Characteristics of Trabeculated Myocardium Burden in Young and Apparently Healthy Adults

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Increased myocardial trabeculations define noncompaction cardiomyopathy (NCC). Imaging advancements have led to increasingly common identification of prominent trabeculations with unknown implications. We quantified and determined the impact of trabeculations' burden on cardiac function and stretch in a population of healthy young adults. One hundred adults aged 18 to 35 years (28 ± 4 years, 55% women) without known cardiovascular disease were prospectively studied by cardiovascular magnetic resonance. Left ventricular (LV) volumes, segmental function, and ejection fraction (EF) and left atrial volumes were determined. Thickness and area of trabeculated (T) and dense (D) myocardium were measured for each standardized LV segment. N-terminal pro-brain natriuretic peptide (Nt-pro-BNP) was measured. Eighteen percent of the subjects had ≥1 positive traditional criteria for NCC, and 11% meet new proposed NCC cardiovascular magnetic resonance criteria. Trabeculated over dense myocardium ratio (T/D) ratios were uniformly greater at end-diastole versus end-systole (0.90 ± 0.25 vs 0.42 ± 0.13, p <0.0001), in women versus men (0.85 ± 0.24 vs 0.72 ± 0.19, p = 0.006), at anterior versus nonanterior segments (1.41 ± 0.59 vs 0.88 ± 0.35, p <0.0001), and at apical versus nonapical segments (1.31 ± 0.56 vs 0.87 ± 0.38, p <0.0001). The largest T/D ratios were associated with lower LVEF (57.0 ± 5.3 vs 62 ± 5.5, p = 0.0001) and greater Nt-pro-BNP (203 ± 98 vs 155 ± 103, p = 0.04). Multivariable regression identified greater end-systolic T/D ratios as the strongest independent predictor of lower LVEF, beyond age and gender, left atrial or LV volumes, and Nt-pro-BNP (β = −9.9, 95% CI −15 to 4.9, p <0.001). In conclusion, healthy adults possess variable amounts of trabeculations that regularly meet criteria for NCC. Greater trabeculations are associated with decreased LV function. Apparently healthy young adults with increased trabecular burden possess evidence of mildly impaired cardiac function. **(Am J Cardiol 2014;114:1094−1099)**

Interest in myocardial trabeculations has recently risen because of their importance in noncompaction cardiomyopathy (NCC). This entity is currently classified as a primary genetic cardiomyopathy by the American Heart Association[1] and an unclassified cardiomyopathy by the European Society of Cardiology.[2] Its main feature is the persistence of a double-layered left ventricular (LV) myocardium including a prominent inner layer of trabeculated myocardium. However, autopsy studies revealed that prominent trabeculations are highly prevalent in normal hearts of all ages.[3] So far, there is no single definition of NCC, but the current diagnostic criteria rely chiefly on the number and extension of trabeculae (Supplementary Table 1).[4−8] Echocardiography, traditionally used as first imaging option, not only observes a wide variation in the prevalence of trabeculations[9] but also between trabeculations in explanted hearts and those observed in vivo.[10] Cardiovascular magnetic resonance (CMR) is the gold standard imaging method for LV morphology and function[11] and allows superior LV characterization including more refined delineation of trabeculae.[12] Using CMR, new diagnostic criteria for NCC based on ratios or mass of noncompacted to compacted myocardium have been proposed.[7,8,13,14] However, when imaged by CMR, trabeculae are not only commonly seen in patients with decreased systolic function[15] but also in patients without suspected cardiomyopathy. We question whether these observations in apparently healthy subjects represent a surprising increase in subclinical NCC, an alternate form of subclinical cardiomyopathy, or a normal variant. We prospectively quantified trabeculations in a large cohort of otherwise healthy adults by CMR and determined the associations of trabeculae with cardiac function and plasma markers of myocardial stress.

Methods

One hundred twenty-six consecutive healthy subjects aged 18 to 35 years were prospectively enrolled through

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See page 1098 for disclosure information.

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Table 1
Population characteristics

Variables	Total (n = 100)
Age (years)	28 ± 4
Women (%)	56 (56)
Weight (kg)	65.7 ± 9.0
BMI (kg/m^2)	24.0 ± 4.2
Heart rate (bpm)	71 ± 11
Systolic blood pressure (mm Hg)	120 ± 11
Diastolic blood pressure (mm Hg)	74 ± 8
White blood count (10^{12}/L)	6.0 ± 0.8
Platelets (10^3/mL)	236 ± 57
Hemoglobin (g/dL)	142 ± 12
Total cholesterol (mg/dL)	179.4 ± 19.5
HDL-C (mg/dL)	61.9 ± 19.3
LDL-C (mg/dL)	96.7 ± 30.9
Triglycerides (mg/dL)	88.6 ± 62.0
Nt-pro-BNP (pmol/L)	168 ± 103
Indexed left atrial end-diastolic volume (mL/m^2)	32.5 ± 7.3
Indexed left atrial end-systolic volume (mL/m^2)	17.1 ± 4.6
Left atrial ejection fraction (%)	47.0 ± 6.2
Indexed left ventricular end-diastolic volume (mL/m^2)	58.2 ± 8.0
Indexed left ventricular end-systolic volume (mL/m^2)	23.1 ± 5.2
Stroke volume (mL/m^2)	35.7 ± 4.9
Left ventricular ejection fraction (%)	60.5 ± 5.8
Cardiac index (L/min/m^2)	2.5 ± 0.5
Indexed left ventricular mass (g/m^2)	46.5 ± 8.5

BMI = body mass index; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

e-mail and/or word-of-mouth and provided signed informed consent approved by the institution ethics board. Subjects were excluded, based on a standardized questionnaire and a physical examination, if any of the following conditions were present: any congenital or acquired cardiovascular disease, cardiovascular risk factors (hypertension, dyslipidemia, or diabetes mellitus), or presence of renal, hepatic, or blood disorders. Finally, subjects were not included if they possessed standard contraindications to CMR. Pregnant women or those within 1 year of childbirth were excluded. In addition, patients were evaluated with a 12-lead electrocardiogram at rest and N-terminal pro-brain natriuretic peptide (Nt-pro-BNP; analytical sensitivity 5 fmol/ml; proBNP 8-29 ELISA; Biomedica Gruppe and Alpco Diagnostics, Salem, NH). Finally, subjects with cardiac congenital anomalies seen at CMR were excluded. The population, therefore, consisted of 100 young adults without known cardiovascular or systemic disease, without cardiovascular risk factors, with a normal electrocardiogram at rest, with Nt-pro-BNP within normal limits, and without congenital cardiac disease on CMR.

Imaging was performed with a 1.5 T Philips Achieva scanner operating, release 2.6, level 3 (Philips Healthcare, Best, The Netherlands). Cine imaging of cardiac morphology and function was performed by steady-state free precession technique at 30 phases per cardiac cycle in apnea. Short-axis (8 mm thickness and 0 mm gap) and 3 radial long-axis planes were performed covering the entire cardiac silhouette (time repetition/time echo 3.17/1.58 ms, flip angle 60°, number of excitations = 1, in-plane spatial resolution 1.6 × 2 mm). Gadolinium contrast was not used.

Image analysis was performed off-line in an experienced core laboratory using a standardized approach by trained technicians supervised by an experienced cardiologist (EL) following the 16-segment model (CMR Mass, version 7.1; Medis, Leiden, The Netherlands).[16] Cardiac volumes and function measurements were performed as previously described. In summary, for LV volume analysis, the endocardial and epicardial borders were manually determined for all 30 phases of the cardiac cycle, and cardiac phases that had the larger and smallest ventricular cavity volumes were defined as end-diastole (ED) and end-systole (ES), respectively. Papillary muscles were included in the initial LV wall measurements (equivalent to weighting the LV) and excluded from LV cavity measurements (equivalent to blood pool techniques).[17] For cardiac volumes and functional measurements, the endocardial border was defined as the border between trabeculations and the ventricular blood pool, excluding papillary muscles (trabeculations were included in the LV wall and excluded from the blood pool). The LV end-diastolic volume, LV end-systolic volume (LVESV), LV stroke volume, LV ejection fraction (LVEF), and LV mass were computed using Simpson's rule adjusted to body surface area.[18] Segmental wall thickness was measured at ED by the centerline method (average of 20 to 30 chords/segment) and was compared with the average chord thickening at ES in each segment to determine segmental wall function. Decreased LV segmental wall function was considered present if systolic wall thickening was <30%.[19] Segment 17 was excluded. Left atrial (LA) endocardial borders were also determined for all 30 phases, and the ED (largest) and ES (smallest) volumes and the EF were calculated from Simpson's method.[20] LA appendix volumes were included in the total LA volumes.

Following standard measurements, LV trabeculated versus nontrabeculated myocardium were specifically analyzed by 2 experienced readers (HT and EL) blinded to each other and to all other variables, followed by resolution of any differences by consensus. Slices from short-axis (SA), 4-chamber (4CH), and 2-chamber (2CH) planes were analyzed. Analysis was performed at ED and ES in 3 planes of SA (basal, mid, and apical LV) and in a single plane of 2CH and a single plane of 4CH views (the planes in which the papillary muscles were easier to distinguish from trabeculations) to mirror the approach used for clinical interpretation by most CMR readers. Segmentation followed the American Heart Association recommendations. We first measured the combined sum of trabeculated (T) and dense (D) myocardium by delineating the epicardial border and the trabeculations border. Delineation of the trabeculations border for measurement of T + D was performed by connecting the inner tips (toward the center of the LV cavity) of all the trabeculations. The full thickness of T + D was then measured by the centerline method along 20 to 30 chords per segment, providing (1) maximum and (2) mean thickness and (3) area objectively and avoiding investigator bias associated with individual selection of the measurement site. Afterward, without altering the delineation of the trabeculations border, the inner border of dense myocardium was delineated. Trabeculations were defined per protocol as any muscular structure that moved synchronously with the inner myocardial border (endocardium) over the cardiac cycle and