Relation of Left Ventricular Mass at Age 23 to 35 Years to Global Left Ventricular Systolic Function 20 Years Later (from the Coronary Artery Risk Development in Young Adults Study)

Satoru Kishi, MD[a], Anderson C. Armstrong, MD[a], Samuel S. Gidding, MD[b], David R. Jacobs, Jr., PhD[c], Stephen Sidney, MD, MPH[d], Cora E. Lewis, MD, MSPH[e], Pamela J. Schreiner, PhD[c], Kiang Liu, PhD[f], and João A.C. Lima, MD[a,*]

Left ventricular (LV) mass and the LV ejection fraction (LVEF) are major independent predictors of future cardiovascular disease. The association of LV mass with the future LVEF in younger populations has not been studied. The aim of this study was to investigate the relation of LV mass index (LVMI) at ages 23 to 35 years to LV function after 20 years of follow-up in the Coronary Artery Risk Development in Young Adults (CARDIA) study. CARDIA is a longitudinal study that enrolled young adults in 1985 and 1986. In this study, participants with echocardiographic examinations at years 5 and 25 were included. LVMI and the LVEF were assessed using M-mode echocardiography at year 5 and using M-mode and 2-dimensional imaging at year 25. Statistical analytic models assessed the correlation between LVMI and LV functional parameters cross-sectionally and longitudinally. A total of 2,339 participants were included. The mean LVEF at year 25 was 62%. Although there was no cross-sectional correlation between LVMI and the LVEF at year 5, there was a small but statistically significant negative correlation between LVMI at year 5 and the LVEF 20 years later ($r = -0.10$, $p < 0.0001$); this inverse association persisted for LVMI in the multivariate model. High LVMI was an independent predictor of systolic dysfunction (LVEF <50%) 20 years later (odds ratio 1.46, $p = 0.0018$). In conclusion, LVMI in young adulthood in association with chronic risk exposure affects systolic function in middle age; the antecedents of heart failure may occur at younger ages than previously thought. **(Am J Cardiol 2014;113:377−383)**

Left ventricular (LV) mass and the LV ejection fraction (LVEF) are major independent predictors of future cardiovascular disease.[1−3] Quantification of LV function and geometry provides significant information for the evaluation and management of patients with heart disease.[4,5] In cross-sectional studies, LV mass has been associated with decreased regional systolic function.[6] Furthermore, in an elderly population, increased LV mass has shown predictive ability for a depressed LVEF over a 5-year follow-up period.[7] The Coronary Artery Risk Development in Young Adults (CARDIA) study prospectively assessed a young adult biracial cohort and reported a depressed LVEF as a strong predictor of incident heart failure in black participants over a 10-year follow-up period.[2] However, the association of LV mass with the future LVEF in younger populations has not been studied. Using the CARDIA cohort, we investigated the role of greater myocardial mass in young adults as a predictor of LV dysfunction over a 20-year follow-up period, evaluating the association between LV mass at the ages of 23 to 35 years with the LVEF 20 years later. We also explored the relations of LV mass with LV volumes. We hypothesized that LV mass and ejection capability are not necessarily strongly correlated early in life (when mass is generally normal and ejection power is at its peak) but that small echocardiographic differences in LV mass early in life predict the development of reduced ejection performance as early as middle adulthood.

Methods

CARDIA is a National Institutes of Health−sponsored multicenter study designed to investigate the development of coronary disease in young adults. Initially, 5,115 black and white men and women 18 to 30 years of age at the time of enrollment (1985 to 1986) were recruited and examined at 4 CARDIA field centers in Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California. Echocardiography was performed in the cohort at the follow-up year 5 and 25 examinations. The overall design and

[a]Johns Hopkins University, Baltimore, Maryland; [b]Nemours Cardiac Center, Wilmington, Delaware; [c]University of Minnesota, Minneapolis, Minnesota; [d]Kaiser Permanente Division of Research, Oakland, California; [e]University of Alabama, Birmingham, Alabama; and [f]Northwestern University, Chicago, Illinois. Manuscript received June 10, 2013; revised manuscript received and accepted August 22, 2013.

This study was supported by the Coronary Artery Risk Development in Young Adults (CARDIA) contract (clinics, N01-HC-48047 to N01-HC-48050; coordinating center, N01-HC-95095; year 5 echocardiographic reading center, N01-HC-45134; and year 25 echocardiographic reading center, NIH NHLBI-HC-09-08). This report has been reviewed by CARDIA for scientific content. A full list of participating investigators and institutions can be found at *http://www.cardia.dopm.uab.edu*, along with access to publications and information concerning collaboration and data sharing of CARDIA resources.

See page 382 for disclosure information.

*Corresponding author: Tel: (410) 614-1284; fax: (410) 614-8222.
E-mail address: jlima@jhmi.edu (J.A.C. Lima).

0002-9149/13/$ - see front matter
http://dx.doi.org/10.1016/j.amjcard.2013.08.052

objectives of the CARDIA study have been presented elsewhere.[8] Of the 4,352 participants attending the year 5 examination, 4,243 participants underwent echocardiography. Of the 3,498 participants attending the year 25 examination, 3,474 underwent echocardiography. For this study, we evaluated 3,145 participants with echocardiographic assessments at CARDIA examinations for year 5 (baseline, from 1990 to 1991) and year 25 (2010 to 2011). Exclusion criteria were pregnancy at either exam (n = 38), year 5 LVEF <50% (n = 88), and absence of specific echocardiographic variables or other risk factors (n = 680). The remaining 2,339 patients were included in our analytic cohort.

CARDIA participants at year 5 underwent 2-dimensionally guided M-mode echocardiography to assess LV mass, as previously described.[9] LV functional parameters (LV end-diastolic volume [LVEDV], LV end-systolic volume [LVESV], and the LVEF) at the year 5 examination were assessed using M-mode echocardiography in a parasternal acoustic window, using the Teichholz technique.[10] CARDIA participants at the year 25 examination underwent 2-dimensinoally guided M-mode echocardiography in a parasternal window and 2-dimensional (2D) 4-chamber apical views following American Society of Echocardiography recommendations.[11] All studies were recorded in digital format using an Artida cardiac ultrasound scanner (Toshiba Medical Systems, Tokyo, Japan) and read at the Johns Hopkins University Echocardiography Reading Center in Baltimore, Maryland. Measurements were made by experienced analysts from digitized images using a standard software off-line image analysis system (Digisonics, Inc., Houston, Texas). LV mass index (LVMI) was acquired after dividing LV mass by body surface area at years 5 and 25.[10] The LVEF was assessed using the formula LVEF = [(LVEDV − LVESV)/LVEDV] × 100. At year 5, LVEDV and LVESV were assessed using the M-mode technique (Teichholz method). At year 25, LVEDV and LVESV were measured from apical 2D 4-chamber images. The LVEFs at year 25 between M-mode and 2D imaging were positively correlated ($r = 0.41$, $p < 0.0001$), and the mean difference was 8.2% (the M-mode LVEF was greater than the 2D LVEF; $p < 0.0001$). For the end point of LV volumes, LVEDV and LVESV were indexed to body surface area (LVEDV and LVESV).

Standardized protocols were used to measure height, weight, cholesterol, heart rate, blood pressure, smoking, educational level, and physical activity at baseline (year 5).[8] Gender and race were self-reported by the study participants. We used the average of the second and third of 3 blood pressure measurements after 5 minutes of rest; blood pressure was measured by random-zero sphygmomanometry at year 5 and using an Omron (Kyoto, Japan) device at year 25. Weight (in kilograms) and height (in meters) were measured in light clothing, and body mass index was calculated. Cigarette smoking was determined by self-report at each examination. Physical activity (in exercise units) was determined by a questionnaire.[12] Diabetes mellitus was determined as fasting glucose ≥126 mg/dl or the use of medication for diabetes. We used fasting glucose level at the year 0 examination as a year 5 variable because glucose was not measured at year 5. Total cholesterol, triglycerides, and high-density lipoprotein cholesterol were determined using an enzymatic assay; low-density lipoprotein cholesterol was calculated using the Friedewald equation.[13] Educational level was categorized into 2 groups: ≤12 years or equivalent and >12 years. History of heart disease at year 25 was determined using a questionnaire.

Descriptive statistics for the participants were summarized using means and SDs for continuous variables. Categorical variables are presented as numbers and percentages. Chi-square tests and F tests were used to compare the differences in the prevalence of various risk factors among the subgroups. Univariate linear regression analysis was conducted to assess the association of the LVEF at years 5 and 25. The correlations between LV mass and LV functional parameters (LVEDV, LVESV, and the LVEF) were assessed on a cross-sectional basis at years 5 and 25 to evaluate whether a longitudinal association between LV mass and LV functional parameters could be explained by a baseline cross-sectional relation between the 2 parameters. A longitudinal analysis explored the relations between year 5 LV mass and year 25 LV functional parameters. We created 3 multivariate linear regression analysis models to evaluate the association of year 5 LVMI with the year 25 LVEF. In model 1, we adjusted for the following year 5 variables: age, gender, and race. Model 2 was adjusted for model 1 plus educational level, systolic blood pressure, heart rate, body mass index, diabetes status, use of antihypertensive medications, smoking status (current smokers or former or nonsmokers), total physical activity score, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol. Model 3 was adjusted for model 2 plus the year 5 LVEF.

For a categorical approach, systolic dysfunction at year 25 was defined as an LVEF <50%.[14,15] We explored relations between LVMI at year 5 (per SD increase) and clinically relevant systolic dysfunction at year 25 using univariate and multivariate logistic regression analysis, reporting odds ratios and 95% confidence intervals. In multivariate logistic regression models, LVMI was adjusted for the same variables used in the multivariate linear regression analysis models. In additional analyses, the association between year 5 LVMI and year 25 LVEDV index or LVESV index was explored, because the LVEF is computed using measurements of LVEDV and LVESV. In model 1, we adjusted for the year 5 covariates age, gender, race, educational level, systolic blood pressure, heart rate, body mass index, diabetes status, use of antihypertensive medications, smoking status (current smokers or former or nonsmokers), physical activity score, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol. Model 2 was adjusted for model 1 plus year 5 LVEDV index or LVESV index, according to the dependent variable under investigation. Two-sided p values <0.05 were considered to indicate statistical significance. All statistical analyses were performed using JMP version 10.0 for Windows (SAS Institute Inc., Cary, North Carolina) and Stata version 11.0 (Stata Corp LP, College Station, Texas).

Results

Demographic and risk factor data for the 2,339 CARDIA participants at baseline and echocardiographic parameters at years 5 and 25 are listed in Table 1. The study population was