Radiology

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Journal:	*Radiology*
Manuscript ID	RAD-16-1995.R1
Manuscript Type:	Original Research
Manuscript Categorization Terms:	Adults < 1. SUBJECT MATTER, MR-Imaging < 2. MODALITIES/TECHNIQUES, Cardiac < 4. AREAS/SYSTEMS, Heart < 5. STRUCTURES, Fractal Analysis < 6. TOPICS

Hypertrabeculated left ventricular myocardium in relationship to myocardial function and fibrosis: The Multi-Ethnic Study of Atherosclerosis

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Advances in knowledge

- In the MESA cohort, greater trabeculation of the left ventricle is associated with worse myocardial strain (B=4.0% per unit fractal dimension increase in trabeculation; p<0.0001).
- In the MESA cohort, greater left ventricular trabeculation is not associated with myocardial fibrosis as measured by native and post contrast T1 mapping cardiac MR.

Implications for patient care

- 21% (230/1123) of MESA participants have excess trabeculation of the left ventricle exceeding the current diagnostic threshold for left ventricular non compaction disease using fractal analysis with a cut-off of FD ≥1.3.
- Excess greater LV trabeculation is associated with decreased average regional myocardial function as measured by myocardial strain.

Summary statement

Average regional myocardial function is worse in individuals with greater LV trabeculation.

Abstract

Purpose: To determine if excess greater LV trabeculation is associated with decreased average regional myocardial function and/or diffuse fibrosis.

Methods: This was a HIPPA-compliant institutional board approved multicenter study; all participants provided written informed consent. Study participants of the Multi-Ethnic Study of Atherosclerosis (MESA) underwent a comprehensive cardiac magnetic resonance (cardiac MR) exam. Trabeculation of the LV was measured by the maximal apical fractal dimension (FD) a novel marker of endocardial complexity. Demographic covariates, cardiovascular risk factors and cardiac MR measures were compared across quartiles of FD. Associations between FD and peak regional systolic circumferential strain (Ecc) and T1-time, a surrogate for diffuse myocardial fibrosis, were assessed in multivariable linear regression models.

Results: 1123 subjects (53% female, mean age±SD: 67±9 years) had FD and Ecc measurements and 992 subjects had T1 and Ecc measurements. The mean FD was 1.2±0.07; the mean Ecc was -18.3±2.27. Global volumes and ejection fraction showed no differences between quartiles of FD. However, with increasing FD–quartile, Ecc was greater (indicating worse average regional function) ($p<0.0001$). After adjustment, greater trabeculation was associated with 21% worse myocardial strain (relative to the mean) per unit change FD (B=4.0%; $p=0.0001$). There was no association between the degree of trabeculation and diffuse fibrosis measured by T1 mapping.

Conclusion: Average regional LV function was worse in individuals with greater LV trabeculation, supporting the concept of hypertrabeculation being an epiphenomenon of disease.

Introduction

The trabeculae carneae are a network of slim columns of myocardial cells covered by endocardial cells at the luminal surface of the left and right ventricle. During embryonic cardiac development, trabeculae form by invagination of cardiomyocytes into the lumen (1). Trabeculated myocardium functions to increase cardiac output and enable oxygen supply prior to coronary vascularization. As the myocardium develops, trabeculae compact leading to an increase in thickness of the compact myocardium, that represents the major part of myocardial mass of the mature heart. Simultaneously coronary vessels develop (1).

Abnormal trabecular compaction is a diagnostic imaging feature of left ventricular noncompaction cardiomyopathy (LVNC), a rare primary genetic cardiomyopathy characterized by excess myocardial trabeculation more than twice as thick as the underlying myocardial wall (2). LVNC is associated with heart failure, regional wall motion abnormalities and myocardial fibrosis (3-11). However, individuals without overt cardiovascular disease and normal cardiac function frequently show excess trabeculation; over 30% of normal individuals have a ratio of noncompacted to compacted myocardium greater than 2.3 (12). In such individuals, the clinical significance of excess trabeculation as a sign of current or future disease expression is not currently understood. Mechanistically, it would seem likely that regions of hypertrabeculated myocardium may have lower contractility compared to normal myocardium. However the relationship of hypertrabeculated myocardium to contractile function and fibrosis in individuals without LNVC disease is currently unknown.

The ratio of the thickness of noncompacted (NC) versus compacted (C) myocardium (NC/C) is a simple and fast method to quantify trabeculation that is currently most widely used (13). A more comprehensive measure of LV trabeculation can be performed by fractal

analysis (14). The fractal dimension is a unitless index to assess endocardial complexity (14, 15). The maximal FD in the apical half of the LV (FD) is higher in patients diagnosed with LVNC compared to healthy volunteers (14). Compared to the calculation of the NC/C ratio, the fractal method has been demonstrated to be more accurate and reproducible (14).

Although the importance of detecting excess trabeculation is reasonably well understood in overt LVNC disease, the significance of this common finding is not understood in individuals who do not have overt clinical cardiomyopathy. We hypothesized that myocardial strain is impaired in subjects with greater trabeculation and may be associated with diffuse fibrosis. Therefore, the purpose of our study was to determine if excess greater LV trabeculation is associated with decreased average regional myocardial function and/or diffuse fibrosis.

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-compatible.

The Multi-Ethnic Study of Atherosclerosis (MESA) is an ongoing population-based longitudinal study initiated in July 2000. At enrollment, study participants were free of clinically recognized cardiovascular disease (16). Ten years after baseline examination, 3015 subjects had an additional cardiac MR exam and a subset of those had regional function assessment (using MRI tagging), late gadolinium enhancement (LGE) imaging and T1-mapping. Participants with a focal myocardial scar on LGE imaging were excluded since

focal LGE is associated with regional myocardial dysfunction, which would otherwise confound the analysis. In addition, participants with inadequate MR image quality hampering analysis and missing data were also excluded (Figure 1).

In a previous publication (17) the range of fractal dimension and its determinants were described for 2547 subjects of the MESA population. The current study focusses on the analysis of the relationship between the fractal dimension and average regional myocardial function and diffuse myocardial fibrosis, respectively in a subset of these participants.

Cardiovascular MR

Cardiac MR exams were performed at the six MESA field centers on 1.5 Tesla MR scanners as previously described (18, 19). In brief, electrocardiogram (ECG) gated long and short axis (SAX) cine images were acquired using a steady-state free precession (SSFP) sequence with temporal resolution ≤40msec, 8mm slice thickness, 2mm gap, repetition time (TR)/echo time (TE) 2.2/1.1msec, 45-70° flip angle. Tagged images were obtained with a segmented k-space, ECG gated fast low angle shot pulse sequence acquired in three SAX slices with two orthogonally oriented parallel striped tags using spatial modulation of magnetization with a field of view (FOV) of 360x360mm, flip angle 10°, TE 2.5ms, matrix size 256x128, slice thickness 10mm, 9 phase encoding views per segment, spatial resolution 1.4x2.8x10mm^3, temporal resolution 25ms, tag spacing 7mm. Participants without contraindications underwent late contrast enhancement (LGE) images 15min after an intravenous bolus injection of gadopentetate dimeglumine (0.15mmol/kg [Magnevist, Bayer Healthcare Pharmaceuticals, Montville, New Jersey]) to identify myocardial scar. As described previously (19), T1-mapping sequences included pre-contrast and delayed images 12 and 25 minutes after contrast injection using a modified Look-Locker (MOLLI) sequence consisting of 11 source images in 17 heartbeats with flip angle 35°; TR/TE

2.2/1.1ms; FOV 360×360mm; matrix 192×183; slice thickness 8mm; generalized autocalibrating partially parallel acquisitions factor 2.

Image evaluation

LV volumes and function were measured using CIM software version 6.2 (Auckland, New Zealand) (20). FD was measured on SAX cine SSFP images (figure 2) (by G.C. with 6 years of experience in cardiac MR imaging) as described previously (17). In brief, afer image segmentation to identify the endocardial border, the FD of the endocardial border was calculated using a box counting method. Maximal apical FD (FD) was the maximum value derived from the apical half of the LV stack. Thickness of the compact and noncompact (trabeculated) LV myocardium were measured at end-diastole on long axis SSFP images in the middle of 8 LV regions (by F.Z. and N.K.B. with 6 and 8 years of experience in cardiac MR imaging, respectively) (12). Maximal NC/C (NC/C) was calculated as the maximum value of the 8 segments in cases where measurements were performed for all 8 segments.

T1-mapping data was evaluated using MASS research software (MASS V2010-EXP; Leiden University Medical Center, Leiden, The Netherlands) (by C.Y.L. and B.A.V. with 13 and 12 years of experience in cardiac MR imaging, respectively). The extracellular volume (ECV) was calculated as $\Delta R1_{myocardium}/\Delta R1_{blood}$*(1-hematocrit),
where $\Delta R1_{myocardium}=1/T1_{myocardium\ pre\ contrast}- 1/T1_{myocardium\ post\ contrast}$
and $\Delta R1_{blood}=1/T1_{blood\ pre\ contrast}-1/T1_{blood\ post\ contrast}$ (21).

Tagged short axis slices were analyzed using Harmonic Phase software (Diagnosoft, Palo Altro, CA) (22). Peak regional systolic circumferential strain (Ecc) was calculated for 12 segments: anterior, inferior, septal, and lateral at basal, midcavity and apical level (23). Mean peak Ecc was calculated as the mean of the 12 segments in cases where

measurements were performed for all 12 segments. Ecc is a negative value; *lower* (more negative) values indicate *greater* circumferential strain and thus better regional function.

Statistical analysis

Demographic indices, cardiovascular risk factors and cardiac MR measures of volume and function were evaluated for the entire cohort and were compared across quartiles of FD using one-way analysis of variance (ANOVA) for continuous covariates and chi-square test for categorical covariates. Continuous variables are presented as mean±SD and categorical variables as frequencies and percentages.

The missing data approach was complete-case analysis, which uses only participants who have all variables observed. To avoid bias when calculating the mean Ecc only those cases where measuring Ecc was feasible for all 12 segments were included.

The associations between the independent variable FD and the dependent variables Ecc, T1-time and ECV, respectively were assessed by linear regression in univariate and multivariable models per subject. Additionally, regression analysis was performed with NC/C instead of FD as independent variable. Normality of dependent variables was assessed by Shapiro-Wilk test. Multivariable models were adjusted for demographic covariates (model 1) including age, gender, ethnicity, height and weight, additionally for traditional cardiovascular risk factors (model 2: systolic blood pressure, hypertension, smoking, diabetes mellitus, high density lipoprotein, lipid-lowering medication and total cholesterol) and for cardiac MR measures (model 3: LV end-diastolic volume [LVEDV] and LV ejection fraction [LVEF]). Models including pre-contrast T1-time were additionally adjusted for heart rate.

Probability values <0.05 were considered statistically significant. Statistical analysis was performed using SPSS statistical software (version 23) and STATA (version 14.0).

Results

Participant characteristics

Table 1 indicates the population demographic characteristics, traditional cardiovascular risk factors and mean and standard deviation of the cardiac MR variables for subjects included in the analysis of the relationship between trabeculation and strain and T1-time, respectively. There were no clinically relevant differences in demographics between the subsets of subjects included in the analysis and the 1840 subjects of the MESA 5 cohort with a cardiac MR exam including LGE imaging. The mean of FD was 1.2±0.07. The mean of NC/C was 2.1±0.68. The mean Ecc was -18.3±2.27. Mean T1-times were 974.7±42.1ms pre-contrast, 455.3±40.0 at 12 minutes and 518.8±40.2 at 25 minutes after contrast administration. Mean ECV was 0.27±0.3.

230/1123 (21%) subjects had a FD of ≥1.3, considered the threshold for LVNC using fractal analysis (14). For comparison, 33% (247/745) of subjects had a NC/C >2.3, which is considered the cut-off for LVNC in cardiac MR imaging (13).

Table 2 shows demographic characteristics, traditional risk factors and cardiac MR measures stratified by FD. Participants with a higher FD were more likely to be male and of Black or Hispanic ethnicity while the proportion of Chinese was higher in the lower quartiles. Subjects in the quartiles with higher FD were taller, had a higher body weight, were more likely to have diabetes, had on average a higher systolic blood pressure and were more likely to be smokers. Mean HDL cholesterol tended to be lower in higher FD -

Quartiles while total cholesterol was lower. There were no statistically significant differences in LVEDV and LVEF between quartiles of FD. Circumferential strain tended to be more positive (indicating worse regional function) with increasing FD –quartile (figure 3).

Relationship between trabeculation and circumferential strain

In univariate analysis, a higher maximal apical FD was associated with more positive peak global circumferential strain (indicating *worse* average regional function) (regression coefficient [B]=6.6%; p<0.0001). The association persisted after adjustment for demographic covariates (B=4.0%; p<0.0001), traditional cardiovascular risk factors (B=3.6%; p<0.0001) and after adjustment for cardiac MR measures of left ventricular volume and function (B=2.8%; p=0.002) (table 3). In the fully adjusted model, in addition to FD , age, male gender, weight, diabetes mellitus and systolic blood pressure were also associated with more positive (worse) circumferential strain (table 4).

In an analysis parallel to that performed above for FD, in 745 individuals with complete data, there was no relationship between the conventional measure of trabeculation (NC/ C) in the fully adjusted model (p =0.073).

Relationship between fractal dimension and T1-time and ECV, respectively

In univariate analysis and multivariable models (n=992) maximal apical FD was not associated with pre-contrast T1-time nor with T1 time at 12 minutes and 25 minutes after contrast administration. There was no association of FD with ECV persisting in multivariable analysis.

NC/C was not associated with pre-contrast or post-contrast T1 times (n=650) nor ECV (n=372) (p>0.05 for all).

Discussion

SSFP cine cardiac MR images readily demonstrate variations in the degree of trabeculation of the left ventricle. In genetic LVNC disease, the degree of trabeculation seems to be related to disease severity. Using fractal analysis, this study shows that **average regional myocardial function is worse in individuals with greater LV trabeculation.** Interestingly, greater trabeculation was not associated with diffuse myocardial fibrosis as measured by alteration in T1 time. These results suggest a mechanical "link" between LV trabeculation and the effectiveness of myocardial function.

Relationship between left ventricular trabeculation and average regional myocardial function

The present study supports the hypothesis that LV function is at least in part dependent on the degree of trabeculated myocardium. In the MESA cohort, subjects with highly trabeculated LV myocardium had worse average regional function. This relationship was found even after adjustment for demographic and clinical factors as well as global LV function. Of interest, greater NC/C ratio was unable to detect these relationships. This supports accumulating evidence that, although NC/C ratio is easy to measure in the clinic, it is not specific (33% [247/745]of subjects in the MESA cohort with NC/C ratio >2.3). In addition, NC/C ratio is a 1-dimensional measurement at a single point in the left ventricle which does not comprehensively describe myocardial trabeculation. Fractal dimension reflects myocardial complexity in a region of myocardium, in a fashion similar to the concept of average regional myocardial strain.

In a previous publication, Zemrak et al. (24) found that subjects with abnormal NC/C ratio had no deterioration of ejection fraction over the prior 10 years. However, it is well known that ejection fraction can be normal while myocardial strain is impaired (e.g., as in the case of heart failure with preserved ejection fraction). It remains unknown if subject

with hypertrabeculation and impaired strain will subsequently develop deterioration of global function and clinical symptoms or if myocardial dysfunction will remain stable and subclinical.

In this cohort, the average FD in the myocardial apex was 1.2. Captur et al. previously reported patients with LVNC disease have a FD greater than 1.3 (14) indicating small changes in FD may be clinically meaningful. Similarly, myocardial strain is a sensitive measure of LV function and strain is highly conserved in normal individuals (25). In the current study, the mean circumferential strain was -18.3%. In our unadjusted analysis, a 0.1 unit increase in FD was associated with an absolute increase of +0.6% strain, or approximately 3% of the mean value. Our sample size was sufficient to account for 14 additional variables that might affect regional function in multivariable models. Even in fully adjusted models, the association of greater trabeculation with worse average regional function remained statistically significant. Not surprisingly, less sensitive measures of trabeculation and function (NC/C ratio and ejection fraction, respectively), did not reveal these associations.

Relationship between left ventricular trabeculation and measures of diffuse myocardial fibrosis

In previous publications focal myocardial fibrosis has been described as a feature of LVNC (4, 5, 8, 10). Besides these reports of focal fibrosis/scars in LVNC, in a study by Jenni et al histopathology revealed also interstitial fibrosis as a finding in 6 of 7 hearts diagnosed with LVNC (26). In a study recently published by Zhou et al, subjects with a diagnosis of LVNC had a significantly longer native T1-time (used as surrogate of diffuse myocardial fibrosis) compared to healthy volunteers independent of the presence of LGE (27).

In this context our aim was to investigate the relationship between extent of trabeculation and diffuse myocardial fibrosis using T1-time and ECV, respectively measured by cardiac MR as surrogate. However, in our subset of study participants without known cardiovascular disease at enrollment there was no association between trabeculation and native or post contrast T1-time or ECV.

Participants in our population-based study had a broad spectrum of trabeculation. The FD in the highest quartile was between 1.24 and 1.45. Twenty one percent (21%, 230/1123) of our subjects had a FD ≥1.3, previously defined as the threshold for LVNC and 33% [247/745] of subjects in this study had a NC/C ratio >2.3, still widely used as cut-off for LVNC in cardiac MR imaging. This discrepancy is explained by a lack of diagnostic criteria for a LVNC with a high specificity. The current criteria focus on thickness or amount of trabeculation. Given the overlap with normal population and the results of this study, improved LVNC criteria may incorporate some measurement of systolic function (28) and/or morphologic criteria such as the presence of a layer of tissue between the noncompacted myocardium and the ventricular cavity (29). The current study shows once more that revision of the current criteria is required to distinguish between LVNC disease as a genetic disorder and morphologically hypertrabeculated LV.

A limitation of this study is the cross-sectional design, which precludes a causal interpretation of the results. It remains unclear if hypertrabeculation leads to a deterioration of average regional function or if increased trabeculation might be an adaptive process resulting from an impaired function. The latter would be of biological interest as it would suggest that LV trabecular patterning imprinted at birth, is modulated throughout life as a consequence of cardiac loading and other haemodynamic conditions.

The present data indicates that hypertrabeculation might be a epiphenomenon of disease associated with an impaired average regional function.

References

1. Samsa LA, Yang B, Liu J. Embryonic cardiac chamber maturation: Trabeculation, conduction, and cardiomyocyte proliferation. Am J Med Genet C Semin Med Genet. 2013;163C(3):157-68.
2. Maron BJ, Towbin JA, Thiene G, et al. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. Circulation. 2006;113(14):1807-16.
3. Bellavia D, Michelena HI, Martinez M, et al. Speckle myocardial imaging modalities for early detection of myocardial impairment in isolated left ventricular non-compaction. Heart. 2010;96(6):440-7.
4. Burke A, Mont E, Kutys R, Virmani R. Left ventricular noncompaction: a pathological study of 14 cases. Hum Pathol. 2005;36(4):403-11.
5. Dursun M, Agayev A, Nisli K, et al. MR imaging features of ventricular noncompaction: emphasis on distribution and pattern of fibrosis. Eur J Radiol. 2010;74(1):147-51.
6. Kalapos A, Domsik P, Forster T, Nemes A. Left ventricular strain reduction is not confined to the noncompacted segments in noncompaction cardiomyopathy-insights from the three-dimensional speckle tracking echocardiographic MAGYAR-path study. Echocardiography. 2014;31(5):638-43.
7. Niemann M, Liu D, Hu K, et al. Echocardiographic quantification of regional deformation helps to distinguish isolated left ventricular non-compaction from dilated cardiomyopathy. Eur J Heart Fail. 2012;14(2):155-61.
8. Nucifora G, Aquaro GD, Pingitore A, Masci PG, Lombardi M. Myocardial fibrosis in isolated left ventricular non-compaction and its relation to disease severity. Eur J Heart Fail. 2011;13(2):170-6.
9. Pacileo G, Baldini L, Limongelli G, et al. Prolonged left ventricular twist in cardiomyopathies: a potential link between systolic and diastolic dysfunction. Eur J Echocardiogr. 2011;12(11):841-9.
10. Wan J, Zhao S, Cheng H, et al. Varied distributions of late gadolinium enhancement found among patients meeting cardiovascular magnetic resonance criteria for isolated left ventricular non-compaction. J Cardiovasc Magn Reson. 2013;15:20.
11. Wang C, Deng YB, Zhu Y, Liu YN, Bi XJ. Evaluation of subtle myocardial noncompaction by contrast echocardiography in patients with hypertrophic cardiomyopathy and its relationship with regional ventricular systolic dysfunction. J Ultrasound Med. 2012;31(10):1551-7.
12. Kawel N, Nacif M, Arai AE, et al. Trabeculated (noncompacted) and compact myocardium in adults: the multi-ethnic study of atherosclerosis. Circ Cardiovasc Imaging. 2012;5(3):357-66.
13. Petersen SE, Selvanayagam JB, Wiesmann F, et al. Left Ventricular Non-Compaction. Journal of the American College of Cardiology. 2005;46(1):101-5.
14. Captur G, Muthurangu V, Cook C, et al. Quantification of left ventricular trabeculae using fractal analysis. J Cardiovasc Magn Reson. 2013;15:36.
15. Captur G, Karperien AL, Li C, et al. Fractal frontiers in cardiovascular magnetic resonance: towards clinical implementation. J Cardiovasc Magn Reson. 2015;17(1):80.
16. Bild DE, Bluemke DA, Burke GL, et al. Multi-ethnic study of atherosclerosis: objectives and design. Am J Epidemiol. 2002;156(9):871-81.

17. Captur G, Zemrak F, Muthurangu V, et al. Fractal Analysis of Myocardial Trabeculations in 2547 Study Participants: Multi-Ethnic Study of Atherosclerosis. Radiology. 2015:142948.
18. Donekal S, Venkatesh BA, Liu YC, et al. Interstitial fibrosis, left ventricular remodeling, and myocardial mechanical behavior in a population-based multiethnic cohort: the Multi-Ethnic Study of Atherosclerosis (MESA) study. Circ Cardiovasc Imaging. 2014;7(2):292-302.
19. Liu CY, Liu YC, Wu C, et al. Evaluation of age-related interstitial myocardial fibrosis with cardiac magnetic resonance contrast-enhanced T1 mapping: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol. 2013;62(14):1280-7.
20. Young AA, Cowan BR, Thrupp SF, Hedley WJ, Dell'Italia LJ. Left ventricular mass and volume: fast calculation with guide-point modeling on MR images. Radiology. 2000;216(2):597-602.
21. Arheden H, Saeed M, Higgins CB, et al. Reperfused rat myocardium subjected to various durations of ischemia: estimation of the distribution volume of contrast material with echo-planar MR imaging. Radiology. 2000;215(2):520-8.
22. Garot J, Bluemke DA, Osman NF, et al. Fast determination of regional myocardial strain fields from tagged cardiac images using harmonic phase MRI. Circulation. 2000;101(9):981-8.
23. Donekal S, Ambale-Venkatesh B, Berkowitz S, et al. Inter-study reproducibility of cardiovascular magnetic resonance tagging. J Cardiovasc Magn Reson. 2013;15:37.
24. Zemrak F, Ahlman MA, Captur G, et al. The relationship of left ventricular trabeculation to ventricular function and structure over a 9.5-year follow-up: the MESA study. J Am Coll Cardiol. 2014;64(19):1971-80.
25. Moore CC, Lugo-Olivieri CH, McVeigh ER, Zerhouni EA. Three-dimensional systolic strain patterns in the normal human left ventricle: characterization with tagged MR imaging. Radiology. 2000;214(2):453-66.
26. Jenni R, Oechslin E, Schneider J, Attenhofer Jost C, Kaufmann PA. Echocardiographic and pathoanatomical characteristics of isolated left ventricular non-compaction: a step towards classification as a distinct cardiomyopathy. Heart. 2001;86(6):666-71.
27. Zhou H, Lin X, Fang L, et al. Characterization of Compacted Myocardial Abnormalities by Cardiac Magnetic Resonance With Native T1 Mapping in Left Ventricular Non-Compaction Patients- A Comparison With Late Gadolinium Enhancement. Circ J. 2016;80(5):1210-6.
28. Captur G, Syrris P, Obianyo C, Limongelli G, Moon JC. Formation and Malformation of Cardiac Trabeculae: Biological Basis, Clinical Significance, and Special Yield of Magnetic Resonance Imaging in Assessment. Can J Cardiol. 2015;31(11):1325-37.
29. Freedom RM, Yoo SJ, Perrin D, Taylor G, Petersen S, Anderson RH. The morphological spectrum of ventricular noncompaction. Cardiol Young. 2005;15(4):345-64.

Table 1. Characteristics of the Multi-Ethnic Study of Atherosclerosis Study cohort

Characteristic	Subjects with complete FD and Ecc measurements n=1123	Subjects with complete FD and T1 measurements n=992
Female	593 (52.8)	521 (52.5)
Age, years (range)	67.1±8.7 (54-93)	67.1±8.7 (54-93)
Ethnicity		
White	515 (45.9)	519 (52.3)
Chinese	124 (11.0)	114 (11.5)
African American	251 (22.4)	220 (22.2)
Hispanic	233 (20.7)	139 (14.0)
Height, cm	166.1±9.7	166.7±9.8
Weight, kg	77.4±16.5	78.6±17.3
HDL cholesterol, mg/dL	55.5±16.2	55.2±16.3
Total cholesterol, mg/dL	184.6±35.8	183.3±36.3
Lipid medication use	396 (35.3)	364 (36.7)
Diabetes mellitus	178 (15.9)	150 (15.1)
Systolic blood pressure, mmHg	121.8±19.4	121.1±18.7
Hypertension medication use	526 (46.8)	476 (48.0)
Smokers	573 (51.0)	526 (53.0)
LVEDV, ml	124.0±30.1	123.6±30.6
LVEF, %	62.2±6.5	62.4±6.6
Mean Ecc, %	-18.3±2.27	NA
FD	1.2±0.07	1.2±0.07
T1 pre, ms	NA	974.7±42.1
T1 12min, ms	NA	455.3±40.0
T1 25min, ms	NA	518.8±40.2
ECV	NA	0.27±0.3*

Characteristics of subjects available per analysis. Values are mean ± SD or n (%).
HDL, high-density lipoprotein; Lipid medication, lipid-lowering medication; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; Ecc, peak regional systolic circumferential strain; FD, fractal dimension; T1 pre, myocardial T1 time prior to contrast administration; T1 12min, myocardial T1 time 12min after contrast administration; T1 25min, myocardial T1 time 25min after contrast administration; ECV, extracellular volume; *n=544

Table 2. Characteristics of the Multi-Ethnic Study of Atherosclerosis Study cohort for quartiles of maximal apical FD*

Characteristic	Quartile 1 FD: 1.02-1.15	Quartile 2 FD: 1.15-1.19	Quartile 3 FD: 1.19-1.24	Quartile 4 FD: 1.24-1.45	p Value all quartiles	p Value Q1 vs Q4
Female	170 (60.7)	163 (58.0)	148 (52.7)	112 (39.9)	**<0.0001**	**<0.0001**
Age, years	67.4±8.5	65.8±8.4	66.9±8.7	68.4±9.0	**0.003**	0.170
Ethnicity						
White	137 (48.9)	128 (45.6)	131 (46.6)	119 (42.3)	0.469	0.118
Chinese	46 (16.4)	39 (13.9)	26 (9.3)	13 (4.6)	**<0.0001**	**<0.0001**
African American	54 (19.3)	57 (20.3)	65 (23.1)	75 (26.7)	0.148	**0.037**
Hispanic	43 (15.4)	57 (20.3)	59 (21.0)	74 (26.3)	**0.016**	**0.001**
Height, cm	164.7±9.6	165.4±9.6	166.7±10.1	167.5±9.4	**0.002**	**<0.0001**
Weight, kg	73.4±16.9	74.6±14.1	78.8±17.1	82.6±16.3	**<0.0001**	**<0.0001**
HDL cholesterol, mg/dL	57.3±17.1	56.7±16.5	55.4±15.8	52.7±14.9	**0.004**	**0.001**
Total cholesterol, mg/dL	186.8±38.2	185.4±34.1	185.6±34.6	180.5±36.1	0.162	**0.045**
Lipid medication	92 (32.9)	96 (34.2)	92 (32.7)	116 (41.3)	0.107	**0.039**
Diabetes mellitus	40 (14.3)	30 (10.7)	43 (15.3)	65 (23.1)	**0.001**	**0.007**
SBP, mmHg	120.0±18.0	120.0±19.5	122.1±18.8	125.3±20.9	**0.003**	**0.001**
Hypertension medication	117 (41.8)	125 (44.5)	121 (43.1)	163 (58.0)	**<0.0001**	**<0.0001**
Smokers	135 (48.2)	137 (48.8)	140 (49.8)	161 (57.3)	0.109	**0.031**
LVEDV, ml	121.3±28.4	123.3±26.9	126.4±31.1	125.0±33.4	0.216	0.164
LVEF, %	62.4±5.9	62.5±6.2	62.2±6.8	61.8±7.1	0.523	0.244
Ecc, %	-18.7±2.1	-18.6±2.1	-18.3±2.4	-17.5±2.3	**<0.0001**	**<0.0001**

*1123 with complete data. Values are mean ± SD or n (%).
FD, fractal dimension; HDL, high-density lipoprotein; Lipid medication, lipid-lowering medication; SBP, systolic blood pressure; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; Ecc, peak regional systolic circumferential strain; Q1-Q4 quartile 1-4

Table 3. Relationship of maximal apical fractal dimension to mean peak regional systolic circumferential strain.

Analysis	B	p
Univariate	6.556	<0.0001
Multivariable Model 1	4.045	<0.0001
Multivariable Model 2	3.623	<0.001
Multivariable Model 3*	2.838	0.002

Dependent variable, peak regional systolic circumferential strain (Ecc); B, unstandardized regression coefficient, absolute difference in Ecc (%) related to a change of one unit of maximal apical fractal dimension; Model 1 adjusted for age, gender, ethnicity, height and weight; Model 2 additionally adjusted for systolic blood pressure, hypertension, smoking, diabetes mellitus, high density lipoprotein, lipid-lowering medication and total cholesterol; Model 3 additionally adjusted for LV end-diastolic volume and LV ejection fraction; *, for detailed analysis of the relationship between all covariates and circumferential strain see table 4

Table 4. Relationship of maximal apical fractal dimension and covariates to peak regional systolic circumferential strain in the fully adjusted multi-variable model *

Variable	B	β	p
FD	2.838	0.088	**0.002**
Age	0.017	0.064	**0.037**
Male gender	0.874	0.192	**<0.0001**
Chinese ethnicity	-0.312	-0.043	0.179
African American ethnicity	0.015	0.003	0.924
Hispanic ethnicity	-0.435	-0.078	**0.014**
Height	0.011	0.045	0.342
Weight	0.036	0.263	**<0.0001**
HDL cholesterol	0.005	0.035	0.265
Total cholesterol	0.001	0.020	0.534
Lipid medication	0.205	0.043	0.143
Diabetes mellitus	0.424	0.068	**0.018**
SBP	0.015	0.125	**<0.0001**
Hypertension medication	-0.020	-0.004	0.881
Smokers	0.152	0.034	0.230
LVEDV	-0.024	-0.324	**<0.0001**
LVEF	-0.067	-0.193	**<0.0001**

*Dependent variable, peak regional systolic circumferential strain (Ecc); B, unstandardized regression coefficient; absolute difference in Ecc (%) related to a change of one unit of the independent variables; β, standardized coefficient; FD, fractal dimension; HDL, high-density lipoprotein; Lipid medication, lipid-lowering medication; SBP, systolic blood pressure; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction

Figure 1. Participant enrollment

Cardiac MR, cardiac magnetic resonance; w/o, without; LGE, late gadolinium enhancement; FD, fractal dimension

Figure 2. Analysis of fractal dimension

Measuring the fractal dimension by fractal analysis of short axis cine steady-state free precession images in four exemplar subjects from this MESA cohort: one subject with low fractal dimension (top row) and three subjects with high fractal dimension (row 2, 3 and 4). Colored lines show contouring of endocardial borders. The fractal dimension indicates how extensively the contour fills two-dimensional space. The image on the left shows planning of the short axis cine stack. Numbers on top of each short axis image indicate the fractal dimension of the respective slice. The colored panels on the right provide characteristics of the four subjects.

FD, fractal dimension; AfrcAm, African American; Hisp; Hispanic; BMI, body mass index; HT med, hypertension medication; Y, yes; N, no; SBP, systolic blood pressure

Figure 3. Circumferential strain by quartiles of FD

Ecc, peak regional systolic circumferential strain; FD, fractal dimension; Quartile 1, 1.01-1.15; Quartile 2, 1.15-1.12; Quartile 3, 1.12-1.24; Quartile 4, 1.24-1.4; Error bars indicating 95% confidence interval

ACKNOWLEDGEMENTS

This research was supported by contracts N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168 and N01-HC-95169 from the National Heart, Lung, and Blood Institute, by grants UL1-TR-000040 and UL1-TR-001079 from NCRR, and by a grant from Bayer Healthcare for the use of gadolinium contrast agent. G.C. is supported by the National Institute for Health Research Rare Diseases Translational Research Collaboration (NIHR RD-TRC). J.C.M. is directly and indirectly supported by the University College London Hospitals NIHR Biomedical Research Centre and Biomedical Research Unit at Barts Hospital, respectively. 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.

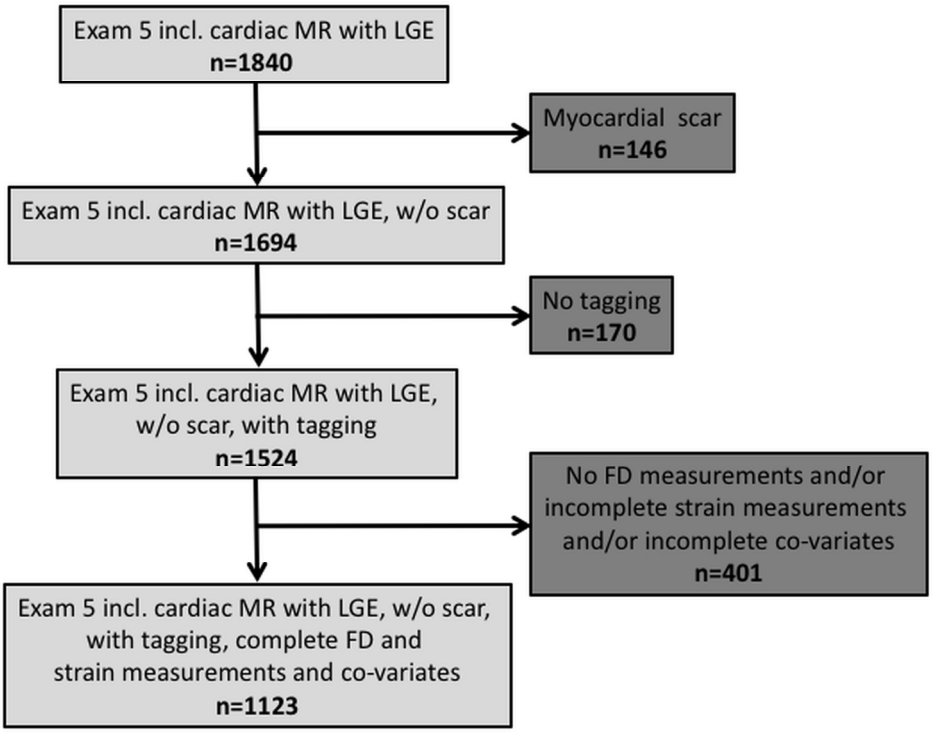

Figure 1. Cardiac MR, cardiac magnetic resonance; w/o, without; LGE, late gadolinium enhancement; FD, fractal dimension.

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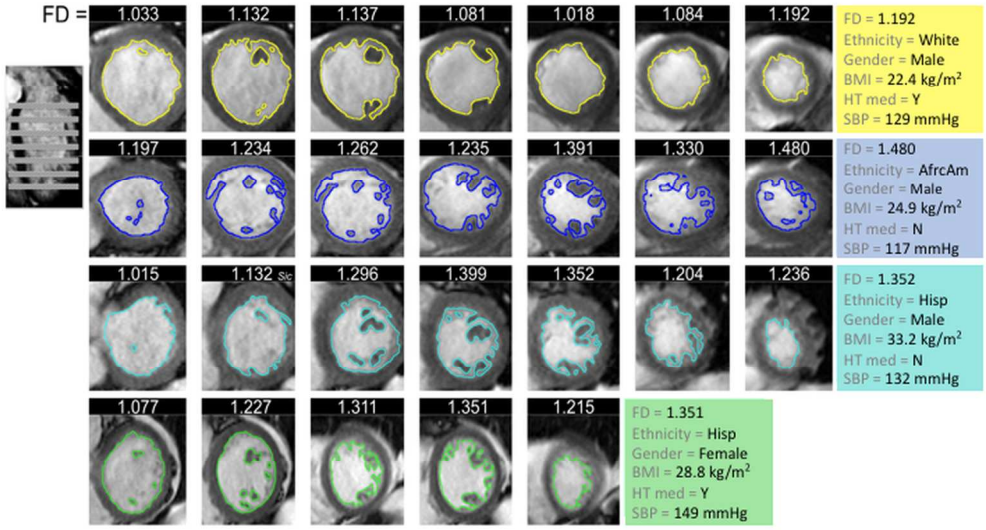

Figure 2. Analysis of fractal dimension. Measuring the fractal dimension by fractal analysis of short axis cine steady-state free precession images in four exemplar subjects from this MESA cohort: one subject with low fractal dimension (top row) and three subjects with high fractal dimension (row 2, 3 and 4). Colored lines show contouring of endocardial borders. The fractal dimension indicates how extensively the contour fills two-dimensional space. The image on the left shows planning of the short axis cine stack. Numbers on top of each short axis image indicate the fractal dimension of the respective slice. The colored panels on the right provide characteristics of the four subjects. FD, fractal dimension; AfrcAm, African American; Hisp; Hispanic; BMI, body mass index; HT med, hypertension medication; Y, yes; N, no; SBP, systolic blood pressure.

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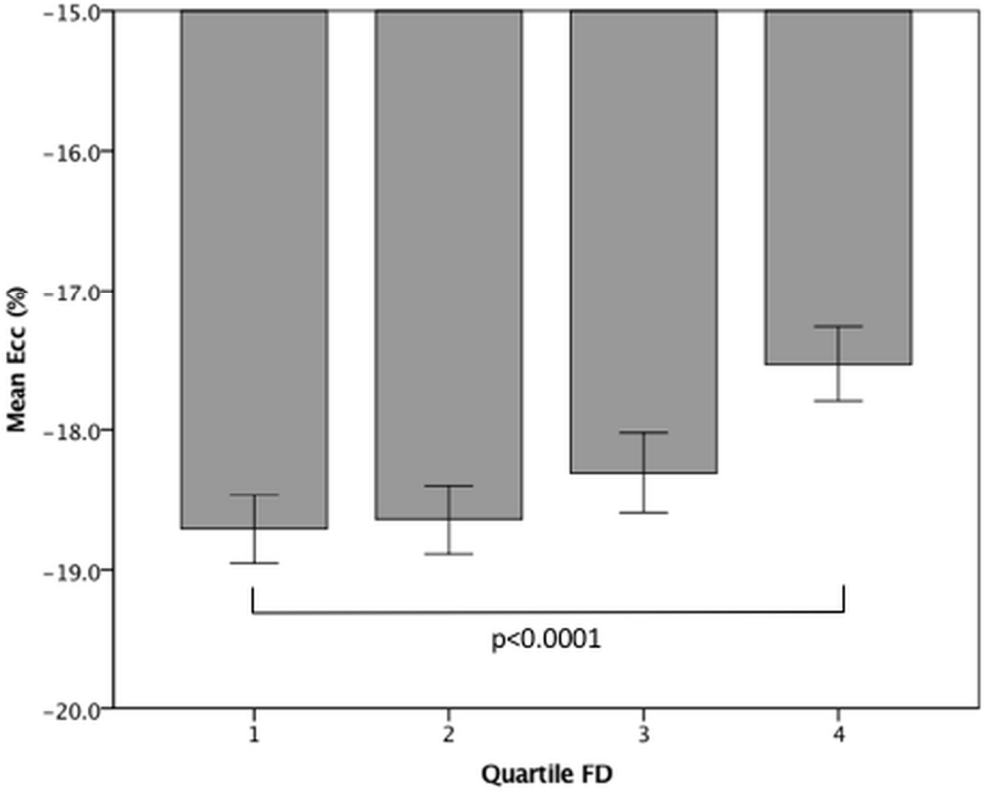

Figure 3. Circumferential strain by quartiles of FD. Ecc, peak regional systolic circumferential strain; FD, fractal dimension; Quartile 1, 1.01-1.15; Quartile 2, 1.15-1.12; Quartile 3, 1.12-1.24; Quartile 4, 1.24-1.4; Error bars indicating 95% confidence interval.

81x65mm (600 x 600 DPI)