown to be predictive of cardiovascular disease and mortality (3), as well as being associated with an increased risk for stroke and transient ischemic attacks (4). The adverse effects of increased LVM are independent of age, gender, blood pressure, cholesterol level, smoking and presence of coronary artery disease (3–7). The mechanisms responsible for the increased stroke risk associated with increased LVM are unknown (8). Thus, preventive strategies to decrease the risk have been generally lacking.

Regular physical activity (PA), even at low levels, has well established benefits for reducing the risk of premature death and cardiovascular disease and has been associated with reduced coronary artery disease incidence (9–11). In recent years, evidence has been accumulating that supports the protective effect of PA on stroke incidence among men and women (12–15). The benefits are apparent even for light-to-moderate activities, such as walking, with additional benefits to be gained from increasing the level and duration of activity (12,15).

The relationship between exercise and left ventricular structure is variable. Strenuous PA is known to affect LV structure, inducing hypertrophy and dilation as normal physiologic adaptations, the relative magnitude of which depends on the type and intensity of the exercise (16–19). Exercise of relatively low-to-moderate intensity and duration has been shown to decrease blood pressure (20) and possibly cause regression of LVM among hypertensive subjects (21). However, the effect of PA on the risk of ischemic stroke associated with increased LVM has not been extensively studied.

We, therefore, used a case-control study design to inves-
Physical Activity, LV Mass and the Risk of Stroke

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ABBREVIATIONS AND ACRONYMS

ADL = Activities of Daily Living
CI = confidence interval
IVS = interventricular septal thickness
LVDD = left ventricular diastolic dimension
LVM = left ventricular mass
METS = metabolic equivalents of the task
NOMASS = Northern Manhattan Stroke Study
OR = odds ratio
PA = physical activity
PWT = posterior wall thickness
QWB = Quality of Well Being

METHODS

Stroke patients and control subjects for the present report were obtained from the Northern Manhattan Stroke Study (NOMASS). NOMASS is a population-based study designed to determine stroke incidence, risk factors and prognosis in a multiethnic, urban population. Details of recruitment, study design and data collection have been previously described (15,22,23).

Study patients. Case subjects met the following criteria: 1) first ischemic stroke confirmed by head computed tomography or magnetic resonance imaging, 2) age > 39 years, and 3) residents of northern Manhattan for at least three months. Controls were eligible if they: 1) had never been diagnosed with a stroke, 2) were aged > 39 years, and 3) resided in northern Manhattan for at least three months. Control subjects were derived though random-digit dialing and matched to cases by age (within five years), race/ethnicity and gender.

Index evaluation of cases and control subjects. Subjects were interviewed by trained research assistants regarding sociodemographic characteristics, stroke risk factors and other medical conditions. Standardized questions were adapted from the Behavioral Risk Factor Surveillance System by the Centers for Disease Control and Prevention (24) regarding the following conditions: arterial hypertension, diabetes mellitus, hypercholesterolemia, transient ischemic attack, cigarette smoking and cardiac conditions such as myocardial infarction, coronary artery disease, angina, congestive heart failure and atrial fibrillation. Subjects also completed a comprehensive functional status assessment, which included Quality of Well Being (QWB) data items and the Barthel Activities of Daily Living (ADL).

Height and weight were determined by the use of calibrated scales. Hypertension was defined as a blood pressure recording ≥140/90 mm Hg (based on the average of two blood pressure measurements) or the patient’s self-report of a history of hypertension or antihypertensive medication use. Diabetes mellitus was defined by the patient’s self-report of such a history or use of insulin or hypoglycemic agent. Coronary artery disease was defined as a history of myocardial infarction or typical angina, the presence of a positive diagnostic test (stress test or coronary angiography) or drug treatment. The presence of atrial fibrillation had to be documented on a current or past electrocardiogram or Holter monitoring. Hypercholesterolemia was defined by a fasting total cholesterol >240 mg/dl or the patient’s self-report of such a history or use of lipid lowering therapy. For this analysis, smoking was defined as cigarette or cigar smoking at the time of the initial evaluation.

PA assessment. The measures of PA adopted in this study have been previously described (15). In brief, a questionnaire administered through a standardized in-person interview and adapted from the National Health Interview Survey of the National Center for Health Statistics (25) was used to measure recent recreational PA. The questionnaire records the frequency and duration of 14 different recreational activities during the two-week period before the interview. Activities were then grouped as light (<4.5 metabolic equivalents of the task [METS]), moderate (5 to 6 METS) and heavy (>6 METS). This survey form has been found to be reliable in evaluating elderly subjects (26).

Echocardiographic evaluation. Transthoracic echocardiography was performed within two to three days of stroke presentation for the cases and on the day of initial assessment for the controls. Hewlett-Packard Sonos 1000 and 2500 ultrasound equipment (Hewlett-Packard Division, Andover, Massachusetts) was used in all study subjects. Studies were performed and measurements taken according to the guidelines of the American Society of Echocardiography (27).

Left ventricular diastolic dimension (LVDD), interventricular septal thickness (IVS) and posterior wall thickness (PWT) were measured in all patients. Left ventricular mass was calculated with the use of the anatomically validated formula (28) (corrected American Society of Echocardiography method):

\[ 0.8 \cdot [1.04 \cdot (IVS + LVDD + PWT)^3 - LVDD^3] + 0.6 \]

Left ventricular mass was divided by body surface area to obtain the LVM index used in the data analysis.

The interpretation of the echocardiographic studies was blinded to case-control status and other clinical characteristics. Interobserver variability in our laboratory for the variables measured in the study is 8% to 10%.

Statistical analysis. Data are reported as mean ± SD for continuous variables and as frequency for categorical variables. Differences between mean values were assessed by unpaired Student t test. Differences between proportions were assessed by the chi-square test. A two-tailed p value of <0.05 was considered significant. One-way analysis of variance was used to compare LVM as a continuous variable across PA categories.

Left ventricular mass was divided into quartiles using...
cutoff points obtained from normal controls: women, quartile 1: ≤74 g/m², quartile 2: 75 to 90 g/m², quartile 3: 91 to 110 g/m², quartile 4: >110 g/m²; men, quartile 1: ≤77 g/m², quartile 2: 78 to 94 g/m², quartile 3: 95 to 117 g/m², quartile 4: >117 g/m².

Using the lowest quartile of LVM as the reference group, a sharp increase in risk of ischemic stroke was observed in the highest quartile. Thus, increased LVM was defined by the highest quartile of LVM and compared with the three lowest quartiles combined for categorical analyses. Unadjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated for the entire study group and for age and gender subgroups by univariate analysis. Variables significantly associated with ischemic stroke at univariate analysis (arterial hypertension, diabetes mellitus, coronary artery disease, hypercholesterolemia and atrial fibrillation) were entered as independent variables in the multivariate conditional logistic regression analysis. Cigarette smoking and body mass index were found not to be univariate cofactors significantly associated with stroke (p = 0.16 and p = 0.08, respectively) in this cohort. Multivariate conditional logistic regression analysis for was used to calculate the ORs and 95% CIs for LVM, PA and ischemic stroke after entering variables significantly associated with ischemic stroke at univariate analysis as potential confounding factors in the model. Adjusted analyses were performed in the overall group and stratified by age (<60 years and ≥60 years) and gender. Similar analyses were not performed by race/ethnic strata given the small number of subjects in some of our subgroups.

Given that 97% of cases and 98% of controls reporting any activity were in the light intensity activity category, an analysis by activity intensity could not be performed. Instead, to test for a dose-response relationship, PA was categorized by duration (none, >0 h/week to <5 h/week and ≥5 h/week). Interactions between any level of PA and LVM were assessed in the multivariate conditional logistic regression model.

SAS version 7.0 (SAS Institute Inc., Cary, North Carolina) was used for all analyses.

**RESULTS**

**Study population.** From July 1, 1993 to December 31, 1998, 394 case subjects with first ischemic stroke and 413 stroke-free control subjects were enrolled. The baseline clinical characteristics of the patients are shown in Table 1. This was a predominantly elderly cohort (76% of the entire cohort is age ≥60 years). Women constituted 54% of the total. Overall, there were 17% non-Hispanic whites, 28% non-Hispanic blacks and 55% Hispanics. There were no differences in height, waist circumference, weight or body surface area between cases and controls. Cases had a greater prevalence of hypertension, coronary artery disease, atrial fibrillation and diabetes mellitus.

**Distribution of PA.** The distribution of PA among our study subjects is shown in Table 2. During the two weeks before study enrollment, 47% of case subjects and 71% of control subjects reported some PA (adjusted OR: 0.30 [95% CI: 0.21 to 0.44]). The mean duration for any activity was 1.7 h/week ± 3.1 for cases and 3.4 h/week ± 4.5 for controls. As expected in this predominantly elderly sample, the predominant category of activity was of light intensity (97% of cases and 98% of controls). Among subjects who reported any PA, walking was the most frequently reported form of exercise.

**PA, LVM and the risk of stroke.** In the entire group, the risk of ischemic stroke increased as a function of LVM (Fig.
1). Because of the substantially greater increase in risk observed with the highest quartile of LVM, we evaluated whether PA modified the risk of stroke associated with increased LVM as defined by the highest quartile. Conditional logistic regression analysis demonstrated that the effect of increased LVM on the risk of stroke was signifi-

<table>
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<tr>
<th>Table 2. Type and Duration of Physical Activity*</th>
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<td></td>
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<tr>
<td>Never</td>
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<tr>
<td>Any activity</td>
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<tr>
<td>Light activity (3–4.5 METS)</td>
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<tr>
<td>Walking</td>
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<td>Dancing</td>
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<td>Calisthenics</td>
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<td>Golf</td>
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<td>Gardening</td>
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<td>Bowling</td>
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<tr>
<td>Moderate activity (5–6 METS)</td>
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<tr>
<td>Bicycle</td>
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<tr>
<td>Swimming</td>
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<tr>
<td>Heavy activity (&gt;6.5 METS)</td>
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<tr>
<td>Jogging</td>
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<td>Aerobics</td>
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*Some subjects reported participating in more than one activity.

METS = metabolic equivalents of the task.

Figure 1. Association between left ventricular (LV) mass and stroke. Left ventricular mass was categorized into quartiles. Adjusted and unadjusted odds ratios (OR) and 95% confidence intervals (CI) for stroke risk are shown. The lowest quartile is the reference group.
cantly attenuated by the presence of PA (Table 3). Increased LVM had a 3.5-fold greater effect on the risk of stroke among subjects who reported no PA. This increased risk of stroke was more than halved among the group who reported some level of PA.

In the unadjusted subgroup analysis (Table 3), the attenuation of the effect of increased LVM on stroke among subjects who were physically active was observed among all age and gender subgroups. In multivariate analysis, the protective effect of PA persisted across gender and age but was somewhat greater among men and subjects aged <60.

Using the no-exercise group as reference, in adjusted analysis we observed a dose-response relationship between duration of PA and decrease in stroke risk. Increased LVM was associated with the highest risk of stroke in the group with no PA (OR: 3.52 [95% CI: 1.94 to 6.42]). The effect of increased LVM on the risk of stroke progressively decreased with increasing PA duration (>0 to <5 h/week, OR: 1.61 [95% CI: 0.94 to 2.75] and ≥5 h/week, OR: 1.43 [95% CI: 0.58 to 3.49]). There was a significant decrease in mean LVM index with increasing duration of exercise (Table 4).

To further clarify the relationship between the presence of increased LVM and PA on the risk of stroke, we stratified cases and controls by these two variables (Table 5). Using subjects with neither increased LVM nor PA as the reference group, we estimated the adjusted ORs for stroke associated with some PA without increased LVM (OR: 0.40 [95% CI: 0.26 to 0.62]), increased LVM and some reported PA (OR: 0.66 [95% CI: 0.39 to 1.12]) and increased LVM without any reported PA (OR: 3.48 [95% CI: 1.92 to 6.33]). The OR for stroke in the group with increased LVM and PA was not significantly different from that observed in subjects without increased LVM, and some reported PA (p = 0.2).

The interaction between increased LVM and PA was tested using multivariate conditional logistic regression. In this model, after adjustment for other stroke risk factors, there was a significant interaction between PA and increased LVM on the risk of stroke with a beta coefficient of 0.45 (95% CI: 0.22 to 0.94; p = 0.033). Therefore, PA decreased the odds of stroke among patients with increased LVM by 55% more than among those without increased LVM.

To assess for other confounding factors that may have affected the level of PA in our study subjects, and especially for baseline health status, we compared the baseline functional assessments among those subjects with increased LVM and PA versus those with increased LVM and no PA. These two groups showed no baseline differences in the median prestroke or pre-enrollment Barthel ADL scores and the total QWB scores. During the baseline functional assessment, all subjects were asked whether their activity was limited by a medical disorder or medication effect. No significant difference in the response to this question was found in subjects with increased LVM and PA versus those with increased LVM and no PA.

**DISCUSSION**

Left ventricular mass is associated with coronary heart disease, congestive heart failure, stroke or transient ischemic attacks, all-cause mortality and sudden death (3–7). The reasons for the increased risk are not immediately clear. It is unknown if increased LVM has a direct role or is a marker for other underlying conditions. However, given the significant cardiovascular risks associated with increased LVM, methods to directly modify LVM have been proposed, mostly involving pharmacologic therapy (28). Increased LVM may be a marker of subclinical disease (29). Left ventricular mass has been shown to correlate with carotid wall thickness and luminal diameter (30,31) and to be predictive of carotid atherosclerosis (32). Increased LVM could represent a time-integrated indicator of the exposure

<table>
<thead>
<tr>
<th>Physical Activity</th>
<th>Odds Ratio (95% CI)</th>
<th>Physical Activity</th>
<th>Odds Ratio (95% CI)</th>
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<tbody>
<tr>
<td>Absent (n = 328)</td>
<td></td>
<td>Present (n = 472)</td>
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<tr>
<td>Total Cohort</td>
<td>4.67 (2.66–8.19)</td>
<td>2.08 (1.35–3.22)</td>
<td>3.53 (1.94–6.42)</td>
</tr>
<tr>
<td>Men</td>
<td>6.95 (2.73–17.74)</td>
<td>2.05 (1.11–3.78)</td>
<td>4.79 (1.78–12.92)</td>
</tr>
<tr>
<td>Women</td>
<td>3.59 (1.77–7.26)</td>
<td>2.12 (1.15–3.92)</td>
<td>2.90 (1.37–6.14)</td>
</tr>
<tr>
<td>Age</td>
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<tr>
<td>40–60 yrs</td>
<td>5.41 (2.03–14.44)</td>
<td>2.06 (0.81–5.25)</td>
<td>3.92 (1.39–11.07)</td>
</tr>
<tr>
<td>&gt;60 yrs</td>
<td>4.31 (2.24–8.31)</td>
<td>2.30 (1.38–3.83)</td>
<td>3.29 (1.64–6.59)</td>
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Cl = confidence interval.

| Table 4. Effect of PA on LVM by Duration of PA in the Entire Cohort |
|------------------------|---------------|---------------|---------------|
| Low PA                 | Moderate PA   | High PA       | p Value       |
| 0 h (n = 328)          | >0 to <5 h    | >5 h (n = 145)|               |
| Mean LVM (SD)          | 112.4 ± 36.1  | 104.2 ± 34.8  | 98.9 ± 33.5   | 0.0002        |

LVM = left ventricular mass; PA = physical activity.
to established risk factors (8,33) such as hypertension and diabetes, whose effect over time might result in significant cerebrovascular pathology, thus affecting the risk of stroke and cardiovascular disease.

Relationship of LVM, PA and stroke risk. Consistent with prior observations from the Framingham Heart study (4), our study confirms that LVM is a risk factor for stroke in a multiethnic population after adjustment for other stroke risk factors. This study, however, is the first ever to investigate the relationship of LVM and PA on the risk of stroke. In recent years, there has been accumulating evidence supporting the protective effects of light-to-moderate PA on stroke risk, independent of hypertension, lipid levels and other stroke risk factors among both men and women (13–15). Our findings suggest that the effect of increased LVM on the risk of stroke is modified by the presence of PA. A significant interaction was observed between increased LVM and PA. Increased LVM was associated with an increased risk of stroke, especially among sedentary patients, while PA decreased the risk of stroke among those with increased LVM to a level comparable to that of patients without increased LVM. Susceptibility to the effect of increased LVM on the risk of stroke was found to increase with decreasing duration of PA, and, conversely, additional protection from the effects of increased LVM was observed with increasing duration of exercise.

Potential mechanisms underlying the associations. The mechanism by which PA attenuates the risk of stroke associated with increased LVM is unclear. A proposed mechanism may involve LVM regression. Although we could not assess for LVM regression over time in our cross-sectional study, we did observe significantly lower LVM in subjects with PA versus those without it. However, because the beneficial effect of PA was greatest among subjects with documented increased LVM than among those without increased LVM, mass regression alone is likely insufficient to explain the results of this study. Also, it is not established if LVM regression is an independent predictor of improved prognosis. It is possible that PA decreases the stroke risk through its known beneficial effect on endothelial function (34,35). Physical activity has also been shown to lower blood pressure levels (20), increase insulin sensitivity (36) and favorably influence lipid profiles (37). It is also possible that these effects of PA on other established stroke risk factors may affect their interaction on the risk of stroke associated with increased LVM. The somewhat greater reduction in the stroke risk from increased LVM with the presence of PA observed among men and subjects aged <60 years old may be related to greater duration of PA performed by subjects in these subgroups.

Study limitations. Our design was an observational case-control study and not a prospective randomized trial. Therefore, causal inferences cannot be made. Our PA assessments were not designed to evaluate lifelong exercise practices, exercise patterns at younger ages, physical conditioning or direct quantitative estimations of energy expenditure. Physical activity was assessed during the preceding two weeks, which may or may not be a reliable indicator of more sustained PA patterns. Physical activity could be a marker of general good health. However, we performed several analyses to assess for differences in several indexes of quality of life, which may have affected the level of individual PA.

Among subjects with increased LVM, who were the ones who benefited most from PA, the frequency of activity limitations because of a medical condition or medication effect, the pre-enrollment or prestroke ADL score and the total QWB scores were all similar among those who were physically active and those who were not (p > 0.05). This observation reduces the likelihood that a better basal health status could be the underlying factor responsible for the decreased stroke risk observed in subjects with increased LVM and PA.

Physical activity was not classified according to intensity, but rather by duration, because almost all of the subjects were in the light intensity activity category, and the predominant activity in this category was walking. As an estimate of intensity, walking may expend between 2.5 to 12 METS (38). Given our predominantly elderly cohort, it is likely that walking was a leisure time PA with an estimated energy expenditure of 3 to 4.5 METS. However, this estimate of intensity may not be sensitive enough to establish if a relationship exists between intensity of exercise and a protective effect on the risk of stroke associated with increased LVM.

Conclusions. We demonstrated that an interaction exists between PA and increased LVM on the risk of ischemic stroke. Having increased LVM without PA conferred the greatest risk of ischemic stroke, whereas the presence of PA brought the stroke risk among those in the highest quartile of LVM down to the level of patients in the lowest quartile. This benefit was apparent for light intensity activities, such as walking, and a modest incremental benefit may be gained from increasing the duration of activity. Although the exact mechanism underlying the role of increased LVM in the pathogenesis of ischemic stroke is not clear, our study suggests that the stroke risk associated with increased LVM may be potentially modifiable by nonpharmacologic means such as PA.

It is recommended that every adult accumulate at least 30 min of PA on most, preferably all, days of the week (39). While PA can be considered a means of reducing the risk of stroke regardless of the presence of increased LVM, our data indicate a stronger influence on patients with increased LVM.
Acknowledgments
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REFERENCES

5. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relationship of left ventricular mass and geometry to morbidity and mortality in men and women with essential hypertension. Ann Intern Med 1991;114:345–55.
25. Kronmal RA, Smith VE, O’Leary DH, Polak JF, Gardin JM, Manolio TA. Carotid artery measures are strongly associated with left ventricular mass in older adults (a report from the Cardiovascular Heart Study). Am J Cardiol 1996;77:628–33.
36. Kronmal RA, Smith VE, O’Leary DH, Polak JF, Gardin JM, Manolio TA. Carotid artery measures are strongly associated with left ventricular mass in older adults (a report from the Cardiovascular Heart study). Am J Cardiol 1996;77:628–33.