Left Ventricular Mass Indexed to Height and Prevalent MRI Cerebrovascular Disease in an African American Cohort

The Atherosclerotic Risk in Communities Study

Ervin R. Fox, MD, MPH; Herman A. Taylor Jr, MD, MPH; Emelia J. Benjamin, MD, ScM; Jingzhong Ding, PhD; Philip R. Liebson, MD; Donna Arnett, PhD; Ernest M. Quin, MD; Thomas N. Skelton, MD

Background and Purpose—Previous studies have demonstrated that echocardiographic left ventricular mass (LVM) is an independent risk factor for stroke in whites. Despite the greater burden of stroke, the echocardiographic predictors of stroke in African Americans remain poorly understood.

Methods—This investigation is a retrospective analysis of prospectively collected data from the Jackson, Miss (all African American), cohort of the Atherosclerotic Risk in the Communities study. Between 1993 and 1995, 2445 participants received an echocardiogram, and a random subset (n=778) received cerebral MRI evaluating presence of infarcts or white matter disease (WMD; 3 on a scale of 0 to 9). Compared with the entire Jackson cohort, the random subset was older, had a lower body mass index (BMI), and a higher systolic blood pressure (SBP). Logistic regression models examined the relations of LVM indexed by height (LVM/height) to MRI findings adjusted for age, gender, BMI, SBP, hypertensive medications, diabetes, total/high-density lipoprotein cholesterol, smoking status, and history of myocardial infarction.

Results—The 667 participants (63% women; 62±4 years of age) had a high prevalence of hypertension (68%), obesity (46%), echocardiographic left ventricular hypertrophy (49%), MRI stroke (n=133), and WMD (n=92). Adjusted LVM/height was significantly associated with prevalent MRI stroke (odds ratio [OR], 1.3; 95% CI, 1.1 to 1.7; P=0.02) and WMD (OR, 1.5; 95% CI, 1.1 to 1.9; P=0.006; OR expressed per 1 SD LVM/height, 45 g/m).

Conclusion—In this randomized subset of a population-based cohort of African American adults, LVM/height was related to MRI evidence of prevalent cerebrovascular disease. The current study supports the hypothesis that LVM/height is an important risk factor for stroke in multiple ethnicities.

Key Words: African American • cerebrovascular disorders • echocardiography • magnetic resonance imaging

Stroke is the third leading cause of death in the United States. African Americans compared with whites have approximately twice the incidence of strokes and nearly twice the mortality from strokes. Data suggest that racial disparities in incidence may be increasing.1 Given the striking racial disparities in incidence and lethality, it is important to determine the risk factors for stroke.

In predominantly white cohorts, echocardiographic left ventricular mass (LVM), left atrial enlargement, and cardiac calcification have been demonstrated to be risk factors for stroke.2–5 The echocardiographic risk factors for stroke in African Americans in the community have not been investigated extensively.1,6–9 Our objective was to describe the echocardiographic correlates of MRI abnormalities (stroke and white matter disease [WMD]) in an African American cohort. The Jackson site of the Atherosclerotic Risk in Communities (ARIC) study provided a unique opportunity to explore the relationships between LVM indexed by height (LVM/height) and MRI abnormalities.

Study Design and Population

This is a retrospective analysis of prospectively collected data from the Jackson, Miss (all African Americans), cohort of the ARIC study. The ARIC study is a prospective population-based investigation of the predictors and outcomes of atherosclerosis. Equal proportions of participants were recruited from 4 US communities (Jackson, Miss; Forsyth County, NC; Washington County, Md; and the northwestern
suburbs of Minneapolis, Minn) between 1987 and 1989. Echocardiograms were performed only in the Jackson cohort and were obtained during the third examination between 1993 and 1995 (n=2445).

During the 1993 and 1994 ARIC study clinical examinations, all cohort members aged ≥55 years at the Jackson, Miss, site and the Forsyth County, NC, site were screened for eligibility for the cerebral MRI examination. After exclusion of ∼4% of participants who were ineligible for the MRI examination (mostly people in occupations with exposure to metal fragments) and 23% of participants who were ineligible for the MRI examination (mostly people in occupations with exposure to metal fragments) and 23% of participants who declined the MRI examination, 1935 participants underwent a cerebral MRI examination. For this study, Jackson, Miss, participants were further excluded for either mitral stenosis or prosthetic mitral or aortic valves (n=5) or LVM/height that could not be calculated (n=106). After exclusion criteria, MRIs were performed on 778 (32%) of the Jackson cohort participants who had also received transthoracic echocardiograms.

This subgroup is considered a random sample of the full cohort in the Jackson study site because examination dates were allocated at baseline through randomly selected induction cycles. Re-examination visits were scheduled according to the anniversary date to the degree possible.

This study was approved by the institutional review board of the University of Mississippi Medical Center, and subjects gave written informed consent. The procedures followed were in accordance with institutional guidelines.

Echocardiography
Participants were examined with 2D and Doppler echocardiography on an Acuson 128XP/10c using 2.5-, 3.5-, and 5.0-MHz transducers. Two-dimensional echocardiography measurements were made using the American Society of Echocardiography (ASE) convention, with 5 separate measurements averaged. LVM was calculated according to the ASE simplified cubed equation. LVM/height normalized heart size to body size. Left ventricular hypertrophy (LVH) was defined as a LVM/height ≥163 g/m for men and as an LVM/height ≥121 g/m for women.

Clinical Covariates
Obesity was defined as a body mass index (BMI) ≥30 kg/m². Hypertension was defined as a systolic blood pressure (SBP) ≥140 mm Hg, a diastolic blood pressure ≥90 mm Hg, or a reported use of hypertension medication within the 2 weeks before the visit. Diabetes was defined as a fasting serum glucose ≥126 mg/dL, random glucose ≥200 mg/dL, history of physician diagnosis of diabetes, or use of insulin or oral hypoglycemic agent. Participants diagnosed with a myocardial infarction (MI) included those with prevalent MI at the baseline examination and those with incident MI between the baseline examination and the time of the echocardiogram. Incident MI was defined as a definite or probable MI at follow-up, using a committee-approved algorithm that implements a combination of hospital records, enzyme status, and ECG diagnosis.

Outcomes
Participants age ≥55 years seen in the first 2 years of the third examination cycle were eligible for cerebral MRI examinations. Details of the MRI recruitment, exclusion criteria, protocol, and scan interpretation have been described previously. Stroke was considered present on MRI if findings consistent with large vessel cerebral infarction or small vessel lacunar infarction were visualized. White matter lesions were graded on a scale of 0 to 9 using visual pattern matching to reference standards as detailed previously. WMD was considered present with a score ≥3.

Statistical Analysis
The randomly selected group was compared with those in the Jackson cohort who were not selected with a t test for continuous variables and a χ² test for categorical variables, respectively. Descriptive data were reported by sex-specific quartiles of LVM/height and expressed as mean value ± SD. P values for the linear trend were derived from logistic regression models with sex, hypertensive medications, diabetes, and MI as dependent variables and from linear regression models with age, BMI, SBP, and total/high-density lipoprotein (HDL) cholesterol as dependent variables.

Then, 2 separate logistic regression models were also used to examine the relations of LVM/height as a continuous independent variable to 2 dichotomous dependent variables (MRI stroke and WMD), respectively. Models were adjusted for age and sex. The fully adjusted model further included BMI, SBP, hypertension medication, total/HDL cholesterol, diabetes, and MI. Finally, logistic regression models were also used to examine the odds of MRI stroke and WMD according to sex-specific quartiles of LVM/height. Dummy variables were used for quartiles of LVM/height in the analysis.

Results
The 667 study participants had a mean age of 62±4 years (range 54 to 74 years), and 63% were women. Compared with those in the Jackson cohort who were not selected, participants in the random selected group were older (mean age 62 versus 57 years; P<0.0001), had a lower mean BMI (29 versus 30 kg/m²; P<0.0001), and a higher mean SBP (141 versus 138 mm Hg; P=0.02). There was no difference with regard to gender, smoking status, use of hypertensive medications, diabetes, history of MI, mean LVM/height, and mean total and HDL cholesterol. It should be noted that study participants had a high prevalence of cardiovascular risk factors: 68% were hypertensive, and 46% were obese. The prevalence of echocardiographic LVH was high: 46%. The

| TABLE 1. Characteristic of Study Sample by Sex-Specific Quartiles of LVM/Height |
|---------------------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
|                                | Q1               | Q2               | Q3               | Q4               | P for Trend       |
| Male LVM/height, g/m           | 61.8–124.6       | 124.7–141.2      | 142.3–177.2      | 177.4–392.9      |                   |
| Female LVM/height, g/m         | 44.0–110.0       | 110.4–128.7      | 128.8–158.1      | 158.3–311.0      |                   |
| Age, y                         | 62               | 63               | 62               | 62               | 0.68              |
| BMI, kg/m²                     | 27.0             | 29.1             | 30.4             | 31.7             | <0.0001           |
| SBP, mm Hg                     | 134              | 138              | 145              | 148              | <0.0001           |
| Total/HDL cholesterol, mg/dL   | 212/59           | 210/57           | 207/55           | 205/55           | 0.07/0.04         |
| Diabetes, %                    | 12%              | 22%              | 20%              | 29%              | 0.0007            |
| MI, %                          | 2%               | 2%               | 4%               | 9%               | 0.002             |

Characteristics are defined at baseline examination (see Methods). Q1 indicates first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile.
mean LVM/height for men was 156±48 gm/m, and for women, it was 137±40 gm/m. Characteristics of the study sample by sex-specific quartiles of LVM/height are shown in Table 1. With increasing quartile of LVM/height, the mean age of the participants and the mean HDL/total cholesterol remained unchanged, but the mean BMI and SBP increased. Additionally, the percentage with diabetes and MI was higher for higher quartiles of LVM/height.

Although only 18 individuals (2.7%) had a clinical history of stroke, 133 (19.9%) had MRI evidence of stroke, and 92 (14.1%) had MRI WMD. After adjusting for age and sex, increasing LVM/height was associated with an increased MRI risk in stroke (odds ratio [OR] per 45 g/m, 1.3; 95% CI, 1.0 to 1.5) and an increased risk of WMD (OR per 45 g/m, 1.7; 95% CI, 1.3 to 2.1). Adjusting for other potential confounders (BMI, SBP, hypertension medication, total/HDL cholesterol, diabetes, smoking, and MI), LVM/height remained significantly associated with stroke and WMD: the ORs for MRI stroke and WMD were 1.3 (95% CI, 1.1 to 1.7; \( P=0.02 \)) and 1.5 (95% CI, 1.1 to 1.9; \( P=0.006 \)), respectively. The association was not statistically different in men and women (ie, \( P \) value > 0.05 for interaction term for LVM/height and gender). For the regression model, the Hosmer and Lemeshow Goodness-of-Fit were satisfied (\( P=0.9 \) for MRI stroke and \( P=0.3 \) for WMD).

As displayed in Table 2, increasing sex-specific quartile of LVM/height was significantly associated with MRI stroke and marginally associated with MRI WMD.

### Discussion

#### Stroke in the ARIC Study Cohort

Stroke is one of the leading causes of morbidity and mortality in older populations, and African Americans have higher rates of stroke than their white counterparts. Given the health implications of cerebrovascular disease (CVD), the search for factors that are reliable early predictors of risk is crucial, particularly in populations in which prevalence is increased. Silent stroke has been shown to be an early form of ischemic CVD in African Americans and white \(^{6,15-19}\); LVH has been closely associated with CVD in white cohorts. \(^{3,6,20}\) The present study demonstrates that LVM/height is independently associated with prevalent MRI stroke and WMD in African Americans, confirming the relationship found in other ethnic groups.

In this African American cohort, there was a high prevalence of CVD and an even higher prevalence of risk factors for atherosclerotic diseases such as hypertension and obesity. The prevalence of atherosclerotic risk factors in ARIC study is somewhat higher than that seen in the non-Hispanic white Framingham Heart Study (FHS) cohort.\(^{17}\)

The majority of strokes and white matter changes noted on MRI were clinically unrecognized. FHS investigators found a 10% prevalence rate of silent stroke among 5184 men and women presenting initially with acute stroke.\(^{17}\) Similar prevalence rates have been reported from the non–population-based National Institutes of Neurological and Communicative Disorders and Stroke Data Bank Study (NINCDS) of patients with acute stroke.\(^{21}\) The relatively high prevalence of silent stroke in the ARIC study cohort (17%) appears to be similar to but somewhat greater than that seen in FHS.

The importance of these silent strokes is underlined by investigations such as the Cardiovascular Health Study (CHS), in which the presence of silent cerebral infarcts on MRI was an independent predictor of symptomatic stroke over a 4-year follow-up in individuals without a clinical history.\(^{4}\) Incidence of stroke was 18.7 per 1000 person years (\( \approx 1.8\% / \) year) in those with silent infarcts compared with 9.5 per 1000 person years in the absence of silent infarcts. This stroke rate was similar to another prospective study of participants with silent infarcts, in which the annual incident stroke rate was 2.8%.\(^{18}\) CHS investigators also found that brain infarction without a clinical history of stroke is strongly associated with impaired cognition and neurological deficits, suggesting that these strokes may not be truly silent or innocuous.\(^{6,22}\)

#### WMD in the ARIC Study Cohort

The pathogenesis of WMD has been linked to cerebral hypoperfusion and atherosclerotic risk factors.\(^{19,23-25}\) In earlier studies, ARIC study investigators found that hypertension is associated with increased odds of WMD, and treated uncontrolled hypertensive participants had greater odds of...
Mechanism Linking LVM With CVD

A number of theories regarding the pathogenesis of the association between LVM and CVD have been proposed; however, the true mechanism(s) remain unclear. It has been hypothesized that LVH and CVD are the result of shared risk factors that predispose to their development. The most important of these appears to be arterial hypertension. The brain and heart are targets for hypertension-induced injury.3,20,26 Similar to CVD, several other atherosclerotic risk factors beyond hypertension have been shown in various populations (FHS, ARIC study, Treatment of Mild Hypertension Study [TOMHS], and CHS) to be significantly associated with LVM.27–30 For example, in FHS, investigators found in a multivariate analysis that age, obesity, and MI are independently associated with echocardiographically determined LVM in both sexes.30

Another explanation linking stroke and LVM/height is that LVM index may predispose to stroke through its association with types of structural heart disease that are known to be related to cerebral embolic events (eg, left atrial enlargement and atrial fibrillation).29 However, contrary to this theory, FHS investigators found that LVM/height remained significantly associated with stroke even after excluding participants with atrial fibrillation and after adjusting for left atrial size in a multivariate model.3

It may be that the relationship between LVM and CVD is more intricate than either of the aforementioned theories. It is postulated that the relationship between LVH and CVD may derive from the impact of atherosclerotic disease on vascular stiffness.31,32 Increased vascular stiffness is thought by proponents of this theory to induce LVM when poorly compliant vessels reflect pressure waves back toward the central circulation, resulting in a late systolic rise in central arterial pressure. This increase in central arterial pressure is thought to occur without necessarily increasing peripheral (measured) SBP; this is supported by the fact that carotid disease has been found to parallel LVM after adjusting for conventionally measured blood pressure.33 Finally, some have speculated that growth factors or genetic influences may also affect LVM through unclear mechanisms, thereby linking CVD with LVM.

Our study has several strengths, including the population-based cohort of African Americans, the standardized measurements of echocardiograms, brain MRI, and clinical covariates, and the careful quality control protocols and blinded assessments of the noninvasive testing. Nevertheless, we must acknowledge several limitations: the cross-sectional nature of the study design precludes firm conclusions about causality and introducing survivor bias; the relatively small sample size, constraining our ability to examine effect modification in subgroups, such as by gender; the narrow distribution of the age sampled, preventing our ability to analyze the generalizability of our findings to individuals >74 years of age; and unavailable information on heart failure and atrial fibrillation, which could have potentially confounded the association.

Conclusion

In the first study of a population-based cohort of African American adults to assess echocardiographic associations with MRI findings, LVM/height was related to MRI evidence of prevalent stroke and WMD. The current study lends support to the hypothesis that LVM/height is an important risk factor for stroke in multiple ethnicities. This may have important prognostic value as well because there are several lines of evidence showing that asymptomatic brain injury is an independent risk factor for future stroke. Knowing that antihypertensive therapies have proven to regress LVH,34 an intriguing question is whether regression of LVH would lead to a decrease in cerebrovascular risk beyond that attributed to the simultaneous decrease in blood pressure readings. With the advent of the very large echocardiographic database of African Americans provided by the Jackson Heart Study, future investigations can focus on whether LVH/height predicts incident stroke in this community and whether regression of LVH can significantly lower that risk.

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