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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Clinical and prognostic relevancy of left ventricular trabeculation assessed by cardiac magnetic resonance in patients with dilated cardiomyopathy

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Abstract

Background and aim: We sought to search for factors associated with the magnitude of trabeculation by cardiac magnetic resonance, and evaluate the impact of trabeculations on outcomes in patients with dilated cardiomyopathy (DCM).

Methods: We evaluated clinical profiles and outcomes of 276 subjects with DCM (age: 33.2 ± 13.3 years, 160 males). Trabeculation was quantified as trabeculated/total myocardial mass ratio (TM/M). Subjects were stratified into three subgroups (A, B, and C) according to the tertiles of rising TM/M values (33% ranges). A group of 30 healthy subjects served as controls. Patients were prospectively followed-up in search of major adverse cardiovascular events for 2.4 years on average (range 0.2–3.9 years).

Results: Dilated cardiomyopathy patients had more trabeculation than controls (27.1 ± 16.9% vs. 17.3 ± 8.1, $p < 0.01$). Group C subjects had lowest N-terminal pro-B-type natriuretic peptide (NT-proBNP) (1445 [984–3843] vs. 873 [440–2633] vs. 529 [206–1221] pg/mL, $p < 0.01$), higher ejection fraction (23.9 ± 10.4 vs. 25.0 ± 9.2 vs. 32.4 ± 2.7%, $p = 0.03$), and lower left ventricular mass index (LVMI) (91.3 ± 21.5 vs. 74.3 ± 31.1 vs. 55.7 ± 23.2 g/m^2, $p < 0.01$). They also had fewer areas of late gadolinium enhancement (69 [46.3%] vs. 31 [38.2%] vs. 15 [32.6%], $p = 0.01$). Male sex ($\beta = 0.21$, SE = 0.13; $p = 0.01$), LVMI ($\beta = –0.32$, SE = 0.08, $p < 0.01$) and NT-proBNP ($\beta = –0.05$, SE = 0.02, $p = 0.02$) were independently related to TM/M. The magnitude of trabeculation was not a predictor of major adverse cardiovascular events. Prognosis was impacted by left ventricular end-diastolic volume index only (HR 2.538, 95% CI –1.734–3.218, $p < 0.01$).

Conclusions: Trabeculation patterns relate to cardiac function and neurohormonal activation but not to survival.

Key words: left ventricular trabeculation, dilated cardiomyopathy, heart failure

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INTRODUCTION

A large spectrum of myocardial trabeculation patterns is observed in patients with dilated cardiomyopathy (DCM) [1, 2]. Its extreme form, left ventricular (LV) noncompaction, is associated with LV dysfunction, ventricular arrhythmias, and thromboembolic events [3]. The morphology is defined by the presence of dual layer myocardium consisting of a thin compacted epicardial tier, and massive hypertrabeculations with deep intertrabecular recesses. However, a different extent of trabeculation is often found in healthy subjects [1, 4].

It is believed that abnormal trabeculation phenotypes coexist with established cardiac disease [5]. The aetiology of hypertrabeculation is unknown. It is considered to be a form of fatal interruption of myocardial compaction processes; on the other hand, it is also postulated that hypertrabeculation is one of the symptoms caused by primary cardiac disease [6, 7].

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Therefore, there is uncertainty regarding the pathophysiology and prognosis in different forms of trabeculation.

Based on the improved capabilities of imaging modalities, numerous echocardiographic and cardiac magnetic resonance (CMR)-derived diagnostic criteria are used to identify pathological hypertrabeculation [8–10]. However, their diagnostic value remains uncertain. These criteria were purely morphological and were based only on trabeculated-to-compacted layer thickness ratios and might be affected by existing co-morbidities such as hypertension. Based on that criterion, a significant proportion of symptomless subjects have been diagnosed with pathological hypertrabeculation [11].

To date, very few studies have investigated how myocardial function, neurohormonal activation, and clinical presentation are disturbed by abnormal myocardial structure. Therefore, in this study we sought to search for clinical parameters that are associated with the magnitude of trabeculation in patients with idiopathic heart failure. Moreover, we include trabeculation quantitative analysis results together with recognised predictors in heart failure to look for reciprocal correlations and survival ascendancy.

METHODS

The study was approved by the Institutional Ethics Committee, and written, informed consent to participate in the study was obtained from all subjects.

Study population

Our study cohort consisted of 276 subjects with diagnosed DCM based on the WHO/ESC criteria: increased LV volume and decreased ejection fraction (EF) of less than 40% measured in CMR. All patients had CMR scan and underwent clinical examination, echocardiography, and laboratory testing as a part of routine evaluation. Coronary artery disease was excluded based on coronary angiography or computed tomography according to the criteria of Felker et al. [12]. Moreover, the presence of subendocardial late gadolinium enhancement (LGE) suggestive of myocardial infarction was an exclusion criterion along with acute myocarditis and secondary or reversible forms of cardiomyopathy caused by cardiotoxicity, HIV infection, neuromuscular diseases, tachyarrhythmias, or endocrine disorders [13, 14]. Normal values for CMR comparisons were sourced from the scans of 30 healthy volunteers (20 males, mean age 32.2 ± 3.1 years) with no significant medical history, with normal physical examination, and 12-lead electrocardiogram.

CMR imaging

Standard CMR study was performed with the use of a 1.5 Tesla scanner (Avanto, Siemens, Erlangen, Germany). A stack of short-axis, breath-hold, steady-state, free precession (SSFP) images (typical imaging parameters: repetition time, 2.2 to 3.6 ms; echo time, 1.2 ms; flip angle, 64 to 79 degrees; slice thickness, 8 mm; gap 2 mm) served for calculation of ventricular volumes and EF with the use of dedicated software (MASS 6.2.1, Medis, Leiden, The Netherlands). The volumetric analysis of LV was performed according to the recommendations of the Society for Cardiovascular Magnetic Resonance Board of Trustees Task Force on Standardised Protocols. A short-axis stack of cine images for ventriculography was planned by adjusting the slice locations on four-chamber and LV two-chamber images in diastole. Both the axial and short-axis stacks were prescribed to ensure complete coverage of the LV. In the short-axis the slices were oriented perpendicular to the ventricular septum on the four-chamber view and care was taken to ensure precise positioning of the mitral valve plane for the accurate calculation of the myocardial volume. The most basal short axis slice was located immediately on the myocardial side of the atrioventricular junction at end-diastole prescribed from the previously acquired long axis cines. The papillary muscles were excluded from the LV mass (LVM) calculation both in diastole and in systole for the purpose of volumetric analysis. Extreme attention was paid to identify the thickening papillary muscles in systole by comparing images from different phases of heart cycle to credibly exclude all trabecular tissue. Manual delineation of endocardial and epicardial contours was performed in end-diastolic and end-systolic phases by two experienced observers (L.M. and J.P. — both reported more than 1500 CMR examinations, both holding ESC CMR Level 3 certification). LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), LVM, and LVEF were calculated. LVEDV, LVESV, and LVM were indexed for the body surface area (BSA) (LVEDVI, LVESVI, LVMI, respectively). Right ventricular end-diastolic diameter and tricuspid annular plane systolic excursion were measured based on cine, four-chamber SSFP view. LGE imaging was performed from 10 to 15 min after intravenous administration of 0.2 mmol/kg gadobutrol (Gadovist, Bayer Pharma AG, Berlin, Germany). LV trabeculations defined as any endocardial wall contour irregularities present in the diastolic phase distinct from papillary muscles and chordae were measured on short-axis diastolic phase images as described elsewhere (Fig. 1) [10]. Myocardial trabeculation mass was measured as the difference between the global LVM (LV trabeculations included in the endocardial tracing) and compacted mass (LV trabeculations excluded from the endocardial tracing) and was reported as the ratio of the trabeculated to total (trabeculated + compacted) mass (TM/M).

To determine the proper inversion time for LGE imaging, an inversion time mapping sequence was performed. It consisted of centric ordered, segmented series echoes obtained over 2–3 heart beats, with each segment corresponding to a different TI value. The series of reconstructed images was visually evaluated to select the best inversion time for optimal myocardial nulling.

Images were visually assessed for the presence of LGE areas for each LV myocardial segment using the 17-segment cardiac model; regions of elevated signal intensity had to

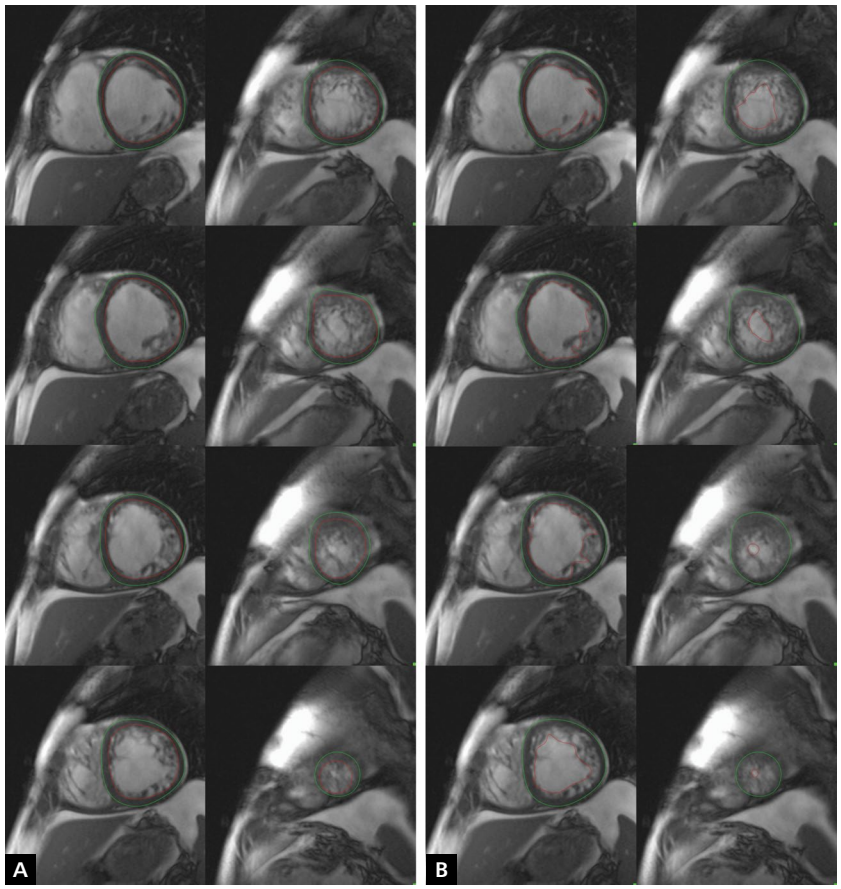

Figure 1. Quantification of trabeculated mass by excluding left ventricular trabeculations from the endocardial tracing; **A.** Global mass without trabeculation; **B.** Global mass with trabeculation included. The difference between B and A is the trabeculation mass. Papillary muscles were always excluded

be confirmed in two spatial orientations. In addition, the quantitative extent of LV LGE was determined. A region of interest (ROI) was selected in effectively nulled myocardium. Mean signal intensity and standard deviation (SD) of the ROI were measured. The LV myocardium was delimited by endocardial and epicardial contours, which were traced manually. Enhanced myocardium was defined as myocardium with a signal intensity > 6 SDs above the mean of the ROI. The extent of LGE was expressed as a percentage of the LVM (LGE%LV).

Mitral regurgitation volume was computed as the difference between LV stroke volume and phase-contrast aortic forward flow.

All subjects from the study group underwent a full protocol CMR examination; in controls, no gadobutrol was administered.

Follow up

Patients were prospectively followed-up in search of major adverse cardiovascular events (MACE) defined as death, heart transplantation, LV assist device implantation, or resuscitated cardiac arrest. Follow-ups were performed by analysing inpatient and outpatient medical records at our site. No patient was lost for follow-up.

Statistical analysis

All continuous variables were expressed as mean ± SD or as median and interquartile range and were tested for normal distribution with the use of the Kolmogorov-Smirnov test. Comparisons between groups were performed using the Student t test or Wilcoxon-Mann-Whitney U test for continuous variables and χ^2 or Fisher exact test for categorical variables as appropriate. In order to assess the significance of differences between groups A/B/C, we used the analysis of variance ANOVA. Post-hoc multiple comparisons (Bonferroni test) were performed to determine which means were significantly different in cases of significance differences between groups in ANOVA. For post-hoc analysis, three values of p were presented — $p_{A/B}$, $p_{B/C}$, and $p_{A/C}$ — for significance level between groups A and B, groups B and C, and groups A and C,

respectively. For comparison of New York Heart Association (NYHA) class between A, B, and C groups Kruskal-Wallis with Dunn post-hoc analysis was used.

A linear regression analysis was conducted to identify factors associated with trabeculation. Multiple regression was performed with the following variables entered into the model irrespective of the results of the univariate analysis: age, male sex, LVEF, LVEDVI, LVMI, N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration, presence of LGE, presence of left bundle branch block (LBBB), LGE%LV, left atrium (LA) area, NYHA class, and glomerular filtration rate (GFR). After entering all variables to the model, the variables that showed the least significant associations were subsequently excluded until all variables remained significant ($p < 0.05$). The model fit for multiple regression was assessed with the use of R2 (coefficient of determination) and adjusted R2 (coefficient of determination adjusted for the number of independent variables in a model).

The duration of follow-up was computed using the index date to the date of the first MACE or last clinical follow-up. MACE were as follows: death, heart transplantation, heart assist device implantation, and stroke. Kaplan-Meier survival and Cox proportional hazards analyses were used to assess the relationship between the parameters (age, male sex, LVEF, LVEDVI, LVMI, NT-proBNP concentration, creatinine concentration, presence of LGE, presence of LBBB, LGE%LV, LA area, NYHA class, and estimated GFR) and MACE. Hazard ratios (HR) were expressed as mean and 95% confidence interval (CI). All significant univariate predictors of MACE were proposed for inclusion in multivariate backward stepwise Cox models. The model with the lowest Akaike and Bayesian information criteria was retained. The predictive values of TM/M ratio were evaluated both unadjusted and after adjustment for baseline predictors of MACE. Survival curves for each patient group were compared with the log-rank (Mantel-Cox) test.

Intra- and inter-observer variability were evaluated using the Bland-Altman test and expressed as bias ± SD (95% CI) and intra-class correlation coefficients (ICCs).

A two-sided p value of less than 0.05 was considered to indicate statistical significance. Statistical analyses were performed with the use of IBM Statistical Package for Social Sciences version 24.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Presentations of clinical and CMR parameters are shown in Tables 1 and 2, respectively.

Intra- and inter-observer variability for measuring trabeculation mass were –0.92 ± 4.1% (95% CI –4.2% to 12.9%) and –2.67 ± 4.28% (95% CI –3.19% to 9.51%); ICC were 0.98 and 0.86, respectively.

The study group was divided into subgroups A, B, and C according to the tertiles (33% ranges) of TM/M. Patient count was as follows: group A (first tertile, TM/M: 15–25%)

Table 1. Baseline clinical parameters in whole study group and all subgroups

	Controls (n = 30)	All study group	P (between controls and all study group)	Group A TM/M range 15–25% (n = 149)	Group B TM/M range 26–35% (n = 81)	Group C TM/M range 36–45% (n = 46)	p (ANOVA between groups)	Post hoc multiple comparisons		
								$P_{A/B}$	$P_{B/C}$	$P_{A/C}$
Age [years]	32.2 ± 3.1	33.2 ± 13.3	ns	33.4 ± 12.1	32.2 ± 10.4	34.6 ± 5.9	0.31			
Male sex	20 (66.6%)	160 (57.9%)	ns	82 (55%)	49 (60.4%)	29 (63%)	0.03	0.04	0.03	0.02
BSA [m^2]	1.98 ± 0.2	1.94 ± 0.2	ns	1.9 ± 0.3	2.0 ± 0.3	2.0 ± 0.2	0.25			
Heart rate [bpm]	65 ± 12	80 ± 10	0.02	81 ± 12	79 ± 11	78 ± 9	0.33			
Diabetes mellitus	0	31 (11.2%)	< 0.01	16 (10.7%)	9 (11.1%)	6 (13%)	0.62			
NYHA	NA	2.0 [2]	NA	2.15 [2]	2.0 [2]	2.0 [2]	0.31			
History of stroke	0	23 (8.3%)	< 0.01	12 (8.1%)	7 (8.6%)	4 (8.7%)	0.49			
NT-proBNP [pg/mL]	NA	1124.5 (698.5–3262)	NA	1445 (984–3843)	873 (440–2633)	529 (206–1221)	< 0.01	0.01	0.01	< 0.001
eGFR [mL/min/1.73 m^2]	NA	74.3 ± 21.2	NA	66.2 ± 6.7	80.5 ± 19.6	89.9 ± 14.3	0.01	0.01	0.02	< 0.001
Atrial fibrillation	0	32 (11.5%)	< 0.01	17 (11.4%)	10 (12.3%)	5 (10.8%)	0.63			
LBBB	0	63 (22.8%)	< 0.01	35 (23.4%)	18 (22.2%)	10 (21.7%)	0.39			
Sodium	NA	139.1 ± 2.6	NA	137.6 ± 2.4	140.1 ± 2.8	142.5 ± 2.2	0.02	0.03	0.04	< 0.001
Potassium	NA	4.57 ± 0.4	NA	4.65 ± 0.47	4.5 ± 0.28	4.47 ± 0.12	0.41			
Follow-up time [years]	NA	2.4 ± 1.1	NA	2.5 ± 1.3	2.2 ± 1.1	2.3 ± 0.9	0.48			

BSA — body surface area; eGFR — estimated glomerular filtration rate; LBBB — left bundle branch block; NT-proBNP — N-terminal pro-B-type natriuretic peptide; NYHA — New York Heart Association; NA — non applicable; TM/M — trabeculated/total myocardial mass

Table 2. Cardiac magnetic resonance parameters in whole study group and all subgroups

	Controls	All study group	P (between controls and allstudy group)	Group A TM/M range 15–25% (n = 149)	Group B TM/M range 26–35% (n = 81)	Group C TM/M range 36–45% (n = 46)	p (ANOVA between groups)	Post hoc multiple comparisons		
								$P_{A/B}$	$P_{B/C}$	$P_{A/C}$
LVEDVI [mL/m^2]	87.4 ± 27.2	171.4 ± 40.2	< 0.01	170.1 ± 48.1	179.1 ± 29.9	162.1 ± 29.6	0.21			
LVESVI [mL/m^2]	32.4 ± 22.1	127.5 ± 31.5	< 0.01	129.4 ± 53.9	134.2 ± 40.7	109.5 ± 19.6	0.11			
LVEF [%]	62.9 ± 7.2	25.6 ± 10.5	< 0.01	23.9+/10.4	25.0 ± 9.2	32.4 ± 2.7	0.03	0.87	0.01	0.01
LVMI [g/m^2]	44.5 ± 10.3	80.3 ± 35.1	< 0.01	91.3 ± 21.5	74.3 ± 31.1	55.7 ± 23.2	< 0.01	< 0.001	< 0.001	< 0.001
LA area [cm^2]	16.3 ± 4.5	30 ± 10.5	< 0.01	31.1 ± 4.9	28.4 ± 11.5	29.3 ± 7.5	0.19			
MR volume [mL]	5.2 ± 3.8	21.6 (6.2–27.3)	< 0.01	21.7 (8.2–25.3)	22.1 (6.2–29.3)	20.5(7.1–27.1)	0.47			
Presence of LGE	NA	115 (41.6%)	NA	69 (46.3%)	31 (38.2%)	15 (32.6%)	0.01	0.01	0.01	< 0.001
LGE%LV	NA	0.55 (0.2–1.1)	NA	0.6 (0.2–1.2)	0.5 (0.2–1.0)	0.5 (0.1–0.9)	0.52			
RVEDD	34.1 ± 4.5	37.9 ± 8.1	0.02	39.3 ± 6.1	35.3 ± 9.4	38.4 ± 4.2	0.29			
TAPSE	26.2 ± 6.3	19.3 ± 7.4	< 0.01	19.4 ± 6.1	20.2 ± 5.3	18.2 ± 5.8	0.31			

LA — left atrium; LGE — late gadolinium enhancement; LGE%LV — amount of late gadolinium enhancement as percentage of left ventricle mass; LVEDVI — left ventricular end diastolic volume index; LVESVI — left ventricular end systolic volume index; LVEF — left ventricular ejection fraction; LVMI — left ventricular mass index; NA — non applicable; MR — mitral regurgitation; RVEDD — right ventricular end diastolic diameter; TAPSE — tricuspid annular plane systolic excursion; TM/M — trabeculated/total myocardial mass

— 149 (53.9%) patients; group B (second tertile, TM/M: 26–35%) — 81 (29.4%) patients; and group C (third tertile, TM/M: 36–45%) — 46 (16.7%) subjects.

Patients with DCM had significantly more trabeculation compared to healthy controls (27.1 ± 16.9% vs. 17.3 ± 8.1; $p < 0.01$). 167 (60.5%) patients fulfilled archetypal cut-off TM/M > 20% postulated by Jacqiuer et al. [10]. Noncompacted segments were the most commonly located in mid ventricle and apex in both the study group and normal controls (Fig. 2).

Among controls, two (6.6%) subjects had highest degree of trabeculation (TM/M 36–45%), and five (16.7%) subjects fulfilled Jacqiuer's criteria (TM/M > 20%).

Group C subjects were more frequently male (82 [55%] vs. 49 [60.4%] vs. 29 [63%]; $p = 0.03$) and had lowest NT-proBNP (1445 [984–3843] vs. 873 [440–2633] vs. 529 [206–1221] pg/mL; $p < 0.01$). Moreover, they had higher LVEF (23.9 ± 10.4 vs. 25.0 ± 9.2 vs. 32.4 ± 2.7%; $p = 0.03$) and lower LVMI (91.3 ± 21.5 vs. 74.3 ± 31.1 vs. 55.7 ± 23.2 g/m^2; $p < 0.01$) compared to groups A and B. Furthermore, patients from group C less often had areas of LGE (69 [46.3%] vs. 31 [38.2%] vs. 15 [32.6%]; $p = 0.01$), but the extent of fibrosis was not different across the study groups (p = NS).

Interestingly, we found that estimated GFR (66.2 ± 6.7 *vs.* 80.5 ± 19.6 vs. 89.9 ± 14.3 mL/min/1.73 m^2; $p = 0.01$) and sodium concentration (137.6 ± 2.4 *vs.* 140.1 ± 2.8 *vs.* 142.5 ± 2.2 mEq/mL; $p = 0.02$) were the highest in group C.

A univariate linear regression analysis demonstrated an association of TM/M with male sex, LVMI, presence of LGE, estimated GFR, and NT-proBNP. A multivariate analysis revealed that factors significantly and independently related to TM/M were male sex, LVMI, and NT-proBNP (Table 3).

Follow-up

The follow-up period was 2.4 years on average (range 0.2–3.9 years). During that time, there were 15 deaths (nine in group A, four in group B, and two in group C), 10 cardiac transplantations (six in group A, three in group B, and one in group C), and one LV assist device implantation (group B patient). Five patients had strokes (three in group A, one in group B, and one in group C).

The MACE-free (Fig. 3) and death-free (Fig. 4) survival Kaplan-Meier curves showed that the groups with the lowest degree of trabeculation did not experience worse outcomes than those in the highest tertile of trabeculation.

Cox univariate predictors of MACE are listed in Table 4. TM/M was not associated with a worse prognosis when they were unadjusted or after adjustment for baseline variables. By multivariate analysis, only LVEDVI was an independent predictor of MACE-free survival.

DISCUSSION

The main findings of our study include the following:

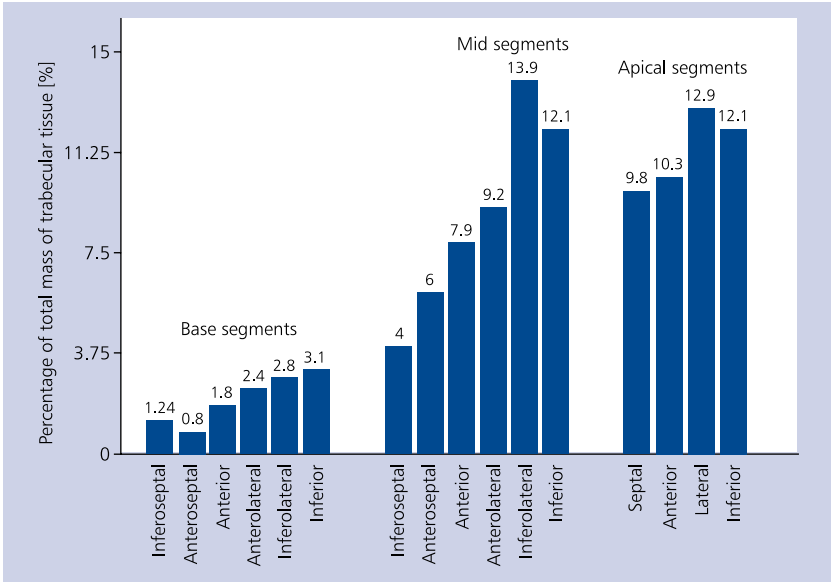

Figure 2. Percentage of total mass of trabecular tissue across all levels and segments of left ventricle in dilated cardiomyopathy subjects

Table 3. Univariate and multivariate analysis of factors associated with trabeculated/total myocardial mass (TM/M)

	Univariate analysis		Multivariate analysis	
	β (SE)	p	β (SE)	p
Age	0.04 (0.01)	0.38		
Male sex	0.26 (0.15)	0.01	0.21 (0.13)	0.01
NYHA	–0.22 (0.48)	0.12		
LVEDVI	– 0.03 (0.02)	0.27		
LVEF	0.21 (0.13)	0.19		
LVMI	– 0.33 (0.06)	< 0.001	–0.32 (0.08)	< 0.001
LGE	–0.17 (0.02)	0.04		
LGE% LV	–0.04 (0.02)	0.26		
LA area	0.26 (0.23)	0.56		
NT-proBNP	–0.08 (0.03)	>0.01	–0.05 (0.02)	0.02
eGFR	0.06 (0.05)	0.04		
LBBB	0.08 (0.02)	0.23		
Model performance				
R^2			0.53	
Adjusted R2			0.51	

eGFR — estimated glomerular filtration rate; LA — left atrium; LBBB — left bundle branch block; LGE — late gadolinium enhancement; LGE%LV — amount of late gadolinium enhancement as a percentage of left ventricle mass; LVEDVI — left ventricular end diastolic volume index; LVEF — left ventricular ejection fraction; LVMI — left ventricular mass index; NT-proBNP — N-terminal pro-B-type natriuretic peptide; NYHA — New York Heart Association; SE — standard error

— young patients with advanced heart failure and DCM had significantly increased trabeculation compared to healthy subjects;
— the degree of trabeculation was associated with male sex, LVM, and neurohormonal activation;
— the magnitude of trabeculation failed to be predictor of MACE-free survival.

Two morphological methods are used to detail myocardial trabeculation in CMR. Petersen`s method [9] is based on the compacted vs. noncompacted layers ratio. While applying

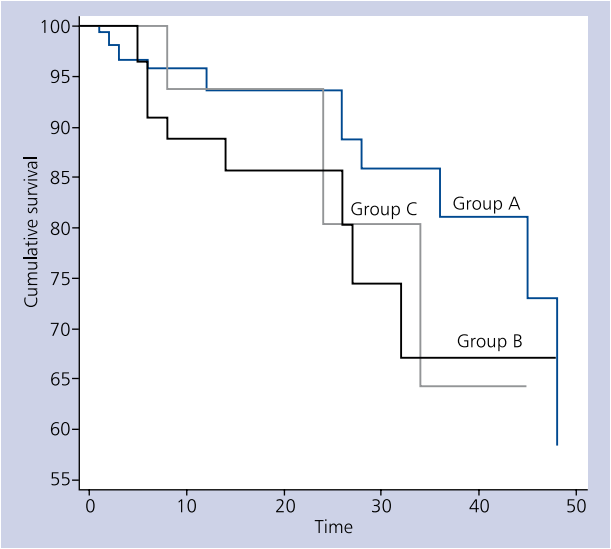

Figure 3. Kaplan-Meier estimates of survival free of major adverse cardiovascular events according to tertiles of noncompacted to compacted myocardium (TM/M); log rank p = 0.511

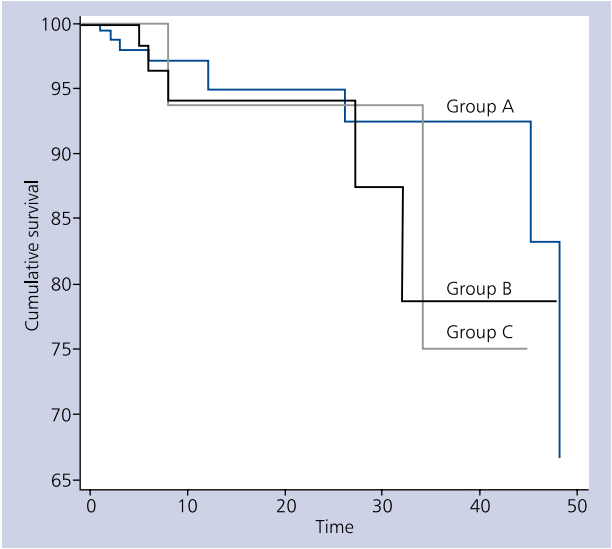

Figure 4. Kaplan-Meier estimates of survival free of death according to tertiles of noncompacted to compacted myocardium (TM/M); log rank p = 0.695

Table 4. Cox univariate and multivariate predictors of major adverse cardiovascular events

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p	HR (95% CI)	p
TM/M	0.920 (0.854–1.339)	0.27		
Age	1.006 (0.997–1.017)	0.67		
Male sex	0.985 (0.963–1.129)	0.29		
NYHA	2.012 (1.264–2.785)	0.01		
LVEDVI	2.152 (1.829–3.199)	< 0.01	2.538 (1.734–3.218)	< 0.01
LVEF	0.741 (0.539–0.841)	0.02		
LVMI	1.211 (0.918–1.319)	0.38		
LGE	1.181 (1.026–1.228)	0.07		
LGE%LV	0.997 (0.918–1.049)	0.82		
LA area	0.971 (0.891–1.033)	0.78		
NT-proBNP	2.684 (1.961–3.519)	0.01		
eGFR	0.981 (0.913–1.039)	0.44		
LBBB	1.172 (0.921–1.239)	0.72		

CI — confidence interval; HR — hazard ratio; eGFR — estimated glomerular filtration rate; LA — left atrium; LBBB — left bundle branch block; LGE — late gadolinium enhancement; LGE%LV — amount of late gadolinium enhancement as percentage of left ventricle mass; LVEDVI — left ventricular end diastolic volume index; LVEF — left ventricular ejection fraction; LVMI — left ventricular mass index; NT-proBNP — N-terminal pro-B-type natriuretic peptide; NYHA — New York Heart Association; TM/M — trabeculated/total myocardial mass

Jacquier's quantitive algorithm [10] it is possible to obtain the exact mass of the trabeculated myocardium. The correlation between these two methods was found to be satisfactory. However, the agreement to classify patients into groups with high and low degrees of noncompaction remains rather poor [15]. Petersen's method is hard to quantify and stratify with considerable hypersensitivity bias, which makes application of that method in our study difficult. On the other hand, Jacquier's method might overestimate the amount of trabecular tissue in case of very irregular, dispersed trabeculations. The delineation of the deep spaces and lacunas between trabeculations remains a challenge because the software used for quantification of trabecular tissue are not designed exactly for that purpose. Nevertheless, despite noticeable disadvantages of Jacquier's algorithm, it still has a huge supremacy over Petersen's and remains a gold standard in quantitative analysis of

trabecular tissue. The extent of trabeculation in patients with DCM reported in our study is concordant with previously published data [1, 4]. However, it is still unclear whether increased trabeculation is a result of distinct cardiomyopathy or rather a sign of the remodelling of the failing heart [16–19]. Previous studies reported that a relatively high percentage of patients with idiopathic heart failure meet criteria for noncompaction [11, 20]. In accordance with these studies, we found that more than half of our population had an abnormal amount of trabeculation. On the other hand, the hypertrabeculation phenotype can be observed in heart diseases other than DCM, such as hypertrophic cardiomyopathy [21], congenital heart diseases [22], or neuromuscular disorders [17]. Some authors have suggested that ventricle dilatation and the separation of the inner myocardial layer make trabeculation more visible [23]. Interestingly, in our study mid-wall fibrosis, which is a characteristic feature of DCM, was found less frequently in patients with high degrees of trabeculation. However, the extent of fibrosis in this study was not associated with the magnitude of noncompaction. Amzulescu et al. [15] did not find any association between noncompaction phenotype or with the presence and the extent of fibrosis. Moreover, in contrast to previous heart failure studies, we did not find fibrosis to be an independent predictor of survival [15]. This disparity can be explained by different methods of fibrosis measurement and the younger age of our study population.

Another important issue raised in previous studies was the threshold for a pathological amount of trabeculation. Jacquier proposed that a noncompacted to compacted ratio > 20% should be considered as abnormal [10]. However, based on the finding that almost 20% of healthy subjects fulfilled archetypal Jacquier criteria, other researchers concluded that this seemed to be inaccurate to credibly ascertain the truly pathological amount of trabeculation [1, 11, 15, 24]. They even postulated that this border should be pushed up to 30% or more [15]. Our results also confirmed that almost one fifth of healthy subjects can be diagnosed with abnormal myocardial structure.

Applied criteria of pathological amounts of noncompacted layer are purely morphological because no differences in clinical profile, heart function, or prognosis were found between subjects with high and low degrees of trabeculation [15]. Our study is the largest to date and the first to stratify patients into tertiles according to the amount of trabeculation. Amzulescu et al. [15] divided their study group into tertiles but only for the purpose of survival analysis. In the MESA study, fractal analysis was performed on a non-heart failure population [1, 24]. Surprisingly, unlike other authors, we found that patients with a high degree of trabeculation had better cardiac function and lower NT-proBNP. Possibly, this can be explained by the tertile study population allotment or by different study group characteristics. Our patient population was much younger with more severe heart failure symptoms compared to either Amzulescu's et al. [15] or MESA's cohorts [24]. Some small studies suggested that noncompaction phenotype might indicate a more severe form of DCM [25]. Our findings not only call this thesis into question but also suggest the opposite scenario: we assert that not the thickening of the noncompacted myocardium but instead the depletion of the trabeculated zone is truly pathological in patients with idiopathic heart failure.

Survival

We observed low mortality in a view of advanced stage of the disease. Also, we found that survival was not affected by the degree of trabeculation. In some cases, the observation time seemed to be short in our study. It is clear that the disease beginning is not the same as the beginning of the observation in DCM subjects. In idiopathic heart failure patients, the disease beginning is often symptomless due to activation of compensation mechanisms, and usually hard to acknowledge. In this study, the beginning of the observation period was at the CMR scan time point, as was determined in previous studies. In the MESA study, hypertrabeculation was not associated with worse outcome in the 10-year follow up [24]. Also, Amzulescu et al. [15] observed a small number of MACEs in patients with a high amount of trabeculation. On the other hand, other studies highlighted that a greater number of events was recorded in patients with noncompaction [26, 27]. However, these studies included patients with preserved cardiac function and patients with DCM. Despite that, it has been shown that the prognosis of heart failure patients is mainly affected by recognised heart failure parameters, such as heart failure symptoms, LV dilatation, and systolic dysfunction. All previous studies concordantly report that survival was not associated with the amount of trabeculation. In agreement with these reports, we found that the parameter reflecting LV remodelling was an independent, statistically significant predictor of outcome in our population.

Limitations of the study

We did not include results of genetic testing in our study. Differentiation between types of diseases could benefit from DNA analysis. Together with further larger studies, this would allow a better understanding of the clinical importance and multifactorial implications of trabeculation patterns in DCM patients.

CONCLUSIONS

The amount of LV myocardial trabeculation in patients with DCM is significantly larger than in healthy subjects. The magnitude of trabeculation is associated with LV function and severity of the disease, but it fails to predict MACE-free survival.

Conflict of interest: *none declared*

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Znaczenie kliniczne i rokownicze beleczkowania lewej komory ocenianego w rezonansie magnetycznym u chorych z kardiomiopatią rozsztrzeniową

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Streszczenie

Wstęp i cel: Celem pracy było obliczenie masy beleczkowania mięśnia lewej komory (LV) za pomocą rezonansu magnetycznego oraz analiza jej wartości rokowniczej u chorych z kardiomiopatią rozstrzeniową (DCM).

Metody: Ilościową analizę beleczkowania LV przeprowadzono u 276 chorych z DCM. Stopień beleczkowania określono jako odsetek masy beleczkowania do całkowitej masy mięśnia (TM/M). Grupa badana została podzielona na trzy podgrupy (A, B i C) w zależności od tercyli TM/M. Okres obserwacji wynosił 2,4 roku (0,2–3,9 roku). Punktami końcowymi były: zgon, transplantacja serca, implantacja mechanicznego urządzenia wspomagającego pracę serca i udar mózgu. Grupę kontrolną stanowiło 30 zdrowych ochotników dobranych po względem wieku i płci.

Wyniki: Pacjenci z DCM charakteryzowali się większym stopniem beleczkowania niż zdrowi ochotnicy (27,1 ± 16,9 *vs*. 17,3 ± 8,1%; $p < 0,01$). U chorych z grupy C stwierdzono najniższe stężenie N-końcowego peptydu natriuretycznego typu B (NT-proBNP) w porównaniu z pacjentami z grup A i B (A: 1445 [984–3843] pg/ml *vs*. B: 873 [440–2633] pg/ml *vs*. C: 529 [206–1221] pg/ml; $p < 0,01$), najwyższą frakcję wyrzutową LV (A: 23,9% ± 10,4% *vs*. B: 25,0% ± 9.2% *vs*. C: 32,4 ± 2,7%; $p = 0,03$) oraz niższą masę LV (A: 91,3 ± 21,5 g/m^2 *vs*. B: 74,3 ± 31,1 g/m^2 *vs*. C: 55,7 ± 23,2 g/m^2; $p < 0,01$). Ponadto u chorych z grupy A częściej występowały obszary późnego wzmocnienia pokontrastowego (A: 69 [46,3%] *vs*. B: 31 [38,2%] *vs*. C: 15 [32,6%]; $p = 0,01$). Analiza regresji logistycznej wykazała, że czynnikami niezależnie związanymi z TM/M były: płeć męska ($\beta = 0,21$, SE = 0,13; $p = 0,01$), masa LV ($\beta = –0,32$, SE = 0,08; $p < 0,01$) i stężenie NT-proBNP ($\beta = –0,05$, SE = 0,02; $p = 0,02$). Stopień beleczkowania LV nie był czynnikiem przewidującym występowanie punktów końcowych. Niezależnym czynnikiem rokowniczym w tej grupie chorych była tylko objętość końcoworozkurczowa LV (HR 2,538, 95% CI –1,734–3,218; $p < 0,01$).

Wnioski: Beleczkowanie ma związek z funkcją LV oraz aktywnością neurohormonalną, natomiast nie ma wpływu na rokowanie u chorych z DCM.

Słowa kluczowe: beleczkowanie lewej komory, niewydolność serca, kardiomiopatia rozstrzeniowa

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