Left Ventricular Systolic Dysfunction and the Risk of Ischemic Stroke in a Multiethnic Population

Allison G. Hays, MD; Ralph L. Sacco, MD; Tanja Rundek, MD; Robert R. Sciacca, EngScD; Zhezhen Jin, PhD; Rui Liu, MD; Shunichi Homma, MD; Marco R. Di Tullio, MD

Background and Purpose—Left ventricular dysfunction (LVD) is associated with cardiovascular mortality. Its association with ischemic stroke has been mainly documented after myocardial infarction. The stroke risk associated with LVD, especially of mild degree, in the general population is unclear. The purpose of this study was to evaluate the relationship between LVD and ischemic stroke in a multiethnic cohort.

Methods—LV systolic function was assessed by transthoracic 2-dimensional echocardiography in a subset of subjects from the Northern Manhattan Study (NOMAS), 270 patients with first ischemic stroke and 288 age-, gender- and race-matched community controls. LV ejection fraction was measured by a simplified cylinder-hemiellipsoid formula, and categorized as normal (>50%), mildly (41% to 50%), moderately (31% to 40%) or severely (≤30%) decreased. The association between impaired ejection fraction and ischemic stroke was evaluated by logistic regression analysis after adjustment for established stroke risk factors.

Results—LVD of any degree was more frequent in stroke patients (24.1%) than in controls (4.9%; P<0.0001), as was moderate/severe LVD (13.3% versus 2.4%; P<0.001). A decreased ejection fraction was associated with ischemic stroke even after adjusting for other stroke risk factors. The adjusted odds ratio for any degree of LVD was 3.92 (95% CI, 1.93 to 7.97). The adjusted odds ratio for mild LVD was 3.96 (95% CI, 1.56 to 10.01) and for moderate/severe LVD 3.88 (95% CI, 1.45 to 10.39). The association between LVD of any degree and stroke was present in all age, gender and race-ethnicity subgroups.

Conclusions—LVD, even of mild degree, is independently associated with an increased risk of ischemic stroke. The assessment of LV function should be considered in the assessment of the stroke risk. (Stroke. 2006;37:1715-1719.)

Key Words: cerebrovascular disorders ■ echocardiography ■ left ventricular function

Ischemic stroke is a major cause of morbidity and mortality in the United States with an annual incidence of 700,000 strokes per year. Congestive heart failure (CHF) is reported to affect about 4.5 million Americans, and is associated with a 2- to 3-fold increase in the relative risk of stroke. Several studies have shown that asymptomatic left ventricular (LV) systolic dysfunction is at least twice as common as overt CHF, may be a precursor to symptomatic heart failure, and is associated with increased mortality. An association between impaired LV ejection fraction (EF) and ischemic stroke has been shown mainly in patients surviving a myocardial infarction, and stroke incidence was not one of the primary end points. There have been no large studies that have investigated an association between LV systolic dysfunction and stroke in the general population. Therefore, it is not known if asymptomatic LV systolic dysfunction may represent an independent risk factor for stroke before progression to clinically overt CHF. Furthermore, little is known about the characterization of LV dysfunction among different race-ethnic groups.

The goal of the present case-control study was to assess the role of left ventricular dysfunction as an independent risk factor for ischemic stroke in the multiethnic population of the Northern Manhattan Study (NOMAS).

Materials and Methods

The patient population of the present study was a part of NOMAS, an epidemiological study that assessed the incidence, risk factors and clinical outcome of stroke in the multiethnic population of Northern Manhattan. Stroke cases were ascertained through prospective surveillance, which consisted of daily screening of all admissions, discharges, and head CT scan logs at New York Presbyterian Hospital, the only hospital in the community where ~80% of all patients in Northern Manhattan with stroke are hospitalized.

Community controls were eligible if they (1) had never been diagnosed with a stroke, (2) were over age 39, and (3) resided in New York, NY 10032. E-mail md42@columbia.edu

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From the Departments of Medicine (R.R.S., R.L., S.H., M.R.Di.T.), Neurology (R.L.S., T.R), Epidemiology and Public Health at the Sergievsky Center (R.L.S.), and Biostatistics (Z.J.), Columbia University Medical Center, New York, NY; and the Department of Medicine, New York University (A.G.H.), New York, NY.

This study was presented in part at the 2003 AHA Scientific Sessions, Orlando, FL.

Correspondence to Marco R. Di Tullio, MD, Professor of Clinical Medicine, Columbia University Medical Center, PH3-342, 622 West 168th Street, New York, NY 10032. E-mail md42@columbia.edu

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Northern Manhattan for at least 3 months in a household with a telephone (95% of all households in 1995). Stroke-free subjects were identified by random digit dialing using dual frame sampling to identify both published and unpublished telephone numbers. Ninety percent of contacted subjects agreed to be evaluated in person; 75% of them accepted to be enrolled in the study.

From January 1, 1994, through December 31, 1997, 1170 subjects (505 stroke patients, 665 control subjects) underwent transthoracic echocardiography as part of NOMAS. The present report is based on a subgroup of 558 subjects (270 patients with first time ischemic stroke and 288 age-, gender- and race/ethnicity-matched controls) in whom LVEF was semiquantitatively determined. The study was approved by the Institutional Review Board of Columbia University Medical Center.

**Diagnostic Evaluation**

Data were collected through interview of cases and controls, review of medical records, physical and neurological examination by study physicians, in-person measurements, and fasting blood specimen drawing. Cases were interviewed as soon as possible after their stroke with a median time of 4 days from onset. If a patient was unable to answer questions because of death, aphasia, coma, dementia, or other conditions, a proxy knowledgeable about the patient’s history was interviewed. Control subjects were interviewed in person and evaluated in the same manner as the stroke patients.

Routine laboratory tests included complete blood counts, coagulation studies, serum electrolytes, liver function tests, glucose and cholesterol determination. Arterial hypertension was defined as presence of a positive history or antihypertensive treatment, or blood-pressure values >140/90 mm Hg during the interview. Hypercholesterolemia was defined as a total serum cholesterol >240 mg/dL or presence of appropriate drug treatment. Diabetes mellitus was defined based on abnormal fasting glucose >125 mg/dL, positive history or presence of oral or insulin treatment. Coronary artery disease included history of myocardial infarction or typical angina or the patient’s reporting of a positive diagnostic test (stress test, coronary angiography) or drug treatment. Clinical CHF was diagnosed by history, clinical examination or medical treatment. Atrial fibrillation was classified by history (current or past ECG or Holter monitoring) and results of an ECG done at the time of enrollment. The neurological work-up 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. Cerebral angiography was performed when clinically indicated.

An infarct subtype diagnosis was determined by a neurologist. The criteria adopted in the classification of strokes by causal mechanism have been described in detail previously.11 Criteria for cardioembolic infarct included atrial fibrillation, bacterial endocarditis, myocardial infarction within the previous 6 weeks, intracranial thrombus, significant aortic or mitral valve disease, atrial myxoma, or pulmonary venous thrombosis.

**Echocardiographic Evaluation**

Transthoracic two-dimensional echocardiography was performed in all subjects, within 3 days from stroke onset in stroke patients, and on enrollment in control subjects. LVEF was measured by a simplified cylinder-hemiellipsoid formula proposed by Weyman12:

\[
LVEF = \frac{(EDD^2 - ESD^2) \times 100}{EED^3} + K
\]

where EDD indicates end-diastolic diameter; ESD, end-systolic diameter; and K is a given value of +10% for a normal apex, +5% for hypokinesis, 0 for akinesis, and −5% for dyskinesis.

LVEF was then categorized as normal (>50%), mildly (41% to 50%), moderately (31% to 40%) or severely (≤30%) decreased. Values calculated with this formula correlated well with the estimation of LVEF using Simpson disk summation method in 25 randomly selected patients with a wide range of ejection fraction values (r=0.88; regression equation y=1.06x−1.3, s=2.9, P<0.0001, and did not differ significantly from the line of identity).

LV mass was calculated from the corrected American Society of Echocardiography method11:

\[
LV mass = 0.8 \times \left[1.04(\frac{LVDD + IVS + PWT}{3} - LVDD)\right] + 0.6
\]

where LVDD indicates LV diastolic diameter; IVS, interventricular septum thickness; PWT, posterior wall thickness. LV mass was then corrected by body surface area to obtain the LV mass index to be used in the multivariate analyses.

**Statistical Analysis**

Data are presented as mean values ±1 SD for continuous variables, and as proportions for categorical variables. Odds ratios (OR) for left ventricular dysfunction (LVD) and stroke were calculated by logistic regression analysis after adjustment for other stroke risk factors (hypertension, diabetes, hypercholesterolemia, cigarette smoking, atrial fibrillation, coronary artery disease, CHF, and LV mass index). To test the effect of age (≥ versus <70 years), gender and race/ethnicity on the association between LVD and stroke, separate variables were fit in the model to quantify the effect of LVD independently for each subgroup. Differences between subgroups were tested using interaction terms. Adjusted OR and 95% CI were calculated from the β coefficients and the standard errors. A probability value <0.05 was considered significant for all analyses.

**Results**

**Patient Characteristics**

The characteristics of stroke patients and controls are shown in Table 1. Thirty-two percent of the population was black, 48% was Hispanic and 18% white. Distribution of stroke risk factors is reported in Table 1. Atrial fibrillation was significantly more frequent in stroke patients than in controls among whites (17.4% versus 1.8%; P=0.006) and Hispanics (9.9% versus 2.9%; P=0.02), but not blacks (8.1% versus 2.2%; P=0.08); arterial hypertension was significantly more frequent in stroke patients than in controls among Hispanics (84.2% versus 68.4%; P=0.002) but not whites (63.0% versus 60.7%; P=0.8) or blacks (77.0% versus 68.1%; P=0.2); cigarette smoking was significantly more frequent in stroke patients than in controls among blacks (38.8% versus 17.0% P=0.0001).

| TABLE 1. Demographics and Risk Factors of the Study Group |
|-----------------|-----------------|-------------|
|                  | Stroke Patients | Control Subjects | P Value |
| Age, mean±SD     | 70±12           | 69±11         |          |
| Race             |                 |               |          |
| Black            | 87 (32%)        | 93 (32%)      |          |
| Hispanic         | 133 (49%)       | 136 (47%)     |          |
| White            | 46 (17%)        | 56 (19%)      |          |
| Gender           |                 |               |          |
| Female           | 150 (56%)       | 165 (57%)     |          |
| Male             | 120 (44%)       | 123 (43%)     |          |
| Risk factors     |                 |               |          |
| Hypertension     | 210 (78%)       | 191 (66%)     | 0.003     |
| Hypercholesterolemia | 101 (38%)     | 128 (44%)     | 0.11      |
| Coronary artery disease | 83 (31%)     | 63 (22%)     | 0.02      |
| Atrial fibrillation | 28 (10%)      | 8 (3%)        | <0.001    |
| Diabetes         | 125 (46%)       | 65 (23%)      | <0.001    |
| Ever smoked      | 155 (58%)       | 151 (52%)     | 0.20      |
| Current smoker   | 60 (23%)        | 47 (17%)      | 0.06      |
22.8%; P=0.02), but not whites (9.3% versus 13%; P=0.6) or Hispanics (17.7% versus 14.7%; P=0.5). Diabetes mellitus was significantly more frequent in stroke patients than in controls among all 3 race-ethnic groups (white: 39.1% versus 14.3%, P=0.004; black: 42.5% versus 23.1%, P=0.006; Hispanic: 50.8% versus 24.3%, P=0.0001).

Sixteen percent of strokes were considered to be atherosclerotic or atheroembolic, 20% cardioembolic, 21% small-vessel lacunar, and 3% from other causes. The remaining 40% of strokes were considered cryptogenic.

LVD and Risk of Ischemic Stroke
LVD of any degree was more frequent in stroke patients (24.1%) than in controls (4.9%; P=0.0001), as were moderate/severe LVD (13.3% versus 2.4%; P=0.001) and mild LVD (10.7% versus 2.4%; P=0.001; Table 2). LVD was associated with ischemic stroke both at univariate analysis and after adjusting for other stroke risk factors. Adjusted OR for stroke in the overall group were 3.92 for LVD of any degree (95% CI, 1.93 to 7.97) and 3.88 for moderate/severe LVD (95% CI, 1.45 to 10.39). Mild LVD was also independently associated with ischemic stroke, with OR of 3.96 (95% CI, 1.56 to 10.01). Among stroke patients, LVD was strongly related to the embolic subtype in comparison with other stroke subtypes combined (OR=7.98, 95% CI, 4.13 to 15.40).

Effect of Age, Gender and Race-Ethnicity
A significant association was observed between LVD and stroke in both men and women. Adjusted OR for LVD of any degree and stroke were 5.53 (95% CI, 1.51 to 20.35) in women and 4.52 (95% CI, 1.45 to 14.14) in men (Table 3). The effect of LVD on stroke risk was not significantly different between genders (P=0.65).

LVD of any degree was significantly associated with ischemic stroke in both subjects younger and older than 70 years (Table 3). In patients under 70, adjusted OR for LVD and stroke was 3.17 (95% CI, 1.21 to 8.29), whereas in older patients OR was 4.83 (95% CI, 1.81 to 12.92; Table 3). There was no significant difference between the 2 age subgroups (P=0.57).

An association between any degree of LVD and stroke was observed in all 3 race-ethnic subgroups (Table 3).

In the multivariate subgroup analyses, moderate/severe LVD was independently associated with ischemic stroke in men and in subjects older than 70 years. Independent significance was not achieved for any race-ethnic subgroup, probably because of the smaller sample size.

Stroke Subtype, LV Function and Stroke Severity
National Institutes of Health Stroke Scale (NIHSS) score 0 to 5 was present in 53.7% of patients, 6 to 13 in 32.5%, and 14 in 13.8%. Scores ≥6 were significantly more frequent in patients with embolic stroke than in other subtypes combined (66.0% versus 41.6%; P=0.001) and in patients with any degree of LVD than in those with normal LV function (63.1% versus 40.9%; P=0.001).

Discussion
LVD and Ischemic Stroke
The present study suggests that decreased LV function is associated with an increased risk of stroke in the community after adjusting for established stroke risk factors.

### TABLE 2. LV Function in Stroke Patients and Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>Stroke Patients, n (%)</th>
<th>Control Subjects, n (%)</th>
<th>Unadjusted OR (CI)*</th>
<th>Adjusted OR † (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal LV function</td>
<td>205 (75.9)</td>
<td>274 (95.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV dysfunction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any degree</td>
<td>65 (24.1)</td>
<td>14 (4.9)</td>
<td>6.21 (3.39–11.37)</td>
<td>3.92 (1.93–7.97)</td>
</tr>
<tr>
<td>Mild</td>
<td>29 (10.7)</td>
<td>7 (2.4)</td>
<td>5.54 (2.38–12.89)</td>
<td>3.96 (1.56–10.0)</td>
</tr>
<tr>
<td>Moderate/severe</td>
<td>36 (13.3)</td>
<td>7 (2.4)</td>
<td>6.87 (3.00–15.75)</td>
<td>3.88 (1.45–10.39)</td>
</tr>
</tbody>
</table>

*95% CI; †adjusted for age, gender, atrial fibrillation, diabetes mellitus, arterial hypertension, hypercholesterolemia, current smoking, coronary artery disease, clinical CHF, and LV mass index.

### TABLE 3. Association Between LVD and Ischemic Stroke by Gender, Age, and Race-Ethnicity

<table>
<thead>
<tr>
<th></th>
<th>LVD Any Degree</th>
<th>Moderate/Severe LVD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted OR (CI)*</td>
<td>Unadjusted OR (CI)†</td>
</tr>
<tr>
<td>Male</td>
<td>5.48 (2.66–11.31)</td>
<td>8.26 (2.75–24.81)</td>
</tr>
<tr>
<td>Female</td>
<td>9.78 (2.87–33.30)</td>
<td>5.53 (1.54–19.82)</td>
</tr>
<tr>
<td>Age &lt;70</td>
<td>4.68 (2.05–10.67)</td>
<td>4.52 (1.45–14.14)</td>
</tr>
<tr>
<td>Age ≥70</td>
<td>8.29 (3.37–20.42)</td>
<td>10.14 (2.96–34.78)</td>
</tr>
<tr>
<td>Blacks</td>
<td>6.76 (1.90–24.12)</td>
<td>5.07 (1.04–24.63)</td>
</tr>
<tr>
<td>Hispanics</td>
<td>3.99 (1.87–8.51)</td>
<td>5.61 (1.84–17.11)</td>
</tr>
<tr>
<td>Whites</td>
<td>29.32 (3.71–231.90)</td>
<td>18.33 (2.24–150.22)</td>
</tr>
</tbody>
</table>

*95% CI; †adjustments as in Table 2.
importantly, the association with increased stroke risk was observed across a wide range of LVD severity, and was strong for dysfunction of mild degree as for dysfunction of moderate or severe degree. This observation seems to contradict the common belief that stroke risk parallels the severity of LVD, and indicates that a significantly increased risk of stroke should be considered to be present even in the much larger fraction of patients with mildly decreased LVEF.

The association between decreased LVEF and risk of ischemic stroke has been mainly studied as a secondary finding in studies conducted in patients surviving a myocardial infarction. A retrospective analysis from the Study of Left Ventricular Dysfunction (SOLVD) found an increased risk of thromboembolic events associated with low LVEF, particularly with severely decreased LVEF, but only in women. Stroke and transient ischemic attack were not primary end points in the study. In the Survival And Ventricular Enlargement trial, every decrease of 5 percentage points in LVEF was associated with an 18% increase in stroke risk in the first 5 years after myocardial infarction. Patients with LVEF of 28% or less had a relative risk of death. Our finding of an increased risk of stroke even for mildly decreased LVEF of stroke rather than consider stroke as a collateral event of a study to assess cardiac risk, and the number of stroke patients included is therefore among the largest of any studies of this type.

One limitation is the case-control design. Differences might exist between cases and controls that were not accounted for in the analysis. To minimize selection bias, cases and controls were matched according to age, race, and sex, and all were from the same geographic location and socioeconomic background. Our study included subjects over the age of 39; therefore, the association between LVD and stroke in younger subjects is not addressed. However, stroke is exceedingly rare in the young. Although no upper age limit for enrollment was used, our stroke population may be slightly younger than expected, possibly reflecting an underrepresentation of very old patients or a younger age at stroke of black and Hispanic subjects, who comprised most of our cohort. There was an insufficient number of subjects to detect interracial differences in stroke risk in patients with moderately to severely reduced LVEF.

Lastly, a limitation might relate to the method used for determining LVEF. The simplified cylinder hemiellipsoid method used is difficult to apply when technical quality of the echocardiogram is poor, or when the LV is geometrically distorted, and regional wall motion abnormalities are present. These limitations, however, apply to virtually any echographic method to determine LVEF. The method used correlated well with the widely used Simpson’s method. Moreover, our results suggest a strong association between stroke and LVD of any degree rather than define specific cutoff points of increased risk, which could be more susceptible to technical differences. The categorization of LVEF we used could be valuable as a screening tool for a quick assessment of the stroke risk in subjects undergoing an echocardiogram.

Implications
The association between LVD of any degree and stroke risk has clinical implications. LVD after a myocardial infarction correlates with a poor long-term prognosis. Pharmacological agents such as angiotensin-converting enzyme inhibitors or β blockers have been shown to result in improved LVEF post-myocardial infarction over time. Further studies are required to assess the possibility that drug treatment may decrease the risk of stroke associated with LV systolic dysfunction.

LVD and Stroke in Age, Gender and Race-Ethnic Subgroups
An association between LVD of any degree and ischemic stroke was detected in all subgroups of gender, age and race-ethnicity. An association was seen among whites, blacks and Hispanics, despite the considerable inter-racial differences observed in the frequency of traditional stroke risk factors. This consistency of the effect of LVD on stroke risk further reinforces the concept of an independent role of LVD on the risk of ischemic stroke.

Strengths and Limitations
This study demonstrates a relationship between LVD and stroke in a multiethnic population. The parent study (NOMAS) was specifically designed to assess risk factors for ischemic stroke rather than considering stroke as a collateral event of a study to assess cardiac risk, and the number of stroke patients included is therefore among the largest of any studies of this type.

Race-Ethnic Subgroups
Asymptomatic LVD, most often of mild degree, is present in a considerable portion of the general population (3% to 6%). and carries a >4-fold increase in risk of developing overt CHF and a 60% increase in risk of death. Our finding of an increased risk of stroke even for mild impairment in LV systolic function suggests that this underdiagnosed condition should be taken into consideration when assessing the individual stroke risk.

The mechanism underlying the association between LVD and stroke is not immediately clear. One possibility is that LVD promotes increased blood stasis in both the LV and left atrium, increasing the chance of thrombus formation and the risk of embolic stroke. In our study, a decreased LVEF was in fact more strongly associated with embolic stroke subtype than with other subtypes, suggesting an embolic mechanism as a possible link between LVD and stroke risk. Embolic strokes and LVD also shared a greater stroke severity as assessed by NIHSS. However, transient arrhythmias, and especially atrial fibrillation, could also be involved in the stroke mechanism. Alternatively, LVD could be a marker for severe and diffuse vascular abnormalities, possibly involving the cerebral vessels. Finally, acute stroke per se may be associated with transient LVD, which would therefore follow the stroke rather than precede it. A negative effect on LVEF, however, appears to be much less frequent for ischemic stroke than for intracranial hemorrhage.

Race-Ethnic Subgroups
The association between LVD of any degree and stroke risk has clinical implications. LVD after a myocardial infarction correlates with a poor long-term prognosis. Pharmacological agents such as angiotensin-converting enzyme inhibitors or β blockers have been shown to result in improved LVEF post-myocardial infarction over time. Further studies are required to assess the possibility that drug treatment may decrease the risk of stroke associated with LV systolic dysfunction.
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Disclosures
None.

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