JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 64, NO. 19, 2014

ISSN 0735-1097/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jacc.2014.08.035

ORIGINAL INVESTIGATIONS

The Relationship of Left Ventricular Trabeculation to Ventricular Function and Structure Over a 9.5-Year Follow-Up

The MESA Study

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ABSTRACT

BACKGROUND Left ventricular (LV) trabeculation is highly variable among individuals and is increased in some diseases (e.g., congenital heart disease or cardiomyopathies), but its significance in population-representative individuals is unknown.

OBJECTIVES The goal of this study was to determine if excessive LV trabeculation in population-representative individuals is associated with preceding changes in cardiac volumes and function.

METHODS For technical reasons, the extent of trabeculation, which is expressed as the ratio of noncompacted to compacted (NC/C) myocardium, was measured on cardiac magnetic resonance (CMR) long-axis cine images in 2,742 participants in the MESA (Multi-Ethnic Study of Atherosclerosis) (mean age 68.7 years; 52.3% women; 56.4% with hypertension; 16.8% with diabetes) at examination 5. These were considered in quintiles of trabeculation extent; the NC/C ratio of quintile 5 was 2.46 to 5.41. We determined the relationship between the maximal NC/C ratio and the preceding change (9.5 years between examinations 1 and 5) in end-systolic volume indexed (ESVi) to body surface area. Secondary analyses assessed the associations between the maximal NC/C ratio and preceding changes in end-diastolic volume indexed (EDVi) to body surface area and the ejection fraction (EF).

RESULTS Over 9.5 years, the ESVi decreased by 1.3 ml/m^2, the EDVi decreased by 5.1 ml/m^2, and the EF decreased by 0.6% ($p < 0.0001$). Even in subjects with excessive trabeculation, there were no clinically relevant differences in LV volumes and systolic function changes among the quintiles of trabeculation extent.

CONCLUSIONS Greater extent of, and even excessive, LV trabeculation measured in end-diastole in asymptomatic population-representative individuals appeared benign and was not associated with deterioration in LV volumes or function during an almost 10-year period. (J Am Coll Cardiol 2014;64:1971–80) © 2014 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CMR = cardiovascular magnetic resonance

EDVi = end-diastolic volume index

EF = ejection fraction

ESVi = end-systolic volume index

LV = left ventricle/ventricular

LVEF = left ventricular ejection fraction

LVNC = left ventricular noncompaction

NC/C = noncompaction to compaction

SSFP = steady-state free precession

Human left ventricular (LV) cardiac trabeculation is highly variable among individuals. Although some differences may be related to ethnicity (1), there have been concerns that extreme trabeculation may be either pathologic or a marker of underlying heart muscle disease. LV noncompaction (LVNC) is considered a distinct form of cardiomyopathy (2,3) in which the hallmark phenotypic feature is extensive LV trabeculation. The disease may lead to cardiac failure, thromboembolism, and malignant arrhythmias. To date, only small studies that used cardiovascular magnetic resonance (CMR) imaging have described patterns and the extent of LV trabeculation in cohorts with a probable LVNC diagnosis on the basis of symptoms, family history, or impaired cardiac function (4,5). However, although increased LV trabeculation is associated with other cardiac conditions, such as cardiomyopathies (6) and congenital heart diseases (7), it has also been frequently observed in healthy individuals (8). Extensive LV trabeculation is commonly detected following CMR imaging. When LVNC imaging diagnostic criteria are met as an incidental finding, a diagnosis of LVNC remains controversial. The natural history and outcomes in people with pronounced LV trabeculation in the absence of any other structural heart abnormalities are unknown.

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This background combined with difficulties in measuring trabeculae raise concerns that extensive trabeculation in apparently normal individuals may be a pre-phenotypic marker of underlying disease, a marker of adverse outcome, or a normal phenotypic variant. Accordingly, individuals with extensive trabeculation may be offered costly long-term follow-up and are subject to the emotional and financial implications of a cardiomyopathy diagnosis.

The purpose of this study was to determine the relationship between the extent of LV trabeculation (using CMR imaging) and myocardial structure and function in a large population-based cohort study. Specifically, our primary aim was to evaluate whether excessive LV trabeculation, which is measured as the maximal ratio of noncompaction to compaction (NC/C), was associated with preceding changes in the end-systolic volume indexed (ESVi) to the body surface area. In secondary analyses, we evaluated the associations between the maximal NC/C ratio and preceding changes in the end-diastolic volume indexed (EDVi) to the body surface area and the development of LV dysfunction, which was expressed by deterioration in the LV ejection fraction (EF).

METHODS

STUDY POPULATION. The MESA (Multi-Ethnic Study of Atherosclerosis) is a population-based prospective cohort study [see the MESA website (9) for a full list of participating MESA investigators]. Between 2000 and 2002, 5,004 of the 6,814 study participants, who were free of clinically recognized cardiovascular disease and from 4 different ethnicities, underwent CMR imaging at enrollment (examination 1) (10). Of these, 3,016 participants underwent CMR imaging between 2010 and 2011 (examination 5). Study participants were excluded due to insufficient image quality (n = 241) and incomplete CMR datasets (n = 33), leaving 2,742 participants (**Figure 1**). Clinical data, including the incidence of heart failure, atrial fibrillation, myocardial infarction, stroke, and transient ischemic attacks, were available for all participants. MESA criteria for clinical events and follow-up procedures were previously described (11). The institutional review boards of each of the 6 participating field sites in the United States approved the study, and all participants provided written informed consent at the time of enrollment into MESA.

MAGNETIC RESONANCE IMAGING. CMR examinations were performed at 6 centers (Baltimore, Winston-Salem, New York, Minneapolis, Los Angeles, and Chicago) using either a Signa Excite (General

National Institute for Health Research Cardiovascular Biomedical Research Unit at Barts. Prof. Petersen's work is supported by awards establishing the Farr Institute of Health Informatics Research at UCLP Partners from the MRC, in partnership with Arthritis Research UK, the British Heart Foundation, Cancer Research UK, the Economic and Social Research Council, the Engineering and Physical Sciences Research Council, the National Institute of Health Research, the National Institute for Social Care and Health Research (Welsh Assembly Government), the Chief Scientist Office (Scottish Government Health Directorates), and the Wellcome Trust (MR/K006584/1). Dr. Prince has patent agreements with GE, Siemens, Philips, Toshiba, Hitachi, Bayer, Bracco, Medrad, Mallinckrodt, Nemoto, and Lantheus. Prof. Petersen has been a consultant for Circle Cardiovascular Imaging Inc., Calgary, Canada. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.
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Manuscript received May 23, 2014; revised manuscript received July 30, 2014, accepted August 6, 2014.

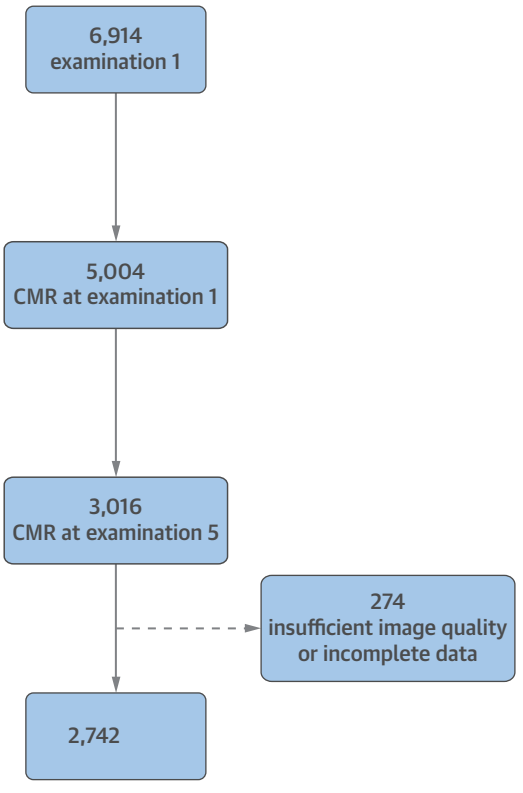

FIGURE 1 Flow Diagram of Exclusion Process

Exclusion criteria of participants from MESA for this study.
CMR = cardiovascular magnetic resonance.

Electric Medical Systems, Waukesha, Wisconsin) or Avanto/Espree (Siemens, Erlangen, Germany) 1.5-T MR scanners for examinations 1 and 5. Planning of the cardiac cine images for both examinations was standardized to minimize variation among centers. Cine images were obtained with a temporal resolution of approximately 50 ms or less using a segmented k-space and an electrocardiographically gated, fast spoiled gradient-recalled echo pulse sequence during MESA examination 1 (12). Retrospectively, electrocardiographically gated long- and short-axis cine images were acquired using a steady-state free precession (SSFP) sequence at MESA examination 5 (13).

IMAGE EVALUATION. LV volumes and function. All MESA examinations 1 and 5 CMR images were analyzed for LV volumes and function in a core laboratory and analyzed at a single image analysis center by readers blinded to clinical outcomes, as previously described (13,14). Calibration between the 2 CMR examinations was performed in 498 participants who had both image sequences acquired at MESA examination 5. The calibration group was selected to be representative of all body sizes. Calibration was performed for both technologist readers (by re-reading 498 MESA examination 1 images) and pulse sequences (same technologist reader, who analyzed both pulse sequences using identical software). All calibration curves were found to be linear and were fitted with ordinary regression methods.

For quality control purposes, all readers independently analyzed every 10th consecutive CMR examination. The overall interobserver intraclass correlation coefficients for LV mass and LV end-diastolic volume were 0.95 and 0.96, respectively, and technical errors of measurement were 6.1% and 5.4%, respectively. The interobserver agreements were similar to those of the baseline study (12).

LV trabeculation. CMR examinations were evaluated for the NC/C ratio using the post-processing software tool, CVI42 (Circle Cardiovascular Imaging Inc., Calgary, Alberta, Canada). The NC/C ratio could only be determined for the MESA examination 5 CMR data because the CMR sequence used at the MESA examination 1 did not provide the level of detail and contrast required. Although there are different approaches to assessing the extent of LV trabeculation in both echocardiography and CMR, we restricted our analysis to the NC/C ratio proposed by Petersen et al. (4).

Horizontal and vertical long-axis cine SSFP images were used for measuring the thickness of the compacted myocardium and of the trabeculations at the center of 8 LV regions: anterior; inferior; septal; and lateral at the mid-ventricular and apical levels at end-diastole, as previously described by Kawel et al. (8) (**Figure 2**). The NC/C ratio was calculated for each segment. Measurements were not performed at the LV base, because trabeculations are not typically observed in this region. In normal individuals, the true apex is usually very thin, with prominent trabeculations; therefore, it was also excluded (4,14). Compacted myocardium was defined as a myocardial layer of homogeneous moderate signal intensity on SSFP images without inclusion of blood with a higher signal intensity. Trabeculations were defined as a meshwork of the trabeculae carneae of moderate signal intensity adjacent to the compacted myocardium interspersed with blood of higher signal intensity. Measurements of the thickness of the compacted myocardium and of adjacent trabeculations were obtained perpendicular to the compacted myocardium. Fifty percent of the thickness of the chemical shift artifact (appearing as a black line) on the epicardial surface was included in the compact myocardium. Papillary muscles that were clearly

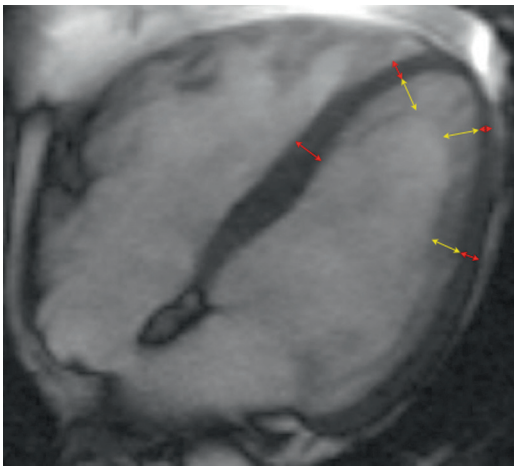

FIGURE 2 Measurement of NC/C Ratios

Example of an end-diastolic, 4-chamber steady-state free precession image of a participant with a very high maximal noncompaction to compaction (NC/C) ratio (= 4.2) in the MESA examination 5. **Red arrows** show measurements of the compacted myocardium; **yellow arrows** represent measurements of the noncompacted (trabeculated) layer.

observed as compact tubular structures were not included in the measurements. Short-axis views and cine mode were used in addition to separate papillary muscles from trabeculation. The orientation of long-axis images was cross-referenced with short-axis views, which allowed exclusion of off-axis images. Measurements of 60 randomly selected studies were repeated by the first reader and by a second reader to quantify intra- and interobserver variability. The NC/C ratio >2.3 was considered a current diagnostic criterion for LVNC (criterion used by Petersen et al.) (4).

STATISTICAL ANALYSIS. Unless otherwise stated, descriptive statistics for continuous variables are presented as mean and the SD, if normally distributed. Categorical variables are presented as a percentage. Differences between quintiles were evaluated by analysis of variance with post-hoc Tukey tests for continuous variables and with chi-square tests for categorical variables.

Simple and multivariate linear regression models were developed to examine the relationship of the independent variables (the maximal NC/C ratio, the NC/C ratio >2.3 in 1 segment, and the NC/C ratio >2.3 in >1 segment) to functional, continuous dependent variables related to heart failure, which included changes in the LV volumes and EF between examination 1 and examination 5. Covariates used for multivariable regression models are listed in Table 1.

All statistical analyses were performed using R software version 3.0.1 (R Foundation for Statistical Computing, Vienna, Austria) (15).

Intraclass correlation coefficients were used to evaluate intra- and interobserver agreement. In all cases, statistical significance was set at $p < 0.05$ (2-tailed).

RESULTS

DEMOGRAPHICS. Detailed demographic and CMR data are presented in Table 2. The mean age of study subjects at examination 5 was 68.7 years (52.3% women). Ethnicity was self-reported as Caucasian or white in 42.1%, Chinese American in 12.5%, African American/black in 24.9%, and Hispanic in 20.5%. Hypertension was present in 56.4% of participants. At examination 5, 536 (19.5%) of the study subjects were treated with angiotensin-converting enzyme inhibitors, 248 (9.0%) with angiotensin II antagonists, 475 (17.3%) with beta-blockers, and 1,035 (37.7%) subjects were treated with 1 or more of the previous agents. Four hundred twenty-three participants (15.5%) were being treated for diabetes, and 1,456

TABLE 1 Regression Models With Maximal NC/C Ratio, Demographic Data, CMR Data, and Classic Risk Factors

Exposure Variable	Outcome Variables (Change Between Examinations 1 and 5)	Univariable Regression		Multivariable Regression: Model 1		Model 2		Model 3	
		Beta (95% CI)	R^2	Beta (95% CI)	R^2	Beta (95% CI)	R^2	Beta (95% CI)	R^2
Maximal NC/C ratio	End-diastolic volume index (ml/m^2)	1.6* (0.9 to 2.3)	0.008	1.9* (1.2 to 2.6)	0.034	2.7* (2.1 to 3.3)	0.261	2.6* (2.0 to 3.3)	0.269
	End-systolic volume index (ml/m^2)	0.3 (−0.1 to 0.8)	0.0009	0.5† (0.1 to 0.9)	0.026	1.0 (0.6 to 1.4)	0.195	1.0* (0.6 to 1.4)	0.200
	EF (%)	0.4 (−0.1 to 0.8)	0.0009	0.3 (−0.1 to 0.7)	0.013	−0.2 (−0.6 to 0.2)	0.324	−0.2 (−0.6 to 0.1)	0.320

Univariate and multivariate linear regression analysis models for the changes in the end-diastolic volume index (EDVi), end-systolic volume index (ESVi), and ejection fraction (EF) between MESA examinations 1 and 5 as dependent variables in models incorporating the maximal noncompaction to compaction (NC/C) ratio, demographic data, baseline cardiac magnetic resonance (CMR) parameters at MESA examination 1, and traditional risk factors as predictor variables. Model 1: adjusted for age, sex, and ethnicity. Model 2: adjusted for Model 1 parameters plus baseline EDVi (for change in EDVi), ESVi (for change in ESVi), and EF (for change in EF). Model 3: adjusted for Model 2 parameters plus diabetes, smoking history, total cholesterol, systolic blood pressure, and BMI. *p <0.001; †p <0.05.

CI = confidence interval.

TABLE 2 Demographic and CMR Data at MESA Examination 5

	All (n = 2,742)	Quintile 1 NC/C: 0-1.41 (n = 549)	Quintile 2 NC/C: 1.42-1.71 (n = 548)	Quintile 3 NC/C: 1.72-2.00 (n = 548)	Quintile 4 2.01-2.45 (n = 548)	Quintile 5 2.46-5.41 (n = 549)	p Value
Age, yrs	68.7 ± 9.1	69.1 ± 9.2	69.1 ± 9.3	68.6 ± 8.9	68.6 ± 9.0	68.0 ± 9.2	0.29
Women	1,435 (52.3)	266 (48.5)	286 (52.2)	261 (47.6)	304 (55.5)	318 (57.9)	<0.01
Race							
Caucasian	1,154 (42.1)	230 (41.9)	242 (44.2)	207 (37.8)	238 (43.4)	237 (43.2)	0.49
Chinese American	343 (12.5)	60 (10.9)	75 (13.7)	82 (15.0)	69 (12.6)	57 (10.4)	0.18
Black/African American	682 (24.9)	148 (27.0)	141 (25.7)	139 (25.4)	131 (23.9)	123 (22.4)	0.61
Hispanic	563 (20.5)	111 (20.2)	90 (16.4)	120 (21.9)	110 (20.1)	132 (24.0)	0.07
Body mass index, kg/m^2	27.9 ± 5.1	28.3 ± 5.2	28.1 ± 5.2	28.1 ± 5.3	28.0 ± 5.2	27.2 ± 4.7	<0.01
Height, cm	165.7 ± 9.8	166.0 ± 9.8	165.5 ± 9.5	165.7 ± 10.1	165.7 ± 10.0	165.5 ± 9.7	0.91
Weight, kg	76.9 ± 16.5	78.0 ± 16.0	77.3 ± 17.1	77.5 ± 17.5	77.0 ± 16.5	74.8 ± 15.4	<0.05
Hypertension	1546 (56.4)	323 (58.8)	326 (59.5)	314 (57.3)	305 (55.8)	278 (50.6)	<0.05
Systolic blood pressure, mm Hg	122.6 ± 20.0	123.7 ± 21.1	125.7 ± 20.8	122.9 ± 20.3	121.4 ± 19.0	119.4 ± 18.1	<0.0001
Diastolic blood pressure, mm Hg	68.3 ± 9.9	69.0 ± 9.8	69.0 ± 10.4	68.8 ± 9.8	67.6 ± 9.7	67.0 ± 9.7	<0.001
Diabetes by 2003 ADA (n = 2,613)							
Normal	1,702 (62.5)	337 (61.7)	319 (58.5)	329 (60.5)	341 (62.5)	376 (69.2)	0.24
Impaired fasting glucose	564 (20.7)	104 (19.0)	122 (22.4)	118 (21.7)	118 (21.6)	102 (18.8)	0.57
Untreated diabetes	35 (1.3)	8 (1.5)	7 (1.3)	8 (1.5)	5 (0.9)	7 (1.3)	0.93
Treated diabetes	423 (15.5)	97 (17.8)	97 (17.8)	89 (16.4)	82 (15.0)	58 (10.7)	<0.05
Family history of a heart attack	1127 (43.5)	240 (46.2)	226 (44.1)	206 (39.9)	243 (46.6)	212 (40.8)	0.1
Coronary disease	96 (3.5)	27 (4.9)	14 (2.6)	15 (2.7)	19 (3.5)	21 (3.8)	0.21
Smoking							
Never	1275 (46.7)	242 (44.2)	260 (47.7)	262 (48.1)	247 (45.2)	264 (48.4)	0.82
Former	1249 (45.7)	260 (47.4)	240 (44.0)	245 (45.0)	262 (47.9)	242 (44.3)	0.78
Current	207 (7.6)	46 (8.4)	45 (8.3)	38 (7.0)	38 (6.9)	40 (7.3)	0.84
Education							
No school	9 (0.3)	3 (0.5)	0 (0.0)	0 (0.0)	3 (0.5)	3 (0.5)	–
Grades 1-8	196 (7.2)	39 (7.1)	45 (8.2)	38 (7.0)	32 (5.9)	42 (7.7)	0.66
Grades 9-11	119 (4.3)	26 (4.7)	22 (4.0)	31 (5.7)	17 (3.1)	23 (4.2)	0.34
Completed high school	445 (16.3)	87 (15.8)	73 (13.4)	98 (17.9)	101 (18.5)	86 (15.7)	0.24
Some college but no degree	435 (15.9)	84 (15.3)	90 (16.5)	92 (16.8)	98 (17.9)	71 (12.9)	0.31
Technical school certificate	203 (7.4)	39 (7.1)	44 (8.1)	44 (8.1)	40 (7.3)	36 (6.6)	0.88
Associate degree	145 (5.3)	26 (4.7)	36 (6.6)	26 (4.8)	25 (4.6)	32 (5.8)	0.53
Bachelor's degree	555 (20.3)	116 (21.1)	110 (21.1)	95 (17.4)	109 (19.9)	125 (22.8)	0.36
Graduate or professional school	630 (23.0)	129 (23.5)	126 (23.1)	122 (22.3)	122 (22.3)	131 (23.9)	0.97
LV end-diastolic volume index, ml/m^2	65.2 ± 13.6	62.4 ± 14.3	63.5 ± 13.4	65.7 ± 13.1	66.0 ± 13.3	68.3 ± 13.2	<0.0001
LV end-systolic volume index, ml/m^2	25.0 ± 8.5	24.1 ± 9.3	23.9 ± 8.0	25.4 ± 8.6	25.5 ± 8.4	26.3 ± 8.0	<0.0001
LVEF, %	62.0 ± 7.3	62 ± 7.4	62.8 ± 7.3	61.7 ± 7.8	61.7 ± 6.8	61.9 ± 7.0	0.1
LV mass index, g/m^2	66.4 ± 13.8	68.1 ± 14.3	68.2 ± 14.9	67.3 ± 14.0	65.1 ± 12.8	63.1 ± 12.4	<0.0001

Values are mean ± SD or n (%). Subjects with the highest trabeculation (quintile 5) had larger left ventricular volumes, end-diastolic mass index, and blood pressure values, and lower incidence of treated diabetes, weight, and body mass index.

ADA = American Diabetes Association; LV = left ventricle; LVEF = left ventricular ejection fraction; NC/C = noncompaction to compaction ratio.

(53.3%) were current or former smokers. Impaired systolic function (EF <50%) was present in 111 (4.0%) subjects at baseline examination 1, but they were symptom-free, and there were no differences among the quintiles of the maximal NC/C ratio (p = 0.62).

Extent of LV trabeculation. The NC/C ratio was calculated in 19,320 (88.1%) segments; 2,616 (11.9%) segments were excluded because of insufficient contrast between the blood pool and the myocardium to confidently measure the NC/C ratios. The intraclass correlation coefficient was 0.83 (p < 0.0001) for intraobserver NC/C ratio measurements and 0.82 (p < 0.0001) for interobserver measurements. The LVNC criterion (NC/C ratio >2.3) used by Petersen et al. (4) was fulfilled in 706 (25.7%) participants for at least 1 cardiac segment and in 218 (8.0%) participants for at least 2 segments.

The mean of the maximal NC/C ratio of each participant's analyzed segments was 1.96 ± 0.66. This was higher in women (2.0 ± 0.68 vs. 1.92 ± 0.64; p < 0.001), but independent of age (p = 0.051). There were no differences in the maximal NC/C ratio among

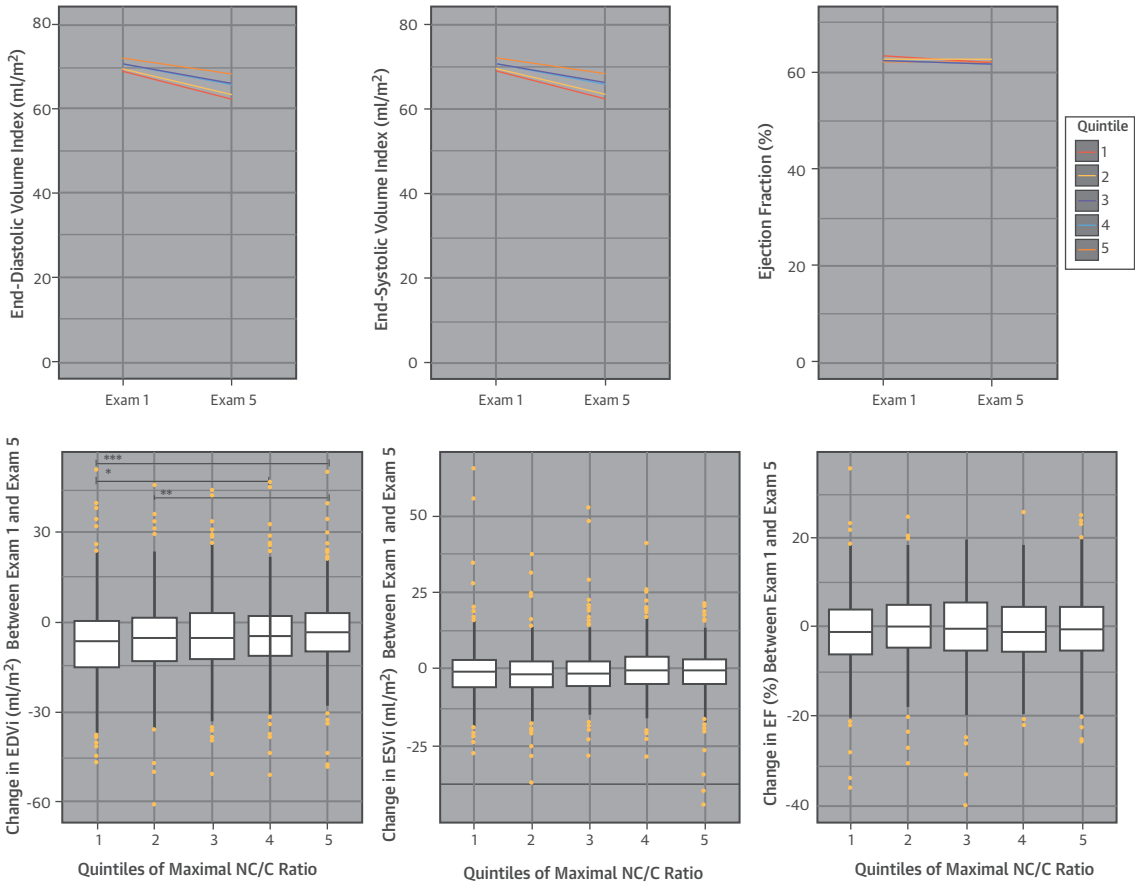

FIGURE 3 Changes in Cardiac Volumes and Function

Changes in left ventricular volumes and function between MESA examinations 1 and 5 and the relationship to the extent of LV trabeculation (in quintiles) at examinations 5 presented in 2 ways: the **bottom panel** shows box and whisker plots and the lack of clinically relevant changes in volume or function; the **top panel** shows similar slopes for the quintiles of trabeculation extent with regard to volumes and function between both examinations. **Boxes** represent the interquartile range and **whiskers** are within 1.5 times interquartile range. Outliers are plotted as points. The **line within the box** represents the median. *p <0.05; **p <0.01; ***p <0.001. NC/C = noncompacted to compacted ratio. Exam = examination.

TABLE 3 Cardiovascular Adverse Outcomes in Relation to the Extent of LV Trabeculations

	All	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Atrial fibrillation	24	10 (1.9)	7 (1.3)	1 (0.2)	3 (0.6)	3 (0.6)
Congestive heart failure	22	4 (0.7)	5 (0.9)	5 (0.9)	4 (0.7)	4 (0.7)
Stroke	28	4 (0.7)	8 (1.5)	10 (1.9)	2 (0.4)	4 (0.7)
Transient ischemic attack	17	4 (0.7)	3 (0.6)	4 (0.7)	4 (0.7)	2 (0.4)
Myocardial infarction	41	15 (2.8)	2 (0.4)	8 (1.5)	9 (1.7)	7 (1.3)
Hard cardiovascular endpoints	68	19 (3.6)	10 (1.9)	18 (3.4)	11 (2.0)	10 (1.9)
All cardiovascular endpoints	121	31 (6.0)	21 (4.0)	25 (4.8)	20 (3.8)	24 (4.6)

Values are n or n (%). The incidence of cardiovascular adverse outcomes in the whole studied cohort and quintiles of maximal NC/C ratio are shown. Hard cardiovascular endpoints included myocardial infarction, resuscitated cardiac arrest, and stroke. All cardiovascular endpoints include hard cardiovascular endpoints plus definite angina, probable angina followed by coronary revascularization.

Abbreviations as in Table 2.

the 4 ethnicities studied in MESA (1.98 ± 0.69 in Caucasians, 1.91 ± 0.56 in Chinese Americans, 1.93 ± 0.66 in African Americans, and 2.00 ± 0.65 in Hispanics; p = 0.08).

The maximal NC/C ratio was correlated with the number of segments that fulfilled the LVNC criteria (r = 0.76; p < 0.0001) and was greater in larger LV cavities; the ratio increased by 0.2 ± 2.1 for each 100-ml larger end-diastolic volume (p < 0.0001) and by 0.3 ± 3.6 for each 100-ml larger end-systolic volume (p < 0.0001). There was no association of the maximal NC/C ratio with the LVEF (p = 0.16).

Relationship between extent of trabeculation and precedent changes in LV volumes and EF. We divided the cohort into quintiles by the extent of

EXTENT OF NC/C RATIO IN QUINTILES	Quintile 1 (0 to 1.41)	Quintile 2 (1.42 to 1.72)	Quintile 3 (1.73 to 2.01)	Quintile 4 (2.02 to 2.45)	Quintile 5 (2.46 to 5.41)	p Value
CHANGE IN ESVI (ML/M²)	-1.3 ± 8.0	-2.1 ± 7.1	-1.4 ± 7.5	-0.9 ± 7.4	-1.0 ± 7.2	0.08
CHANGE IN EDVI (ML/M²)	-6.5 ± 13.1	-6.0 ± 12.4	-5.1 ± 12.1	-4.4 ± 12.3	-3.6 ± 11.3	<0.001
CHANGE IN EF (%)	-1.4 ± 8.2	-0.1 ± 7.6	-0.4 ± 8.0	-0.8 ± 7.5	-0.3 ± 7.9	0.053

Zemrak, F., et al., J Am Coll Cardiol. 2014; 64(19):1971–80.

CENTRAL ILLUSTRATION Changes Over a 9.5-Year Period in the ESVi, EDVi, and EF

The changes over this time period in the end-systolic volume index (ESVi) and ejection fraction (EF) were not different among the quintiles of maximal noncompaction to compaction ratio (NC/C), even in participants in whom the current "normal value" (<2.3) was exceeded. The decrease in the end-diastolic volume index (EDVi) was smaller with an increasing extent of trabeculation; significant differences were seen between quintiles 1 and 4 ($p < 0.05$), between quintiles 1 and 5 ($p < 0.001$), and between quintiles 2 and 5 ($p < 0.01$), but these changes were clinically insignificant.

the maximal NC/C ratio. Detailed demographic data and CMR parameters are presented in Table 2.

In the 9.5-year interval between examinations 1 and 5, the ESVi decreased, on average, by 1.3 ± 7.3 ml/m² ($p < 0.0001$), and there were no differences among the quintiles of the maximal NC/C ratio (Figure 3).

Similarly, the ESVi decreased, on average, by 5.1 ± 12.3 ml/m² ($p < 0.0001$). The decrease was smaller with an increasing extent of trabeculation; significant differences were seen between quintiles 1 and 4 (-6.5 ± 13.1 ml/m² vs. -4.4 ± 12.3 ml/m²; $p < 0.05$), between quintiles 1 and 5 (-6.5 ± 13.1 ml/m² vs. -3.6 ± 11.3 ml/m²; $p < 0.001$), and also between quintiles 2 and 5 (-6.0 ± 12.4 ml/m² vs. -4.4 ± 12.3 ml/m²; $p < 0.01$) (Figure 3, Central Illustration).

The EF decreased by 0.6% ± 7.8% ($p < 0.0001$) over 9.5 years; however, there were no differences among the quintiles of the maximal NC/C ratio (Figure 3). Several demographic parameters and clinical characteristics differed by small amounts, but these reached statistical significance in univariate analyses with regard to the extent or distribution among the quintiles of the maximal NC/C ratio (Table 2).

After adjustment for age, sex, ethnicity, and baseline CMR imaging parameters from examination 1 (Model 2), a 1-U greater maximal NC/C ratio (e.g., from 1 to 2, from 2 to 3, and so forth) was associated with a 2.7 ± 16.1 ml/m² ($p < 0.0001$) decrease in the EDVi and a 1.0 ± 10.2 ml/m² ($p < 0.0001$) decrease in the ESVi. These models accounted for 26.1% and 19.5% of the variances in the volume changes, respectively (Table 1). Multivariate regression models with conventional risk factors (body mass index, systolic blood pressure, diabetes, smoking, total cholesterol to high-density lipoprotein ratio) (Table 1), as well as exercise, education, and a family history of heart attack showed similar findings to Model 2 (data not presented). Overall, despite statistical significance, the observed changes in the EDVi and ESVi in relationship to the NC/C ratio were not clinically relevant. The maximal NC/C ratio was not associated with a change in the LVEF.

Sensitivity analysis. The relationships described earlier for the maximal NC/C ratio as a continuous variable were repeated using the NC/C ratio >2.3 and the number of segments with the NC/C ratio >2.3. All results showed the same trends as for the continuous NC/C ratio variable.

Extent of LV trabeculation and adverse clinical events. The incidence of atrial fibrillation, congestive cardiac failure, stroke, transient ischemic attack, history of myocardial infarction, composite cardiovascular endpoints, and all cardiovascular endpoints in the quintiles of the maximal NC/C ratio are presented in Table 3. In view of the low-event incidence, no formal statistical analysis was performed.

DISCUSSION

The long-term relationship between excess LV trabeculation and changes in myocardial function and

structure was not previously known. This is the first study to show that a greater extent of LV trabeculation was not associated with an absolute increase in end-systolic and end-diastolic volumes during the approximately 10 years of the MESA study. A greater NC/C ratio was not associated with a decline in systolic function.

These results advance our understanding of ventricular morphology in regard to "asymptomatic trabeculation" in relatively healthy individuals in the community. In particular, MESA subjects with greater trabeculation had only minor relative changes in left ventricular end-diastolic volume index compared to subjects with lesser trabeculation that, although statistically significant, were unlikely to have clinical implications.

PREVALENCE OF IMAGING DIAGNOSIS LVNC. The estimated prevalence of LVNC is between 0.014% and 1.3% in the general population (2,16,17). However, all echocardiographic or CMR-based imaging criteria for LVNC were established on pre-selected, symptomatic individuals with heart failure or cardiovascular complications. It is important to emphasize that there are currently no diagnostic tools, neither genetic nor imaging, to identify patients affected by LVNC with absolute certainty. This is the main reason cardiac imaging studies have limitations when attempting to determine diagnostic accuracies on the basis of a likely LVNC diagnosis, rather than a definitive diagnosis.

Recent studies that used high-resolution imaging techniques, such as multidetector computed tomography and CMR, revealed the frequent presence of pronounced trabeculation that reached diagnostic thresholds for LVNC in healthy volunteers (8,18).

This study, which extended the analysis by Kawel et al. (8) of 323 MESA participants who were free from cardiovascular disease to the whole MESA cohort, showed that only 25.7% fulfilled the current diagnostic criteria for LVNC, compared with the 43% described by Kawel et al (8). This discrepancy is likely to be partly related to software differences. The CVI42 software used in this analysis allowed identification of "off-axis acquisitions," whereas the software used by Kawel et al. did not provide a cross-reference tool.

ASSOCIATION OF EXTENT OF LV TRABECULATION ON ADVERSE CARDIAC REMODELING AND CLINICAL OUTCOMES. Baseline LV dimensions and the EF are among the most powerful predictors of survival in heart failure and in people without cardiovascular disease, and are now well-established surrogate markers in heart failure trials (19–22). In this study, we evaluated the change in the ESVi, EDVi, and EF. Our main findings were that the maximal NC/C ratio and other measures of the extent of LV trabeculation were associated with small, but clinically negligible, changes in LV parameters over the almost 10-year MESA study period. The multivariate regression model incorporating the maximal NC/C ratio, demographic data, and the baseline CMR data (Model 2, **Table 1**) increased the explained variance almost 10-fold compared with the model that incorporated only the extent of trabeculation and demographic factors (Model 1, **Table 1**). This suggested that the maximal NC/C ratio plays a very small clinical role in cardiac remodeling. The EDVi and ESVi decreased over the 9.5 years of the MESA study period, even in participants with the most pronounced trabeculation (by 3.6 ml/m^2 and 1.0 ml/m^2 in the highest quintile of the maximal NC/C ratio).

In comparison, a previous study by Doughty et al. in subjects with congestive heart failure due to ischemic heart disease described an increase in the EDVi by 10.5 ml/m^2 over only 12 months in the placebo group (23).

Similarly, measures of the degree of LV trabeculation were not associated with the adverse clinical outcomes known to be associated with a clinical diagnosis of LVNC. These data may seem contrary to the many reports of embolic events in patients with LVNC; however, the studied population was considered healthy, and the probability of LVNC (or other cardiac diseases) was extremely low in this group.

IMPORTANCE OF CLINICAL INFORMATION WHEN INTERPRETING IMAGING LVNC CRITERIA. Our study again demonstrates that the criteria in Petersen et al. (NC/C >2.3) are frequent findings in a "healthy" population-representative cohort (24). Importantly, our study underlines the importance of interpreting such an imaging diagnosis in the context of the available clinical information (24). Our findings suggest that in subjects with a low pre-test probability for cardiomyopathy or LVNC and marked trabeculation, regular and frequent imaging and clinical follow-up may be unnecessary.

The criteria in the Petersen et al. study were derived from a group of patients with high pre-test probability who were imaged at a tertiary cardiomyopathy center and showed high sensitivity and specificity for diagnosing LVNC (4). Current diagnostic criteria are applicable as a rule-in test if the suspicion (pre-test probability) of LVNC is >10%; there criteria could theoretically be used as a rule-out test if applied in patients with low pre-test probability for LVNC (24).

STUDY LIMITATIONS. The data of the present study must be interpreted in the context of the study

design. As described in the Methods section, we were only able to analyze trabeculation on the most recent SSFP cine images from the MESA examination 5 data, but could not analyze the gradient-recalled echocardiogram cine images acquired during the MESA examination 1. Although this makes the data more applicable to current clinical practice, we implied that trabeculation had not changed over the approximately 10 years beforehand. The rationale for this implication is the evidence that the development and extent of trabeculations were determined during cardiac development in utero (25). Some case reports describe an undulating phenotype of LV trabeculations, but this is unlikely to be common enough to influence the results of our study. Despite this, survivor bias may be present, and firm conclusions on causality cannot be drawn. This question cannot be addressed without this limitation for another 15 years, until MESA or other large-scale population-based cohort studies, such as UK Biobank, have sufficient serial CMR studies using SSFP cines.

Adverse clinical events were rare and therefore were not treated as primary outcomes in this study. Measurement of the NC/C ratio is operator dependent; however, there was a good intra- and inter-observer agreement. We used only 1 approach to measure the extent of LV trabeculations. Other reported strategies differ with respect to measuring the extent of LV trabeculations in short- or long-axis views, measuring at end-diastole or end-systole, calculating ratios based on the thicknesses of trabeculated and compacted myocardial layers or trabecular mass as a percentage of total LV mass. There is currently no consensus as to the best approach because each has advantages and disadvantages with respect to its reported diagnostic accuracy, reproducibility, observer variability, and ability to avoid inadvertent inclusion of papillary muscle in the measurements.

CONCLUSIONS

Although there is the potential for confounding and survivor bias, this study did not find a clinically relevant impact of trabeculae on LV function measured in end-diastole over an almost 10-year period in a population of representative adult individuals.

This information should guide clinical decision making in the common scenario of identifying patients with marked LV trabeculation and low pre-test probability of LVNC, that there is no clear need for follow-up imaging or pharmacotherapy in these patients.

ACKNOWLEDGMENTS The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: More extensive LV trabeculation (the ratio of NC/C) did not predict the development of clinically significant LV enlargement or systolic dysfunction over a decade of follow-up.

TRANSLATIONAL OUTLOOK: Because adverse changes in myocardial structure and function are an uncommon sequela of LVNC, further studies in which large numbers of individuals are followed for longer periods are needed to identify predictors of phenotypic cardiomyopathy.

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KEY WORDS cardiac magnetic resonance, left ventricular function, left ventricular trabeculations