

Fractal Analysis of Myocardial Trabeculations in 2547 Study Participants: Multi-Ethnic Study of Atherosclerosis¹

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Purpose:

To quantitatively determine the population variation and relationship of left ventricular (LV) trabeculation to LV function, structure, and clinical variables.

Materials and Methods:

This HIPAA-compliant multicenter study was approved by institutional review boards of participating centers. All participants provided written informed consent. Participants from the Multi-Ethnic Study of Atherosclerosis with cardiac magnetic resonance (MR) data were evaluated to quantify LV trabeculation as a fractal dimension (FD). Entire cohort participants free of cardiac disease, hypertrophy, hypertension, and diabetes were stratified by body mass index (BMI) into three reference groups (BMI <25 kg/m²; BMI ≥25 kg/m² to <30 kg/m²; and BMI ≥30 kg/m²) to explore maximal apical FD (FD_{MaxApical}). Multivariable linear regression models determined the relationship between FD and other parameters.

Results:

Included were 2547 participants (mean age, 68.7 years ± 9.1 [standard deviation]; 1211 men). FD_{MaxApical} are in arbitrary units. FD_{MaxApical} reference ranges for BMI 30 kg/m² or greater ($n = 163$), 25 kg/m² or greater to less than 30 kg/m² ($n = 206$), and less than 25 kg/m² ($n = 235$) were 1.203 ± 0.06 (95% confidence interval: 1.194, 1.212), 1.194 ± 0.06 (95% confidence interval: 1.186, 1.202), and 1.169 ± 0.05 (95% confidence interval: 1.162, 1.176), respectively. In the entire cohort, adjusted for anthropometrics, trabeculation was higher in African American participants (standardized β [$s\beta$] = 0.09; $P \leq .001$) and Hispanic participants ($s\beta = 0.05$; $P = .013$) compared with white participants and was also higher in African American participants compared with Chinese American participants ($s\beta = 0.08$; $P = .01$), and this persisted after adjustment for hypertension and LV size. Hypertension ($s\beta = 0.07$; $P < .001$), LV mass ($s\beta = 0.22$; $P < .001$), and wall thickness ($s\beta = 0.27$; $P < .001$) were positively associated with FD_{MaxApical} even after adjustment. In the group with BMIs less than 25 kg/m², Chinese American participants had less trabeculation than white participants ($s\beta = -0.15$; $P = .032$).

Conclusion:

Fractal analysis of cardiac MR imaging data measures endocardial complexity, which helps to differentiate normal from abnormal trabecular patterns in healthy versus diseased hearts. Trabeculation is influenced by race and/or ethnicity and, more importantly, by cardiac loading conditions and comorbidities. Clinicians who interpret cine MR imaging data should expect slightly less endocardial complexity in Chinese American patients and more in African American patients, Hispanic patients, hypertensive patients, and those with hypertrophy.

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Abnormal trabecular patterns of the ventricular myocardium coexist with established cardiac disease (1–5), and a spectrum of so-called normal trabeculation with interethnic differences has also been observed in healthy hearts (2,6). Because of this large variability, trabecular phenotypes are hard to measure, but the recently described (3) fractal method applied to cardiac magnetic resonance (MR) imaging provides a sensitive mathematical solution. It evaluates the section-by-section fractal properties of the left ventricle (LV) and derives a fractal dimension (FD), which is a highly reproducible, dimensionless index of endocardial complexity capable of detecting even subtle subclinical trabecular phenotypes (3).

Previous studies that used cardiac MR imaging focused on variants of the noncompacted (ie, trabeculate)-to-compacted (ie, nontrabeculate) myocardium ratio (7,8). By using these methodologic analyses, a significant proportion of individuals who did not have cardiac disease at baseline had noncompacted-to-compacted ratios (>2.3) that were higher than expected, which put them in the pathologic range for trabeculation (1). The noncompacted-to-compacted

wall thickness ratio (1), by its nature, incorporates a measure of wall thickness that opens it up to confounding comorbidities such as hypertension. FD solely evaluates the extent to which endocardial contours fill two-dimensional space, independent of the influence of wall thickness.

There may be added clinical utility in the use of the FD to measure endocardial complexity and to identify pathologic patterns of trabeculation (3), but it starts by understanding the healthy population variation of this parameter. A sufficiently large analysis cohort is required to appraise the effect of ethnicity and/or racial background on trabecular patterns after accounting for factors such as body size, sex, cardiac loading conditions, wall thickness, and comorbidity. By applying our in-house fractal analysis software to the large cardiac MR data set in the Multi-Ethnic Study of Atherosclerosis (MESA) we aimed to quantitatively determine the population variation and relationship of LV trabeculation to LV function, structure, and clinical variables.

Materials and Methods

Study Participants

This study was approved by the institutional review boards of each of the participating field sites in the United States, and all participants provided written informed consent. All sites were Health Insurance Portability and Accountability Act-compliant. The

Implications for Patient Care

- Defined normal variation of trabeculae by fractal analysis will help to avoid mislabeling of healthy patients with diseases like LV noncompaction at the time of cardiac MR examination.
- Serial fractal measurements of the LV over time may permit the tracking of abnormal trabecular phenotypes in patients with comorbidities.



authors had control of the data and information submitted for publication.

The MESA study is an ongoing population-based longitudinal study. Participants were white, African American, Hispanic, and Chinese American men and women, aged 45 to 84 years and free of clinical cardiovascular disease at enrollment. Enrollment took place from July 2000 through September 2002 (Appendix E1 [online]). At the MESA fifth evaluation point (MESA-5), which began in 2010, 3016 participants underwent cardiac MR imaging. This population-based group, however, had significant comorbidities (eg, hypertension and diabetes) and many were either overweight or obese. Accordingly, four groups were defined in our analysis (Fig 1). We assembled an entire cohort that consisted of all consecutive MESA-5 participants with complete covariate data and a full complement of evaluable (ie, technically adequate, breath held, and well gated) LV short and long-axis cines.

Advances in Knowledge

- Fractal analysis of cardiac MR imaging data can objectively quantify endocardial complexity in the adult left ventricle (LV) to improve our ability to distinguish normal from abnormal trabecular profiles in healthy versus diseased hearts.
- Population-based analysis shows how the trabeculations are influenced by ethnicity (higher in African American participants [maximal apical fractal dimension $\{FD_{MaxApical}\}$, 1.223 ± 0.08 ; $P < .001$] and Hispanic participants [$FD_{MaxApical}$, 1.211 ± 0.07 ; $P = .013$] and lower in Chinese American participants [$FD_{MaxApical}$, 1.197 ± 0.07 ; $P = .01$]) and by cardiac loading conditions.

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Abbreviations:

BMI = body mass index
 FD = fractal dimension
 $FD_{MaxApical}$ = maximal apical FD
 LV = left ventricle
 MESA = Multi-Ethnic Study of Atherosclerosis
 MESA-5 = MESA fifth evaluation point
 $s\beta$ = standardized β

Author contributions:

Guarantors of integrity of entire study, G.C., J.C.M.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, G.C., S.E.P., W.J.M., J.C.M.; clinical studies, J.A.C.L., D.A.B.; experimental studies, C.L.; statistical analysis, G.C., F.Z., S.E.P., P.B., J.C.M.; and manuscript editing, G.C., F.Z., V.M., S.E.P., P.B., N.K.B., W.J.M., P.M.E., J.A.C.L., D.A.B., J.C.M.

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Conflicts of interest are listed at the end of this article.

Figure 1

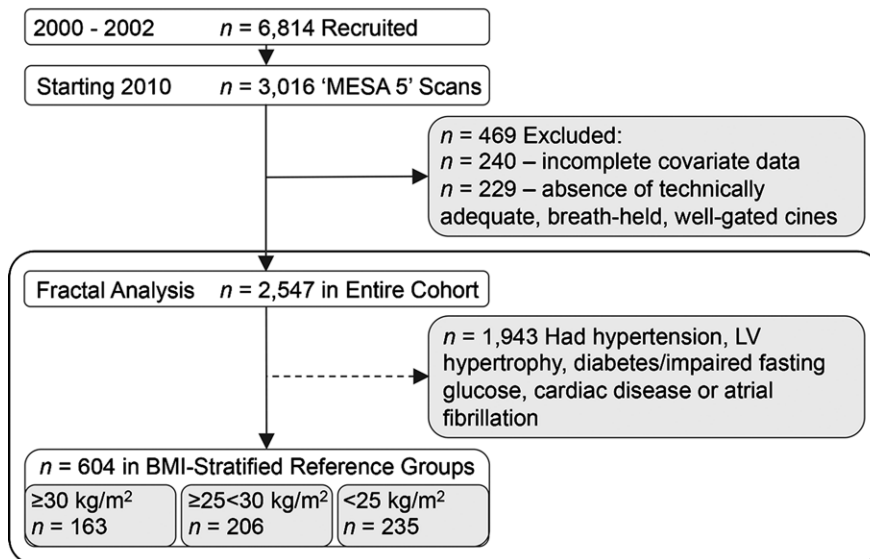


Figure 1: Flowchart shows exclusion process and stratification. The entire cohort consisted of 2547 participants with complete covariate data and evaluable images from MESA-5. To determine the reference groups, hypertension was defined according to Joint National Committee 7 report criteria (9) as systolic blood pressure 140 mmHg or higher, diastolic blood pressure 90 mmHg or higher, or current drug treatment for hypertension. LV hypertrophy was defined on the basis of maximal wall thickness 15 mm or greater, elevated LV mass shown by using MR imaging, or Novacode electrocardiographic criterion (10). Known cardiac disease was defined as a history of myocardial infarction, LV ejection fraction 50% or less, or detectable scar on contrast agent-enhanced MR imaging. *BMI* = body mass index.

Recent work by Zemrak et al (8) revealed statistically significant differences in BMI between quintiles of noncompacted severity measured by using the noncompacted-to-compacted ratio method. For this reason, all participants from within the entire cohort who did not have hypertension or LV hypertrophy, diabetes or impaired fasting glucose (11), and known cardiac disease or atrial fibrillation were further stratified by BMI into the following three reference groups: a reference group for BMI 30 kg/m² or greater, a reference group for BMI 25 kg/m² or greater to greater than 30 kg/m², and a reference group for BMI 25 kg/m² or less. Overweight was defined as a BMI 25 kg/m² or greater but less than 30 kg/m² and obese was defined as BMI 30 kg/m² or greater (12).

Image Analysis

Methods that describe the MR imaging and nonfractal image analysis are provided in the Appendix E1 (online).

Fractal analysis was performed by using software (Matlab; Mathworks, Natick, Mass) and a plugin (Osirix; A Rosett, www.osirix-viewer.com). All analysis took place at the National Institutes of Health by a single observer blinded to clinical information (G.C., with >3 years of experience in cardiac MR imaging). The box-counting analysis has been previously described in detail (3); it is performed on the end-diastolic frames of each short-axis cine section in the LV stack (Fig 2). A region-based level-set segmentation algorithm (13) (Fig 3) was used to extract the endocardial contours (14). The most apical ventricular section was excluded from all analyses because of partial voluming effects. Maximal apical FD ($FD_{MaxApical}$) was derived from the apical half of the LV stack (by consistently discounting the median section in unevenly numbered stacks after apical exclusion). Validation experiments for the fractal method were

previously reported (3). Intra- and interobserver variability of calculated $FD_{MaxApical}$ were evaluated by two independent readers on 40 randomly selected examinations from within the MESA-5 cardiac MR database.

Statistical Analysis

Statistical analysis was performed by using statistical software (R Package version 3.0.1; R Foundation for Statistical Computing, Vienna, Austria) (15). MESA data were curated by using REDCap data tools hosted at University College London (16). Descriptive data are expressed as mean \pm standard deviation except where otherwise stated. Distribution of data was assessed on histograms and by using Shapiro-Wilk test. Categorical variables were compared with χ^2 or Fisher exact test. Correlation was assessed with Pearson coefficient. Baseline characteristics included a measure of physical activity computed as the sum of minutes of activity for each discrete activity type and multiplied by metabolic equivalent level.

Simple linear regression was used to model the data, and reference ranges were established as mean and 95% confidence intervals. For reference group of BMI less than 25 kg/m², a multivariable linear regression model determined the relationship between FD and age, sex, race and ethnicity, height, and weight (model 1i). This was repeated after substituting height and weight for body surface area and BMI (models 1ii and 1iii, respectively). A variance inflation factor of less than three excluded near multicollinearity. The relationship of FD to LV function parameters (LV ejection fraction, LV end-diastolic volume, and LV end-systolic volume) was individually assessed after adjustment for the following model-1 parameters: model 2i (model 1ii and LV ejection fraction), model 2ii (model 1ii and LV end-diastolic volume), and model 2iii (model 1ii and LV end-systolic volume). To avoid collinearity, LV function parameters were not combined into the same model. For the entire cohort, relationship of FD to hypertension, diabetes, exercise, myocardial scar, and atrial

Figure 2

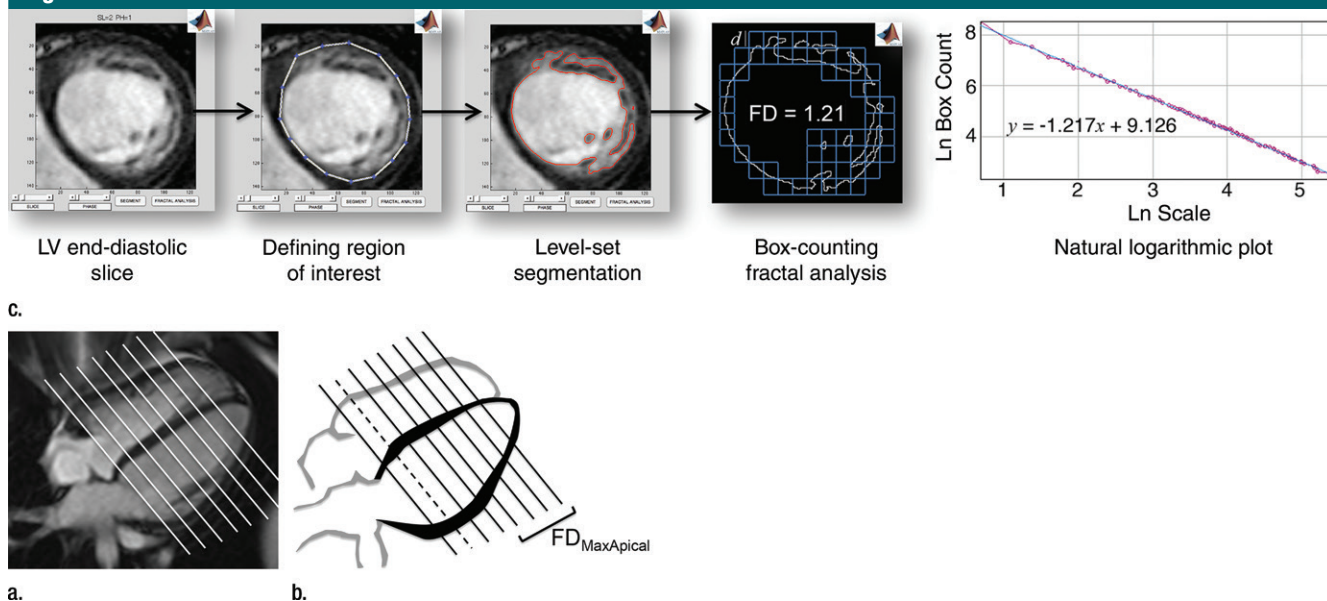


Figure 2: Fractal analysis procedure. (a) Four-chamber end-diastolic image on cine steady-state cardiac MR image from a 44-year-old male MESA participant. Tangential lines are piloted according to the location of the respective cine sections (eight sections in this representation), and the apical section has been discarded. Fractal analysis of section 2 (b, broken line) is shown in detail (c): The user defines the region of interest (second from left); segmentation extracts the endocardial borders (middle image); and the FD is computed by using the box-counting algorithm (*natural logarithmic plot*, far right) where the maximum grid caliber (box size, d in image labeled *box-counting fractal analysis*) is dictated by the dimensions of the bounding box (not shown). The minimum grid size is set to 2 pixels. Four sets of grid calibers are applied to each contour. The average gradients of the four natural logarithm (Ln) plots provide the FD. FD is a noninteger value between 1 (least complex) and 2 (most complex) that provides an estimate of how extensively the contour fills two-dimensional space.

Figure 3

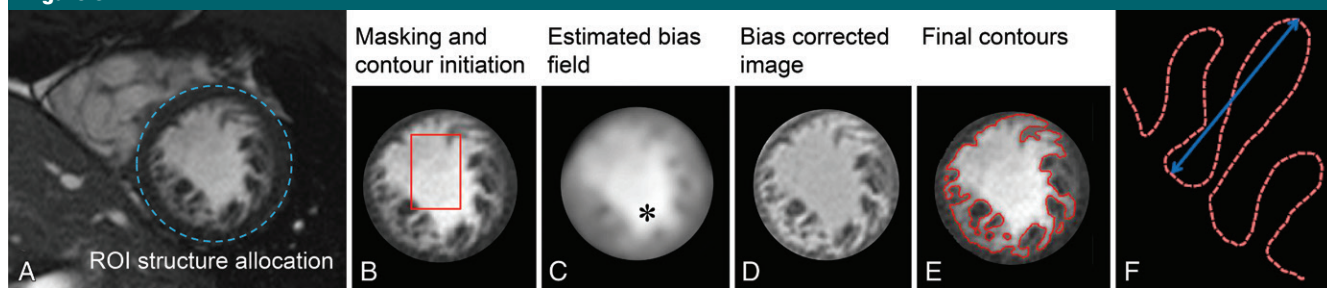


Figure 3: Region-based level-set segmentation applied to cine cardiac MR images for optimal extraction of endocardial contours and trabecular quantification. In the level-set method, contours with complex topologic structure, like the trabeculae, are represented in a natural way as the 0-level set of the level-set function. The segmentation problem is solved in a principled way by using calculus of variations and partial differential equations. A, Image shows region-of-interest (ROI) structure allocation, which is user dependent; B–D, the steps shown (and the fractal analysis, not shown) are fully automated. B, Pixels outside the region of interest are set to 0 and the curve evolution process is depicted by the initial rectangular contour. Here a region-based model identifies a region descriptor in the region of interest to guide the motion of the active contour, which provides, E, an edge as the final segmentation result. The method simultaneously estimates (compacted) and corrects for, D, the bias field of the MR image in case of any intensity inhomogeneities (* represents an intensity inhomogeneity relative to the upper left zone of the blood pool in this LV cine). F, The noncompacted wall thickness is a linear measurement (blue line) derived from a single segment; the noncompacted-to-compacted ratio results from its division by compacted wall thickness; FD (dotted pink line) differs from the noncompacted-to-compacted ratio: a heart that is both heavily trabeculated (ie, high noncompacted wall thickness) and hypertrophied (ie, high compacted wall thickness) would still register a high FD by fractal analysis, but its noncompacted-to-compacted ratio would be attenuated due to the size of its denominator (compacted wall thickness).

fibrillation was evaluated after adjusting for parameters in model 1. Because both white and Chinese American

participants had lower FD, multivariable models were repeated after the white reference race was substituted

for Chinese American. Intraclass correlation coefficient was used to compare variability within and between

readers. Coefficient of variation for repeat measures was calculated as the standard deviation of the differences between repeated measurements divided by the average of the averages of repeated measurements and is quoted as a percentage. A two-sided P value less than .05 was considered to indicate significance.

Results

Participant Characteristics

Table E1 (online) summarizes participant characteristics at the time of MR examination in the entire cohort group, BMI 30 kg/m² or greater group, BMI 25 kg/m² or greater to less than 30 kg/m² group, and BMI less than 25 kg/m² group. Details that relate to participant exclusion and cohort stratification are provided in Figure 1. In the entire cohort, age distribution of men (47.5% [1211 of 2547]) and women was not dissimilar (mean age for men, 69 years \pm 9 [age range, 54–94 years]; mean age for women, 69 years \pm 9 [age range, 54–93 years]). Mean ages of the entire cohort, BMI 30 kg/m² or greater group, BMI 25 kg/m² or greater to less than 30 kg/m² group, and BMI less than 25 kg/m² group were, respectively, 68.7 years \pm 9.1 (range, 54–94 years), 62.9 years \pm 6.6 (range, 54–82 years), 65.1 years \pm 8.3 (range, 54–91 years), and 66.2 years \pm 8.2 (range, 54–89 years). In the entire cohort, 0.82% (21 of 2547) of participants were underweight, 30.5% (778 of 2547) were of healthy weight, 39.9% (1015 of 2547) were overweight, and 28.7% (732 of 2547) were obese. Additionally, 61.8% (1574 of 2547) had systemic hypertension and 3.3% (85 of 2547) had LV hypertrophy by wall thickness.

Compared with the entire cohort, reference participants who did not have cardiac disease, hypertension, LV hypertrophy, and diabetes with BMI less than 30 kg/m² had LV mass that was 11 g smaller with 0.7 mm less maximal wall thickness, while those with BMI less than 25 kg/m² had LV mass that was 17 g smaller with 0.9 mm less maximal

wall thickness. Of the latter, only 1.6% (three of 2547) were underweight.

Regional Patterns and Reference Values for LV Trabeculation

Fractal analysis showed a consistent base-to-apex pattern of endocardial complexity along the length of the LV. In the group that had BMIs less than 25 kg/m² (Fig E1 [online]), and for all other subpopulations, the highest FD was registered in the midcavity region where papillary muscles are generally located. The second most complex region was the LV apical half, and the smoothest (least complex) zone was the base.

Standard reference values for $FD_{MaxApical}$ derived from participants who had BMI less than 25 kg/m² and who were free of cardiac disease, hypertension, LV hypertrophy, and diabetes are provided in Table E2 (online). $FD_{MaxApical}$ data stratified by race and ethnicity for participants of any weight but with cardiac disease, hypertension, LV hypertrophy, or diabetes are presented separately in Table 1, and they apply to studies of unselected individuals.

A total of 55 participants from the entire cohort (2.2%) scored $FD_{MaxApical}$ of greater than 1.385 (ie, in the LV noncompacted range) (2). Compared with the entire cohort average, these individuals exhibited 1.27 mm more noncompacted wall thickness, 25 g more LV mass, 3 mm more wall thickness, 2.5 kg/m² higher BMI, and 22.1% greater prevalence of hypertension, and they were 9.2% more likely to be either Hispanic or African American, but noncompacted-to-compacted ratios were similar (for both, noncompacted-to-compacted ratio of 1.9).

Trabeculation and Demographic or Anthropometric Parameters

Table 2 shows quintiles of $FD_{MaxApical}$ for the entire reference group and the group with BMI less than 25 kg/m². Univariable analysis of the group with BMI less than 25 kg/m² revealed no association between trabeculation and age or BMI ($P = .566$ and $.143$, respectively) and a positive association between trabeculation and men, height, weight,

and body surface area (respectively, standardized β [$s\beta$] = 0.150, $P = .037$; $s\beta = 0.181$, $P = .005$; $s\beta = 0.188$, $P = .004$; $s\beta = 0.194$, $P = .003$). None retained significant independent influence on multivariable analysis after adjusting for other model-1 parameters.

Trabeculation and Cardiac Size and Function

In the BMI less than 25 kg/m² group, ejection fraction, LV end-diastolic volume, and LV end-systolic volume showed no significant association with trabeculation after adjustment for age, sex, ethnicity, and body surface area. In the entire cohort, a 10-mL increase in LV end-diastolic volume was associated with $FD_{MaxApical}$ increase of 0.004 ($P < .001$; Fig E2a [online]) even after adjustment for hypertension and mass ($\beta = -0.0008$ /mL; $P < .001$).

Trabeculation and Ethnicity and/or Racial Background

In the entire cohort, LV trabeculation was influenced by ethnicity and/or racial background (Fig 4). At multivariate analysis and after adjustment for model-1 parameters, African American and Hispanic participants had $FD_{MaxApical}$ that was 0.02 and 0.01 higher, respectively, compared with white participants ($P < .0001$ and $P = .013$, respectively), and African American participants had $FD_{MaxApical}$ that was 0.01 higher compared with Chinese American participants ($P = .01$). These relationships persisted after further adjustment for hypertension and LV volume ($s\beta = 0.084$, $P < .001$; $s\beta = 0.038$, $P = .048$; $s\beta = 0.087$, $P = .005$, respectively). In the reference group of BMI less than 25 kg/m², Chinese American participants showed the least trabeculation and $FD_{MaxApical}$ was lower than in white participants after adjusting for age, sex, and BMI ($s\beta = -0.148$; $P = .032$).

Trabeculation and Comorbidity

Fractal complexity of the adult LV is higher in hypertension (Fig E3 [online]) and LV hypertrophy. In the entire cohort, hypertension was associated with increased $FD_{MaxApical}$ ($s\beta = 0.070$,

Table 1

FD_{MaxApical} and Noncompacted-to-Compacted Values for the LV Stratified by Race or Ethnicity in the Entire Cohort

FD Estimate	White Participants (n = 971)	Chinese American Participants (n = 274)	African American Participants (n = 585)	Hispanic Participants (n = 482)
FD _{MaxApical} (au)	1.206 ± 0.08 (1.201, 1.211)	1.197 ± 0.07 (1.189, 1.205)	1.223 ± 0.08 (1.217, 1.229)	1.211 ± 0.07 (1.205, 1.217)
Maximal noncompacted-to-compacted ratio	1.979 ± 0.67 (1.951, 2.001)	1.896 ± 0.56 (1.873, 1.919)	1.931 ± 0.67 (1.904, 1.958)	1.988 ± 0.65 (1.961, 2.015)

Note.—Data are means ± standard deviation; data in parentheses are 95% confidence intervals. These data (n = 2312) exclude reference participants with BMI less than 25 kg/m². Data apply to participants of any body weight in the presence of comorbidity, such as cardiac disease, hypertension, left ventricular hypertrophy, or diabetes. au = arbitrary units.

$P < .001$; Fig E2b [online]) and it retained association after it was adjusted for LV mass at multivariable analysis ($s\beta = 0.044$; $P = .033$). LV hypertrophy, defined as an increased LV mass or increased compacted wall thickness (compacted value), resulted in higher FD_{MaxApical} (increased LV mass: $s\beta = 0.215$, $P < .001$; increased compacted wall thickness: $s\beta = 0.266$, $P < .001$; Fig E2c, E2d [online]) even after adjustment for hypertension.

In the entire cohort, FD_{MaxApical} was higher in participants with diabetes ($s\beta = 0.042$; $P = .031$), but not after adjustment for hypertension. Myocardial scar showed some association with increased trabeculation but not after adjustment for LV mass. Atrial fibrillation, exercise (as total intentional exercise and moderate and/or vigorous physical activity), and maximal noncompacted-to-compacted ratio ($s\beta = -0.011$, $P = .715$; Fig E2e [online]) showed no association with FD_{MaxApical}.

Intra- and Interobserver Variability

Intraclass correlation coefficients for repeated intra- and interobserver measurements of FD_{MaxApical} were high (intraobserver intraclass correlation coefficient, 0.92 [95% confidence interval: 0.87, 0.96]; interobserver intraclass correlation coefficient, 0.92 [95% confidence interval: 0.86, 0.95]). Coefficients of variation for intra- and interobserver readings were 3.8% and 3.9%, respectively.

Discussion

Fractal analysis permits a more objective quantification of LV trabeculation

than by traditional linear measurements. It is therefore possible to explore the relationship of trabeculation to LV function, structure, and clinical variables more extensively.

The main findings from this study are as follows: (a) a typical FD for healthy-weight patients who do not have cardiac disease or comorbidity was 1.169 ± 0.05 ; (b) the LV was more trabeculated in African American and Hispanic participants and smoothest in Chinese American participants; (c) hypertension and LV hypertrophy increase the FD of the LV; and (d) the noncompacted-to-compacted ratio appears confounded by the wall thickness measurement (compacted), and fractal analysis of LV endocardium measures an independent biologic signal.

The fractal procedure is semiautomated: Contour extraction is mathematically driven through a level-set segmentation method (11). Intraobserver and, especially, interobserver reproducibility for FD_{MaxApical} (0.92 for both) is better than that for the manual noncompacted-to-compacted calculates (intraobserver, 0.91; interobserver, 0.84) (7).

Reference ranges for FD_{MaxApical} in our study mirror those previously reported (2,3) for a single-center healthy population (1.199 ± 0.05). Previously published FD values in unequivocal noncompacted LV were significantly higher (1.392 ± 0.01). Of note, no reference participant in the current study registered that degree of endocardial complexity; in all reference groups, the highest FD_{MaxApical} was 1.279.

In keeping with previously published data (7,17), the fractal complexity of

the LV was not influenced by age. Similar to Kawel et al (18), we show that before we adjust for body size, men are positively associated with trabecular complexity in the reference population.

This study confirms an association between African American and Hispanic background and increased LV endocardial complexity compared with a white background, and a tendency for reduced trabeculation in Chinese Americans compared with African Americans. Interethnic differences were best measured in the entire cohort and attenuated to some extent in the reference groups where subgrouping led to under representation of specific ethnic or racial subgroups. The association between African background and increased trabeculation has been previously reported (2,6,19,20), but fractal analysis additionally shows a positive and negative association, respectively, between Hispanic and Chinese American participants with trabeculation.

In 323 reference MESA participants without cardiac disease or hypertension, Kawel et al (7) measured slightly more trabeculation in Chinese American participants compared with white participants, which counters these fractal findings. First, different cohort definitions resulted in fewer Chinese Americans in the entire and reference cohorts of Kawel et al (7) (entire cohort for Kawel et al vs our study, Chinese Americans were 8.1% [81 of 1000] vs 12.9% [329 of 2547], respectively; for the reference cohort, Chinese Americans were 12.5% [46 of 367] vs 23.4% [55 of 235], respectively). Second, the nonequivalence of the two calculates is made clear: While

Table 2

Demographic, LV Function, and Clinical Characteristics across Entire Group and BMI Less than 25 kg/m² Reference Group Stratified by Quintiles of FD_{MaxApical}

Variable	FD _{MaxApical} Quintiles (20% ranges)				
	Lowest	Second	Third	Fourth	Fifth
Entire group					
Total	510	511	509	507	510
Mean FD _{MaxApical}	1.111 ± 0.03	1.162 ± 0.01	1.199 ± 0.01	1.240 ± 0.01	1.320 ± 0.04
Sex					
Men	192	221	223	265	310
Women	318	290	286	242	200
Mean age (y)	68.7 ± 8.9	67.8 ± 8.8	67.8 ± 9.3	68.6 ± 9.0	70.7 ± 9.3
Race or ethnicity					
White participants	247	221	215	208	208
Chinese American participants	79	91	59	52	48
African American participants	96	94	139	119	163
Hispanic participants	88	105	96	128	91
Hypertension*	287 (56)	289 (57)	307 (60)	304 (60)	387 (76)
Diabetes†	14 (71)	14 (73)	82 (16)	79 (16)	118 (23)
Mean MWTd (mm)	9.69 ± 1.78	9.94 ± 1.74	10.38 ± 2.11	10.56 ± 2.02	11.63 ± 2.46
Mean LV mass _s (g/m ²)	62 ± 12	64 ± 12	66 ± 14	67 ± 13	71 ± 15
Mean LV ejection fraction (%)	62 ± 7	63 ± 7	62 ± 7	62 ± 8	61 ± 8
Group with BMI < 25 kg/m²					
Total	47	47	47	47	47
Mean FD _{MaxApical}	1.093 ± 0.02	1.136 ± 0.01	1.166 ± 0.01	1.202 ± 0.01	1.244 ± 0.02
Sex					
Men	14	23	19	19	25
Women	33	24	28	28	22
Mean age (y)	69 ± 10	66 ± 7	63 ± 7	66 ± 8	67 ± 9
Race or ethnicity					
White participants	25	21	24	24	34
Chinese American participants	12	15	13	10	5
African American participants	5	4	4	8	5
Hispanic participants	5	7	6	5	3
Mean LV mass _s (g/m ²)	58 ± 9	63 ± 10	62 ± 12	63 ± 13	62 ± 11
Mean LV ejection fraction (%)	62 ± 6	62 ± 5	63 ± 6	61 ± 5	64 ± 7

Note.—Data are number of participants except where otherwise stated. The lowest, second, third, fourth, and fifth quintiles for the entire group were 1.02 to less than 1.14, 1.14 or greater to less than 1.18, 1.18 or greater to less than 1.22, 1.22 or greater to less than 1.27, and 1.27 or greater to less than 1.45, respectively, for the group with BMI less than 25 kg/m² they were 1.03 to less than 1.12, 1.12 or greater to less than 1.15, 1.15 or greater to less than 1.18, 1.18 or greater to less than 1.22, and 1.22 or greater to less than 1.28, respectively. Mass_s = LV mass indexed to body surface area, MWTd = maximal wall thickness in diastole. There were 2547 participants in the entire group and 235 participants in the group with BMI less than 25 kg/m². Within the entire group, there were 1099 white participants, 329 Chinese American participants, 611 African American participants, and 508 Hispanic participants. Within the group with BMI less than 25 kg/m², there were 128 white participants, 55 Chinese American participants, 26 African American participants, and 26 Hispanic participants.

* Hypertension defined as a documented history of hypertension or systolic blood pressure 140 mmHg or greater, or diastolic blood pressure 90 mmHg or greater or the use of antihypertensive medication. Data in parentheses are percentages

† Diabetes diagnosis (treated or untreated) defined in accordance with the 2003 American Diabetes Association classification. Data in parentheses are percentages.

FD and noncompacted wall thickness measurements are positively correlated ($r^2 = 0.044$), they appear to measure different biologic signals that provide nonidentical insights into endocardial architecture. FD helps to compute how much of the two-dimensional image space is filled by the contour while the noncompacted-to-compacted wall

thickness ratio is a one-dimensional, segment-specific, caliper measurement measured in millimeters. The noncompacted-to-compacted ratio differs from FD by incorporating a potentially confounding measure of the compacted wall thickness (compacted). As a result, the noncompacted-to-compacted ratio may be a more specific marker

of hypertrabeculation in the disease LV noncompaction where wall thinning (low compacted) is expected. However, noncompacted-to-compacted ratios may systematically misclassify genuinely hypertrabeculated hearts as less or normally trabeculated if they also exhibit hypertrophy (high denominator compacted). Through its added sensitivity

Figure 4

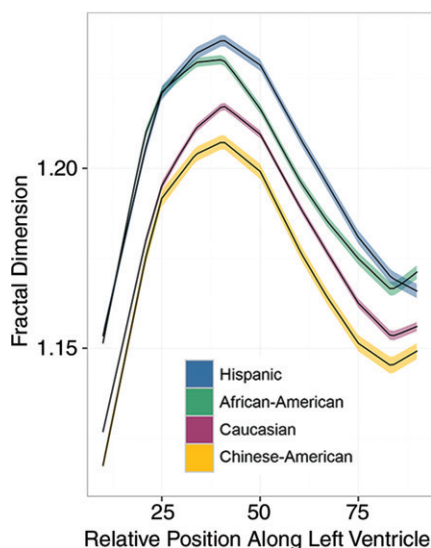


Figure 4: Graph shows relationship of FD to ethnicity and/or racial background. In the entire cohort ($n = 2547$), Hispanic ($n = 508$), and African American ($n = 611$) participants were associated with 0.01 greater $FD_{MaxApical}$ compared with white participants. Chinese American race ($n = 329$) was associated with $FD_{MaxApical}$ 0.02 lower than African American race. Relative section position from base to apex (left to right) is shown on the x-axis. Black lines represent means by linear interpolation; blue, green, purple, and yellow ribbons represent 95% confidence intervals.

and independence from wall thickness, fractal analysis therefore reveals how systemic hypertension and LV hypertrophy morph the trabecular patterning of the LV. By using the noncompacted-to-compacted ratio and noncompacted wall thickness approaches alone, these effects were not detectable in the study by Kawel et al. A combined criteria approach that pools insights from both FD and noncompacted-to-compacted ratios may have added clinical utility.

Data from our study would suggest that increased afterload (in hypertension) or other hypertrophic processes may contribute to physiologic trabecular hypertrophy and higher FD. This fits with recently reported data that showed a similar effect on trabeculation caused by increased preload during pregnancy (21). Taken collectively, results support the theory that abnormal LV trabecular

patterning may be the result of either or a mix of the following two things: a congenital phenomenon related to abnormal embryonic development of the compacted myocardium (22), for which LV noncompaction remains the exemplar disease; or a physiologic epiphenomenon in response to chronically elevated LV afterload or preload or to other hypertrophic (increased LV mass) or physiologic processes. The finding that hypertension and LV hypertrophy may have the capacity to alter the fractal complexity of the LV independent of other parameters should prompt further research to establish whether these subtle endocardial changes are progressive over time, prognostic with linkage to outcomes, or altered (eg, after commencement of antihypertensive treatment).

Our study had limitations. We only included older participants (>45 years; mean age for entire cohort, 68 years). After subgrouping, some ethnicities were underrepresented, but the large study population provided in MESA was a strength because it permitted multivariable analysis of associations of FD with demographic, anthropometric, LV functional, and clinical characteristics.

Fractal analysis of cardiac MR imaging data objectively measured endocardial complexity as an FD and may improve our ability to differentiate normal from abnormal trabecular patterning in health and disease. LV trabeculations are influenced by race or ethnicity and, more importantly, by cardiac loading conditions and comorbidity. Clinicians who interpret LV cine MR imaging data should expect slightly less endocardial complexity in Chinese American patients and more in African American patients, Hispanic patients, hypertensive patients, and patients with hypertrophy.

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