

Diabetic Cardiomyopathy and Subclinical Cardiovascular Disease

The Multi-Ethnic Study of Atherosclerosis (MESA)

ALAIN G. BERTONI, MD, MPH¹
 DAVID C. GOFF, JR., MD, PHD¹
 RALPH B. D'AGOSTINO, JR., PHD¹
 KIANG LIU, PHD²
 W. GREGORY HUNDLEY, MD¹
 JOAO A. LIMA, MD³

JOSEPH F. POLAK, MD, MPH⁴
 MOHAMMED F. SAAD, MD, MRCP⁵
 MOYSES SZKLO, MD, DRPH⁶
 RUSSELL P. TRACY, PHD⁷
 DAVID S. SISCOVICK, MD, MPH⁸

OBJECTIVE— Studies have demonstrated increased left ventricular mass (LVM) and diastolic dysfunction among diabetic patients without clinical cardiovascular disease (CVD), but few have assessed the potential contribution of subclinical CVD to ventricular abnormalities in diabetes. We examined whether diabetic cardiomyopathy is associated with subclinical atherosclerosis and if abnormalities are found with impaired fasting glucose (IFG).

RESEARCH DESIGN AND METHODS— LVM, end-diastolic volume (EDV), and stroke volume were measured by magnetic resonance imaging (MRI), and atherosclerosis was assessed by coronary artery calcium and carotid intima-media wall thickness in 4,991 participants in the Multi-Ethnic Study of Atherosclerosis, a cohort study of adults aged 45–84 without prior CVD. Multivariable linear regression was used to analyze the association between MRI measures and glucose status.

RESULTS— Increased LVM was observed in white, black, and Hispanic participants with diabetes but not among Chinese participants. After adjustment for weight, height, CVD risk factors, and subclinical atherosclerosis, ethnicity-specific differences in ventricular parameters were present. Among whites and Chinese with diabetes, LVM was similar to that in normal subjects; EDV and stroke volume were reduced. In blacks with diabetes, EDV and stroke volume were reduced, and LVM was increased (+5.6 g, $P < 0.05$). Among Hispanics with diabetes, EDV and stroke volume were similar to normal, but LVM was increased (+5.5 g, $P < 0.05$). After adjustment, IFG was associated with a decrease in EDV and stroke volume in whites and blacks only; however, no significant differences in LVM were observed.

CONCLUSIONS— Ethnicity-specific differences in LVM, EDV, and stroke volume are associated with abnormal glucose metabolism and are independent of subclinical CVD.

Diabetes Care 29:588–594, 2006

From the ¹Department of Public Health Sciences, Wake Forest University Health Sciences, Winston-Salem, North Carolina; the ²Department of Preventive Medicine, Northwestern University, Chicago, Illinois; the ³Department of Medicine, Johns Hopkins University, Baltimore, Maryland; the ⁴Department of Radiology, Tufts-New England Medical Center, Boston, Massachusetts; the ⁵Department of Preventive Medicine, Health Sciences Center School of Medicine, Stony Brook, New York; the ⁶Department of Preventive Medicine, Health Sciences Center School of Medicine, Stony Brook, New York; the ⁷Department of Epidemiology, Johns Hopkins University, Baltimore, Maryland; the ⁸Department of Pathology, University of Vermont, Colchester, Vermont; and the ⁸Cardiovascular Health Research Unit, University of Washington, Seattle, Washington.

Address correspondence and reprint requests to Dr. Alain G. Bertoni, Wake Forest University Health Sciences, Department of Public Health Sciences, Medical Center Boulevard, Winston-Salem, NC 27157. E-mail: abertoni@wfubmc.edu.

Received for publication 11 August 2005 and accepted in revised form 2 December 2005.

Abbreviations: CAC, coronary artery calcium; CVD, cardiovascular disease; EDV, end-diastolic volume; ESV, end-systolic volume; IFG, impaired fasting glucose; IMT, intima-media thickness; LVM, left ventricular mass; MESA, Multi-Ethnic Study of Atherosclerosis; MRI, magnetic resonance imaging; NFG, normal fasting glucose.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

© 2006 by the American Diabetes Association.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Heart failure has become a frequent manifestation of cardiovascular disease (CVD) among individuals with diabetes (1). As the prevalence of diabetes increases, it will probably emerge as one of the principal causes of heart failure in the U.S. (2–4). There is significant evidence of the existence of “diabetic cardiomyopathy,” described classically as heart failure in the absence of obstructive coronary disease but now more often defining ventricular abnormalities seen in individuals without coronary disease including increased left ventricular mass (LVM) and impaired diastolic function (3,5–8). Proposed mechanisms include deleterious effects of hyperglycemia, hypertension, and impaired endothelial function, which may lead to compromised myocardial blood flow (8,9). Atherosclerosis may be a contributing factor in diabetic cardiomyopathy, as many studies have not had angiographic data or have focused on the lack of obstructive lesions on coronary angiography and have not determined the presence or extent of subclinical CVD. There is less information available on whether cardiomyopathy is also present in impaired fasting glucose (IFG), although an association between IFG and heart failure has been found (10). Determining the relationship between subclinical atherosclerosis and early abnormalities in diabetic and pre-diabetic hearts would advance our understanding of the pathophysiology of ventricular dysfunction and may suggest interventions to prevent heart failure in at-risk adults. Therefore, we sought to investigate whether ventricular abnormalities related to diabetes are also observed in IFG and whether these abnormalities may be mediated by atherosclerosis in the Multi-Ethnic Study of Atherosclerosis (MESA), a population-based cohort of adults without CVD.

RESEARCH DESIGN AND METHODS

MESA is a population-based sample of 6,814 men and women from four ethnic groups (white, African American, Hispanic, and Chinese) aged 45–84 without clinical CVD before re-

cruitment. Details regarding the design and objectives of MESA have been published (11). Individuals with a medical history of heart attack, angina, coronary revascularization, pacemaker or defibrillator implantation, valve replacement, heart failure, or cerebrovascular disease were excluded from the sample. During the baseline examination (2000–2002), standardized questionnaires and calibrated devices were used to obtain demographic data, tobacco usage, medical conditions, current prescription medication usage, weight, and height. Resting seated blood pressure was measured three times using a Dinamap automated oscillometric sphygmomanometer (model Pro 100; Critikon, Tampa, FL); the last two measurements were averaged for analysis. Fasting blood glucose and lipids were analyzed at a central laboratory. Individuals were considered to have diabetes if they replied “Yes” to the question “Has a doctor ever told you that you had diabetes?” and/or the medication inventory included hypoglycemic drugs or if fasting blood glucose was ≥ 7.0 mmol/l (126 mg/dl). Individuals were considered to have IFG if they did not have diabetes by the preceding criteria and their fasting blood glucose was ≥ 5.6 and < 7.0 mmol/l (> 100 and < 126 mg/dl) in accordance with the 2004 American Diabetes Association definition; others were classified as having normal fasting glucose (NFG) (12). Hypertension was defined on the basis of the medication inventory including blood pressure medicine and a self-report of hypertension or systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg.

Chest computed tomography was performed using either a cardiac-gated electron-beam scanner or a prospectively electrocardiogram-triggered scan acquisition at 50% of the R-R interval with a multidetector system acquiring a block of four 2.5-mm slices for each cardiac cycle in a sequential or axial scan mode (11). Participants were scanned twice over phantoms of known physical calcium concentration. Scans were read centrally; measurement of coronary artery calcium (CAC) was calibrated against the phantom. For each scan, a total phantom-adjusted Agatston score, defined as the sum of calcium measures from the left anterior descending, circumflex, and left and right coronary arteries, was calculated; the mean score was used in these analyses.

Cardiac magnetic resonance imaging

(MRI) was performed using 1.5-Tesla magnets at each center; the MESA protocol has been described in detail (11,13). Briefly, imaging was performed with a four-element, phased-array surface coil placed anteriorly and posteriorly, electrocardiogram gating, and brachial artery blood pressure monitoring. Cine images of the left ventricle were obtained during short breath-holding (12–15 s) at resting lung volume. Quantitative measurements were performed at one reading center using MASS (v4.2) analytical software for reader interpretation (Medis, Leiden, the Netherlands) by one of two trained technicians. Left ventricular wall thickness was defined as the average of six midventricle segment thickness measurements. Left ventricular EDV and end-systolic volume (ESV) were calculated by summing the areas on each separate slice multiplied by the sum of the slice thickness. End-diastolic LVM was determined by the sum of the area between the epicardial and endocardial contours multiplied by the slice thickness; this value was then multiplied by the specific gravity of myocardium (1.05 g/ml). Ejection fraction was calculated as stroke volume divided by EDV. The inter-reader intraclass correlation coefficients were 0.98 for LVM and EDV, 0.94 for ESV and stroke volume, and 0.81 for ejection fraction. The intrareader coefficients for these measures ranged from 0.94 to 0.98.

For carotid ultrasonography, images of the right and left common carotid and internal carotid arteries were captured, including images of the near and far wall, using high-resolution B-mode ultrasound (14). We defined the internal carotid artery intima-media thickness (IMT) as the mean of all available maximum wall thicknesses across both left and right sides.

Statistical analysis

Unadjusted differences in characteristics across three glucose categories (normal, IFG, and diabetes) were examined using ANOVA for continuous variables. Categorical variables were compared using χ^2 analysis. Because LVM and volumes in MESA have been found to differ by sex and ethnicity (13) and differential effects of diabetes on LVM by sex were found in prior literature (6,15), we initially investigated these data using sex and ethnicity-specific strata. We tested both for trend across glucose category and for the comparison of IFG and diabetes versus normal. Differences in ventricular parameters

by glucose status were then assessed using multivariable linear regression, with adjustment for age, sex, race, clinic, weight, and height (model 1). Using interaction terms in these models, we found evidence of a significant interaction between glucose status and ethnicity for several ventricular parameters; in ethnicity-stratified models, we then assessed for a glucose status–sex interaction. Because of the greater evidence for glucose status–ethnicity interaction, further analyses were performed, stratified by ethnicity and adjusting for sex. Subsequent models incorporated risk factors for atherosclerosis (smoking, hypertension, blood pressure, LDL and HDL cholesterol, and triglycerides) and then CAC and carotid IMT to determine whether adjustment for these variables altered the relationship between glucose category and ventricular parameters. We modeled CAC in several ways, including using the Agatston score as a continuous variable, as a categorical variable (CAC present or not), and as quartiles. Because of the large number of individuals with a zero Agatston score, we ended up with three categories when attempting to make quartiles (Agatston scores 0 (51%), 1–87.2 (25%), and > 87.3 (24%). We used these three categories for subsequent analyses. Two-tailed $P < 0.05$ was considered significant. Analyses were performed using STATA 8 (Stata, College Station, TX).

RESULTS— MRI examination participation among the 6,814 subjects recruited by MESA was lower among those with versus those without diabetes (67.0 vs. 76.7%, $P < 0.01$). CAC was less prevalent among those examined by MRI (48.6 vs. 53.4%, $P < 0.01$). Among the 4,991 participants who underwent MRI and for whom glucose status could be ascertained, 26.7% ($n = 1,334$) had IFG and 12.9% ($n = 646$) had diabetes. The prevalence of diabetes was higher among African Americans (18.2%), Hispanics (17.3%), and Chinese Americans (14.4%) compared with whites (6.7%). The prevalence of IFG was higher among Chinese Americans (32.2%), Hispanics (30.1%), and African Americans (25.7%) compared with whites (23.4%). Age, weight, BMI, and systolic blood pressure increased significantly from normal to IFG to diabetes (Table 1). Diabetic patients (of whom 25% were taking a statin drug) had significantly lower total, LDL, and HDL cholesterol compared with those having either NFG (10% with a statin) or IFG

Table 1—Characteristics of MESA participants with MRI data by glucose status at first examination, 2000–2002

Parameter	NFG	IFG	Diabetes	P value
n	3,011	1,334	646	
Age (years)	60.1 ± 10.1	63.2 ± 9.9	64.6 ± 9.3	<0.001
Female (%)	57.4	43.6	47.3	<0.001
Height (cm)	166.3 ± 9.9	166.8 ± 9.9	165.7 ± 10.1	0.1
Weight (kg)	75.0 ± 15.6	80.0 ± 16.5	81.8 ± 16.6	<0.001
BMI (kg/m ²)	27.0 ± 4.7	28.6 ± 5.0	29.7 ± 5.2	<0.001
Body surface area	1.83	1.88	1.90	<0.001
White (%)	45.4	34.2	20.3	<0.001
Chinese American (%)	11.3	16.2	14.6	<0.001
African American (%)	23.9	24.7	36.1	<0.001
Hispanic American (%)	19.4	24.9	29.1	<0.001
Cholesterol (mmol/l)	5.06 ± 0.90	5.05 ± 0.91	4.89 ± 0.98	<0.001
HDL cholesterol (mmol/l)	1.38 ± 0.40	1.26 ± 0.36	1.20 ± 0.34	<0.001
LDL cholesterol (mmol/l)	3.05 ± 0.80	3.09 ± 0.81	2.90 ± 0.85	<0.001
CAC present (%)	43.0	54.2	63.2	<0.001
Agatston score	100.4 ± 329.6	159.0 ± 408.5	250.1 ± 583.4	<0.001
IMT (mm)	0.99 ± 0.53	1.09 ± 0.61	1.26 ± 0.70	<0.001
Hypertension	34.7	48.3	66.7	<0.001
BP medication	26.8	41.5	62.4	<0.001
Systolic BP (mmHg)	122.5 ± 20.7	128.6 ± 20.9	132.6 ± 21.9	<0.001
Diastolic BP (mmHg)	71.1 ± 10.2	73.3 ± 10.3	72.02 ± 10.3	<0.001
Past smoker	34.2	38.3	37.2	0.03
Current smoker	13.0	12.4	11.7	0.6

Data are means ± SD unless otherwise indicated. P value is for difference across categories. BP, blood pressure.

(16% with a statin). Participants with IFG or diabetes had more evidence of subclinical atherosclerosis than those with NFG as measured by the presence of CAC or carotid IMT. Similar patterns were seen for these parameters in each ethnic group (data not shown).

Cardiac structure and function

Ethnicity- and sex-specific ventricular parameters are presented in Table 2. LVM increased significantly across glucose category in all ethnic groups except Chinese. LVM was significantly greater in participants with diabetes versus those with NFG in all ethnicity/sex groups except Chinese. LVM was less consistently elevated with IFG. Wall thickness followed a pattern similar to that of LVM. There were few differences in unadjusted ventricular volumes or ejection fraction by glucose metabolism status.

Multivariate analyses

There was evidence of a differential relationship of glucose status to LVM by ethnicity in our multivariate models (in the final model P for interaction term race × glucose category = 0.002). There was minimal evidence of an interaction between ethnicity and glucose status in volume analyses (P for interaction terms

>0.05 but <0.2). After stratification by ethnicity, we did not find evidence for a sex × glucose category interaction for mass, volumes, or thickness.

Differences in selected ventricular parameters among those with IFG, diabetes, and NFG, stratified by ethnicity, are presented in Table 3. After adjustment for age, sex, height, and weight (model 1), diabetes remained associated with a greater LVM only among blacks and Hispanics. This difference was attenuated after adjustment for atherosclerosis risk factors (model 2) and subclinical CVD (model 3); however, diabetes was still associated with an increased LVM to a similar degree in blacks and Hispanics. Diabetes was associated with increased wall thickness after adjustment for model 1 in all ethnic groups except Chinese, but this association remained significant after full adjustment only in black and Hispanic participants. Both EDV and stroke volume tended to be lower among those with diabetes in all ethnic groups except Hispanics. After adjustment, there was no difference in LVM between IFG and NFG in any ethnic group, and after adjustment, IFG was associated with lower EDV and stroke volume in whites and blacks.

There were no differences in ESV associated with diabetes or IFG after adjust-

ment in any ethnic group (data not shown). Ejection fraction did not generally differ by glucose status in multivariate analyses except for being slightly lower among blacks with diabetes after full adjustment (−1.3%, P < 0.05). We did find one interaction between glucose status and sex in ethnicity-specific analyses of ejection fraction among Hispanics (interaction term P = 0.003). Among Hispanic men with diabetes, the ejection fraction was slightly reduced (−2.1%, P = 0.03) compared with those with NFG after adjustment for variables in model 3; among Hispanic women, after adjustment for variables in model 3, the ejection fraction was similar among those with diabetes versus those with NFG (+1.5, P = 0.1).

In sensitivity analyses we modeled CAC as either a dichotomous (presence or absence) or continuous variable (Agatston score). These alternative models did not result in substantive changes in point estimates or statistical significance level for associations between diabetes or IFG and ventricular parameters.

CONCLUSIONS — In this multiethnic population of individuals without clinical cardiovascular disease, small differences in left ventricular mass, volumes,

and function were detected among those with IFG and diabetes compared with those with NGT; however, the pattern of abnormality and the degree to which risk factors and subclinical atherosclerosis modified the association differed by ethnicity. Among black and Hispanic participants, the observed greater LVM and wall thickness among patients with diabetes was partially explained by risk factors and subclinical atherosclerosis, but remained significantly higher compared with normal subjects. In contrast, neither whites nor Chinese participants with diabetes had increased LVM after adjustment for demographic and anthropomorphic factors. White diabetic participants did exhibit increased wall thickness, which was fully explained by risk factors and subclinical atherosclerosis. Diabetes was strongly associated with lower EDV among whites; the association was more modest among Chinese and blacks and was not present in Hispanics. Stroke volume was significantly lower in whites, Chinese, and blacks with diabetes. In this sample, diabetes and IFG were associated with either small or insignificant changes in ejection fraction. After adjustment for demographic and anthropomorphic factors, IFG was not associated with increased LVM or wall thickness in any ethnic group. IFG was associated with a lower EDV and stroke volume among black and white participants.

Numerous population-based studies have shown abnormal glucose metabolism to be associated with greater LVM, particularly in women (5,6,15–17). The differences observed in MESA in unadjusted as well as adjusted comparisons were smaller than those in most studies; however, previous studies have used echocardiography-derived estimates of LVM, and some have not excluded participants with clinical CVD. There is evidence that both African-American and Hispanic ethnicity is associated with increased LVM (18–20). European whites and Afro-Caribbeans have been shown to differ in the ventricular response to glucose intolerance (21). Although only small increases in LVM associated with diabetes were observed in this study, it is well established that higher LVM predicts subsequent CVD morbidity and mortality (2,22) and is also associated with decreased ejection fraction within the subsequent 5 years (23).

The finding of an increased left ventricular wall thickness in those with diabetes is consistent with our findings of

Table 2—Characteristics of left ventricular structure, volume, heart rate, and cardiac function by glucose status in participants in MESA

	White				Chinese				Black				Hispanic			
	NFG	IFG	Diabetes	P value	NFG	IFG	Diabetes	P value	NFG	IFG	Diabetes	P value	NFG	IFG	Diabetes	P value
Women (n)	789	186	55		203	86	45		405	172	122		331	138	83	
Mass (g)	119 ± 24	125 ± 25	132 ± 31	<0.001, D	105 ± 20	106 ± 17	110 ± 20	NS	133 ± 28	136 ± 31	146 ± 32	<0.001, D	123 ± 26	125 ± 25	135 ± 28	<0.001, D
Thickness (mm)	8.2 ± 1.3	8.6 ± 1.6	9.3 ± 1.9	<0.001, D	7.9 ± 1.2	7.9 ± 1.3	8.1 ± 1.3	NS	8.9 ± 1.6	9.2 ± 1.6	9.7 ± 1.8	<0.001, D	8.5 ± 1.5	8.7 ± 1.5	9.0 ± 1.8†	<0.05, D
EDV (ml)	115 ± 23	113 ± 27	112 ± 27	NS	102 ± 18	100 ± 15	98 ± 18	NS	120 ± 27	116 ± 26	117 ± 26	NS	114 ± 22	114 ± 25	116 ± 23	NS
ESV (ml)	34 ± 12	33 ± 13	33 ± 13	NS	27 ± 7	26 ± 8	25 ± 10	NS	36 ± 13	34 ± 13	35 ± 12	NS	33 ± 11	33 ± 12	32 ± 12	NS
Stroke volume (ml)	81 ± 17	80 ± 18	79 ± 20	NS	75 ± 13	74 ± 12	73 ± 12	NS	84 ± 19	83 ± 19	82 ± 18	NS	81 ± 16	81 ± 16	85 ± 16	NS
Ejection fraction (%)	71 ± 6	71 ± 7	70 ± 10	NS	74 ± 5	74 ± 6	75 ± 6	NS	70 ± 7	71 ± 7	71 ± 6	NS	71 ± 6	72 ± 6	73 ± 7	<0.05, D
Heart rate (bpm)	63 ± 9	67 ± 10	67 ± 10	<0.001, D	63 ± 8	65 ± 9	64 ± 8	NS	63 ± 9	63 ± 9	68 ± 12	<0.001, D	62 ± 9	65 ± 9	69 ± 11	<0.001, D
Men (n)	576	270	77		138	130	49		314	158	122		253	197	105	
Mass (g)	168 ± 32	171 ± 36	176 ± 39	0.07, D	140 ± 28	144 ± 30	144 ± 25	NS	179 ± 37	188 ± 37	191 ± 46	<0.01, D	167 ± 32	166 ± 37	175 ± 43	0.08, D
Thickness (mm)	9.8 ± 1.6	10.2 ± 1.9	10.7 ± 2.2	<0.001, D	9.1 ± 1.5	9.5 ± 1.5	9.6 ± 1.3	<0.05, D	10.8 ± 1.8	11.0 ± 1.8	11.1 ± 2.0	NS	9.9 ± 1.7	10.4 ± 2.0	10.6 ± 2.1	<0.01, D
EDV (ml)	147 ± 33	139 ± 32	138 ± 33	<0.001, D	123 ± 25	122 ± 24	119 ± 21	NS	143 ± 35	146 ± 37	141 ± 34	NS	145 ± 31	137 ± 28	138 ± 35	<0.05, D
ESV (ml)	50 ± 18	48 ± 18	48 ± 16	NS	37 ± 11	36 ± 12	38 ± 13	NS	50 ± 20	51 ± 21	52 ± 23	NS	49 ± 16	46 ± 16	50 ± 26	NS
Stroke volume (ml)	97 ± 22	92 ± 21	91 ± 22	<0.001, D	86 ± 18	85 ± 16	82 ± 15	NS	93 ± 22	95 ± 22	90 ± 19	NS	95 ± 20.3	91 ± 18	88 ± 20	<0.01, D
Ejection fraction (%)	66 ± 7	66 ± 8	66 ± 6	NS	70 ± 5	70 ± 6	69 ± 7	NS	66 ± 8	66 ± 8	65 ± 9	NS	66 ± 6	67 ± 7	65 ± 9	NS
Heart rate (bpm)	60 ± 10	63 ± 10	65 ± 9	<0.01, D	61 ± 7	63 ± 10	65 ± 8	<0.01, D	60 ± 9	62 ± 10	65 ± 10	<0.001, D	60 ± 9	62 ± 8	67 ± 10	<0.001, D

Data are means ± SD. P values are for trend tests across glucose status: I, comparison of IFG vs. NFG significant at P < 0.05; D, comparison of diabetes vs. NFG significant at P < 0.05.

increased LVM and decreased EDV. These alterations are suggestive of the greater ventricular stiffness observed when diastolic relaxation is slowed or incomplete (24). Impaired diastolic function has been demonstrated in individuals with well-controlled diabetes with or without hypertension and in the absence of changes in diastolic dimensions by echocardiography (25,26). One study (12 diabetic men vs. 12 control subjects) in which cardiac MRI was used to demonstrate significantly impaired diastolic function also reported nonstatistically significantly lower EDV (143 vs. 149 ml) and stroke volume (85 vs. 92 ml) (27). However, male diabetic rat ventricles assessed with MRI demonstrated significantly decreased EDV, stroke volume, and ejection fraction compared with controls (28). The lower stroke volume alternatively may be explained by the increased heart rate observed among participants with diabetes. It is unlikely, however, that this small increase in heart rate induced the ventricular differences observed, for tachycardia-induced cardiomyopathy generally is associated with sustained heart rates >100 bpm (29). Prior studies have reported either no difference or a small but significant decrease in ejection fraction or fractional shortening, a proxy of systolic function, between subjects with and without diabetes (5,15,17,30,31).

The strengths of this analysis include the use of a diverse, well-characterized, population-based sample, two measures of subclinical atherosclerosis, and precise determination of ventricular parameters by MRI. The exclusion of participants with clinical CVD resulted in an ideal sample for exploring the potential contribution of subclinical CVD to diabetes-associated cardiomyopathy. We have also applied the most recent criteria for defining glucose metabolism abnormalities. Nevertheless, several limitations deserve mention. Perhaps most significant is our inability to detect diastolic dysfunction, as measures of diastolic filling were not obtained with this protocol. These cross-sectional analyses do not permit the conclusion that abnormal glucose tolerance causes these ventricular abnormalities. Furthermore, our findings may not be directly comparable to studies in which echocardiography was used, although MRI-measured LVM has been shown to be more accurate than echocardiography, which tends to overestimate LVM (32). In most clinical studies of diabetic cardiomyopathy, participants known to be free

Table 3—Differences in left ventricular structure and function between IFG or diabetes and normal after multivariable linear regression among participants in MESA by race/ethnicity

Parameter	White			Chinese			Black			Hispanic			
	IFG	P value	Diabetes	IFG	P value	Diabetes	IFG	P value	Diabetes	IFG	P value	Diabetes	P value
Mass (g)													
Model 1	0.0	NS	1.7	-0.4	NS	1.0	0.7	NS	7.3	-1.0	NS	8.0	<0.01
Model 2	-0.8	NS	-1.6	-1.2	NS	-1.1	-0.1	NS	5.8	-1.5	NS	6.0	<0.05
Model 3	-1.4	NS	-3.3	-1.4	NS	-1.4	0.5	NS	5.6	-1.8	NS	5.5	<0.05
Thickness (mm)													
Model 1	0.1	NS	0.6	0.1	<0.001	0.2	0.2	NS	0.4	0.2	NS	0.4	<0.01
Model 2	0.0	NS	0.3	0.1	<0.05	0.1	0.1	NS	0.4	0.1	NS	0.3	<0.05
Model 3	0.0	NS	0.2	0.1	NS	0.1	-0.2	NS	0.4	0.1	NS	0.3	<0.05
EDV (ml)													
Model 1	-4.9	<0.001	-8.2	-2.3	<0.001	-3.1	-4.2	<0.05	-4.9	-2.4	NS	0.1	NS
Model 2	-4.5	<0.01	-7.3	-2.6	<0.01	-3.5	-3.6	<0.05	-4.3	-2.0	NS	-0.1	NS
Model 3	-4.3	<0.01	-7.1	-2.7	<0.01	-4.0	-3.2	0.08	-4.1	-2.1	NS	-0.1	NS
Stroke volume (ml)													
Model 1	-3.7	<0.001	-6.0	-1.3	<0.001	-3.1	-2.8	<0.05	-4.9	-1.3	NS	-1.1	NS
Model 2	-3.4	<0.01	-5.6	-1.6	<0.01	-3.2	-2.7	<0.05	-5.0	-0.9	NS	-1.6	NS
Model 3	-3.2	<0.01	-5.3	-1.6	<0.01	-3.7	-2.4	0.05	-5.0	-0.9	NS	-1.6	NS

Parameter estimates in table are differences (β coefficients) between normal and IFG or diabetes. Model 1 is adjusted for age, sex, height, weight, and clinic. Model 2: model 1 plus hypertension, systolic blood pressure, smoking status, HDL cholesterol, LDL cholesterol, and triglycerides. Model 3: model 2 plus CAC category and carotid IMT.

of coronary disease have been selected. Although those with clinical CVD were excluded from this sample, participants did not undergo functional evaluations for cardiac ischemia. We evaluated CAC and carotid IMT, though these may be incomplete markers of the total atherosclerosis burden. The definition of IFG and diabetes relied on participant-provided history and a single measure of glucose. This introduces a potential misclassification of glucose status, which may have impaired our ability to detect differences among individuals with normal and abnormal glucose tolerance. Our results for IFG may not be directly comparable to prior studies that defined impaired glucose tolerance on oral glucose tolerance tests or a higher level of fasting glucose.

Finally, our ethnicity-stratified analyses should be interpreted cautiously as we have less power, particularly among the Chinese, given the small differences observed and the substantially smaller sample sizes. Nonetheless, these are perhaps the most intriguing findings. In an insured population with diabetes, the risk for clinical heart failure has been reported to be similar for blacks and whites and significantly decreased for Hispanics and Asians compared with whites (33). In this light, we note that before adjustment for subclinical atherosclerosis, whites and blacks with diabetes both had decreased EDV, stroke volume, and increased wall thickness, whereas in the Chinese with diabetes only stroke volume was reduced and less so than in whites or blacks. Among Hispanics, only LVM and thickness were affected by diabetes. Increased LVM and thickness may be associated to a greater degree with hypertension and atherosclerosis than diabetes in whites and Chinese in the absence of clinical CVD, whereas in blacks and Hispanics diabetes remained independently associated with increased LVM. Our findings may be due, however, to differential subclinical atherosclerosis by ethnicity, which among participants with diabetes has recently been demonstrated in MESA to differ by ethnicity across vascular beds; most notably a lower prevalence of CAC among blacks and Hispanics (34). We also cannot exclude the possibility that ethnic differences in duration, treatment, or control of diabetes are responsible for the differences observed. In this sample, however, data on duration or treatment are missing for one-third of subjects, and HbA_{1c} was not measured. Further investigation will be required to determine whether there

are differences in the incidence of heart failure by ethnicity in this cohort, and, if so, whether the observed difference at baseline will be predictive of the future risk of heart failure or subtype of heart failure.

Acknowledgments— This research was supported by contracts N01-HC-95159 through N01-HC-95165 and N01-HC-95169 from the National Heart, Lung, and Blood Institute.

The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at <http://www.mesa-nhlbi.org>.

References

- Nichols GA, Gullion CM, Koro CE, Ephross SA, Brown JB: The incidence of congestive heart failure in type 2 diabetes: an update. *Diabetes Care* 27:1879–1884, 2004
- Gottdiener JS, Arnold AM, Aurigemma GP, Polak JF, Tracy RP, Kitzman DW, Gardin JM, Rutledge JE, Boineau RC: Predictors of congestive heart failure in the elderly: the Cardiovascular Health Study. *J Am Coll Cardiol* 35:1628–1637, 2000
- Bell DS: Heart failure: the frequent, forgotten, and often fatal complication of diabetes. *Diabetes Care* 26:2433–2441, 2003
- Mokdad AH, Ford ES, Bowman BA, Nelson DE, Engelgau MM, Vinicor F, Marks JS: Diabetes trends in the U.S.: 1990–1998. *Diabetes Care* 23:1278–1283, 2000
- Devereux RB, Roman MJ, Paranicas M, O'Grady MJ, Lee ET, Welty TK, Fabsitz RR, Robbins D, Rhoades ER, Howard BV: Impact of diabetes on cardiac structure and function: the strong heart study. *Circulation* 101:2271–2276, 2000
- Henry RM, Kamp O, Kostense PJ, Spijkerman AM, Dekker JM, van Eijck R, Nijpels G, Heine RJ, Bouter LM, Stehouwer CD: Left ventricular mass increases with deteriorating glucose tolerance, especially in women: independence of increased arterial stiffness or decreased flow-mediated dilation: the Hoorn study. *Diabetes Care* 27:522–529, 2004
- Piccini JP, Klein L, Gheorghade M, Bonow RO: New insights into diastolic heart failure: role of diabetes mellitus. *Am J Med* 116 (Suppl. 5A):64S–75S, 2004
- Solang L, Malmberg K, Ryden L: Diabetes mellitus and congestive heart failure. *Eur Heart J* 20:789–795, 1999
- Rodrigues B, Cam MC, McNeill JH: Metabolic disturbances in diabetic cardiomyopathy. *Mol Cell Biochem* 180:53–57, 1998
- Thrainsdottir IS, Aspelund T, Thorgerisson G, Gudnason V, Hardarson T, Malmberg K, Sigurdsson G, Ryden L: The association between glucose abnormalities and heart failure in the population-based Reykjavik study. *Diabetes Care* 28:612–616, 2005
- Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, Greenland P, Jacob DR Jr, Kronmal R, Liu K, Nelson JC, O'Leary D, Saad MF, Shea S, Szklo M, Tracy RP: Multi-ethnic study of atherosclerosis: objectives and design. *Am J Epidemiol* 156:871–881, 2002
- American Diabetes Association: Diagnosis and classification of diabetes mellitus (Position Statement). *Diabetes Care* 27 (Suppl. 1):S5–S10, 2004
- Natori S, Lai S, Finn PJ, Gomes AS, Hundley WG, Jerosch-Herold M, Pearson G, Sinha S, Olson J, Aria A, Lima JA, Bluemke DA: Cardiac MR imaging in MESA: protocol and normal values by age, gender and ethnicity. *AJR Am J Roentgenol*. In press
- O'Leary DH, Polak JF, Wolfson SK, Jr, Bond MG, Bommer W, Sheth S, Psaty BM, Sharrett AR, Manolio TA: Use of sonography to evaluate carotid atherosclerosis in the elderly: the Cardiovascular Health Study. *Stroke* 22:1155–1163, 1991
- Rutter MK, Parise H, Benjamin EJ, Levy D, Larson MG, Meigs JB, Nesto RW, Wilson PW, Vasan RS: Impact of glucose intolerance and insulin resistance on cardiac structure and function: sex-related differences in the Framingham Heart Study. *Circulation* 107:448–454, 2003
- Ilcercil A, Devereux RB, Roman MJ, Paranicas M, O'Grady MJ, Welty TK, Robbins DC, Fabsitz RR, Howard BV, Lee ET: Relationship of impaired glucose tolerance to left ventricular structure and function: The Strong Heart Study. *Am Heart J* 141:992–998, 2001
- Lee M, Gardin JM, Lynch JC, Smith VE, Tracy RP, Savage PJ, Szklo M, Ward BJ: Diabetes mellitus and echocardiographic left ventricular function in free-living elderly men and women: the Cardiovascular Health Study. *Am Heart J* 133:36–43, 1997
- Kizer JR, Arnett DK, Bella JN, Paranicas M, Rao DC, Province MA, Oberman A, Kitzman DW, Hopkins PN, Liu JE, Devereux RB: Differences in left ventricular structure between black and white hypertensive adults: the Hypertension Genetic Epidemiology Network study. *Hypertension* 43:1182–1188, 2004
- Zabalgaitia M, Ur Rahman SN, Haley WE, Oneschuk L, Yunis C, Lucas C, Yarows S, Krause L, Amerena J: Impact of ethnicity on left ventricular mass and relative wall thickness in essential hypertension. *Am J Cardiol* 81:412–417, 1998
- Rodriguez CJ, Sciacca RR, Diez-Roux AV, Boden-Albala B, Sacco RL, Homma S, DiTullio MR: Relation between socioeconomic status, race-ethnicity, and left ventricular mass: the Northern Manhattan

- study. *Hypertension* 43:775–779, 2004
21. Chaturvedi N, McKeigue PM, Marmot MG, Nihoyannopoulos P: A comparison of left ventricular abnormalities associated with glucose intolerance in African Caribbeans and Europeans in the UK. *Heart* 85:643–648, 2001
 22. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP: Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med* 322:1561–1566, 1990
 23. Drazner MH, Rame JE, Marino EK, Gottdiener JS, Kitzman DW, Gardin JM, Manolio TA, Dries DL, Siscovick DS: Increased left ventricular mass is a risk factor for the development of a depressed left ventricular ejection fraction within five years: the Cardiovascular Health Study. *J Am Coll Cardiol* 43:2207–2215, 2004
 24. Little WC: Assessment of normal and abnormal cardiac function. In *Heart Disease: A Textbook of Cardiovascular Medicine*. 6th ed. Braunwald E, Zipes DE, Libby P, Eds. New York, WB Saunders, 2001, p. 485
 25. Nicolino A, Longobardi G, Furgi G, Rossi M, Zoccolillo N, Ferrara N, Rengo F: Left ventricular diastolic filling in diabetes mellitus with and without hypertension. *Am J Hypertens* 8:382–389, 1995
 26. Zabalgoitia M, Ismaeil MF, Anderson L, Maklady FA: Prevalence of diastolic dysfunction in normotensive, asymptomatic patients with well-controlled type 2 diabetes mellitus. *Am J Cardiol* 87:320–323, 2001
 27. Diamant M, Lamb HJ, Groeneveld Y, Endert EL, Smit JW, Bax JJ, Romijn JA, de Roos A, Radder JK: Diastolic dysfunction is associated with altered myocardial metabolism in asymptomatic normotensive patients with well-controlled type 2 diabetes mellitus. *J Am Coll Cardiol* 42:328–335, 2003
 28. Al Shafei AI, Wise RG, Gresham GA, Carpenter TA, Hall LD, Huang CL: Magnetic resonance imaging analysis of cardiac cycle events in diabetic rats: the effect of angiotensin-converting enzyme inhibition. *J Physiol* 538:555–572, 2002
 29. Shinbane JS, Wood MA, Jensen DN, Ellenbogen KA, Fitzpatrick AP, Scheinman MM: Tachycardia-induced cardiomyopathy: a review of animal models and clinical studies. *J Am Coll Cardiol* 29:709–715, 1997
 30. Poirier P, Bogaty P, Garneau C, Marois L, Dumesnil J-G: Diastolic dysfunction in normotensive men with well-controlled type 2 diabetes: importance of maneuvers in echo-cardiographic screening for pre-clinical diabetic cardiomyopathy. *Diabetes Care* 24:5–10, 2001
 31. Sasso FC, Carbonara O, Cozzolino D, Rambaldi P, Mansi L, Torella D, Gentile S, Turco S, Torella R, Salvatore T: Effects of insulin-glucose infusion on left ventricular function at rest and during dynamic exercise in healthy subjects and noninsulin dependent diabetic patients: a radionuclide ventriculographic study. *J Am Coll Cardiol* 36:219–226, 2000
 32. Bottini PB, Carr AA, Prisant LM, Flickinger FW, Allison JD, Gottdiener JS: Magnetic resonance imaging compared to echocardiography to assess left ventricular mass in the hypertensive patient. *Am J Hypertens* 8:221–228, 1995
 33. Karter AJ, Ferrara A, Liu JY, Moffet HH, Ackerson LM, Selby JV: Ethnic disparities in diabetic complications in an insured population. *JAMA* 287:2519–2527, 2002
 34. Carnethon MR, Bertoni AG, Shea S, Greenland P, Ni H, Jacob DR Jr, Saad M, Liu K: Racial/ethnic differences in sub-clinical atherosclerosis among adults with diabetes: the Multi-Ethnic Study of Atherosclerosis. *Diabetes Care* 28:2768–2770, 2005