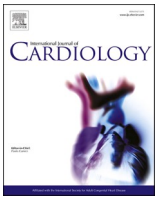
International Journal of Cardiology 397 (2024) 131614

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard



Thinning of compact layer and systolic dysfunction in isolated left ventricular non-compaction: A cardiac magnetic resonance study

Manuel De Lazzari [a,1], Giulia Brunetti [a,1], Enrica Frasson [a,1], Alessandro Zorzi [a,1], Alberto Cipriani [a,1], Federico Migliore [a,1], Giorgio De Conti [b,1], Raffaella Motta [b,1], Martina Perazzolo Marra [a,1], Domenico Corrado [a,1,*]

[a] Department of Cardiac, Thoracic and Vascular Sciences and Public Health, University of Padua, Italy
[b] Department of Medicine, University of Padua, Italy

ARTICLE INFO

Keywords:
Left ventricular non compaction
Spongy myocardium
Cardiac magnetic resonance

ABSTRACT

Background: The Petersen' index reflects an excess of myocardial trabeculation which is not a specific morpho-functional feature of left ventricular non-compaction (LVNC) cardiomyopathy, but a "phenotypic trait" even observed in association with other myocardial diseases and over-loading conditions. The present study was designed to evaluate the relation between a critical thinning of compact layer and the development of systolic dysfunction and LVNC cardiomyopathy.

Methods: We compared CMR morpho-functional features and measurements of LV wall thickness using a 17 segment model of a cohort of patients fulfilling the Petersen criterion for LVNC with LV systolic dysfunction versus those of a cohort of age- and sex-matched controls with LVNC and preserved LV systolic function. All the study patients had an "isolated" LVNC defined as positive Petersen criterion in the absence of other diseases such as hypertrophic and dilated cardiomyopathy, valvular heart disease, or congenital heart disease and over-loading conditions.

Results: he study population included 33 patients with "isolated" LVNC: 11 consecutive index patients with a reduced LV ejection fraction (LVNCrEF) and 22 controls with a preserved LVEF (LVNCpEF). The compact myocardial layer was thinner in patients with LVNCrEF than in those with LVNCpEF patients, both in mid-ventricular and apical LV segments. On linear regression analysis, there was a linear correlation between median thickness of mid-ventricular free wall segments and left ventricular ejection fraction ($r = 0.51$, $p = 0.005$). On the ROC curves analysis, ≥2 segments with a compact myocardial layer <5 mm in the free wall mid-ventricular segments showed the best accuracy for reduced LVEF (100% sensitivity and 60% specificity; AUC 0.81, $p < 0.01$). The negative predictive value for LV systolic dysfunction of <2 free wall mid ventricular segments <5 mm was 100%. On quantitative analysis, the mass of papillary muscles was lower in patients with LVNCrEF [1.2 (0.8–1.4) versus 1.6 (1.1–1.8) g/mq; $p = 0.08$]. Conclusions: A thinned compact layer of mid-ventricular segments of the LV free wall was associated with a reduced systolic function and "isolated" LVNC cardiomyopathy.

1. Introduction

Left ventricular non-compaction (LVNC) is a developmental anomaly of the ventricular myocardium occurring during the embryogenesis [1,2]. The altered myocardial structure of LVNC phenotype is characterized by a 2-layered left ventricular (LV) wall: an outer "compact"

Abbreviaton: LVNC, Left ventricular non compaction; CMR, cardiac magnetic resonance; LV, left ventricle; NC, non compact myocardium layer; C, compact myocardium layer; EF, ejection fraction; EDV, end diastolic volume; LVNCrEF, Left ventricular non compaction with reduced ejection fraction; LVNCpEF, Left ventricular non compaction with preserved ejection fraction.

* Corresponding author at: Inherited Arrhythmogenic Cardiomyopathy Unit, Department of Cardio-Thoraco-Vascular Sciences and Public Health, University of Padua, Via Giustiniani, 2, 35128 Padua, Italy.
E-mail address: domenico.corrado@unipd.it (D. Corrado).

[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

https://doi.org/10.1016/j.ijcard.2023.131614
Received 21 June 2023; Received in revised form 31 October 2023; Accepted 23 November 2023
Available online 26 November 2023

myocardial layer and an inner layer with excessively prominent trabeculation and deep intertrabecular recesses (referred to as "non-compact" myocardial layer) [1]. Cardiac magnetic resonance (CMR) is considered the gold standard imaging technique for diagnosis of LVNC and the generally accepted CMR criterion proposed by Petersen et al. for diagnosis of LVNC is fulfilled in the presence of an end-diastolic non-compacted/compacted wall ratio > 2.3 [3]. However, the Petersen index mostly reflects the excessive trabeculation of the LV wall, which is not disease-specific and may be observed in patients with heart diseases other than LVNC such as dilated and hypertrophic cardiomyopathies, neuromuscular disorders and congenital heart malformations. Moreover, increased trabeculation may be observed in healthy individuals (physiologic phenotypic variant), during pregnancy or after sustained athletic activity (physiologic response to increased and reversible ventricular overload) [2]. These findings make differential diagnosis between "hypertrabeculation phenotype", "non-compaction phenotype" and "LVNC cardiomyopathy" a challenging task [4]. The presence of LV systolic dysfunction in association with a positive Petersen index for "excessive LV trabeculation" may be considered a key feature for diagnosing a true "LVNC cardiomyopathy" [4]. Previous studies failed to demonstrate a relation between the extent of trabeculation and LV systolic dysfunction [5–7]. Hence, the present study was designed to evaluate the pathophysiologic role of a critical thinning of compact layer to the development of systolic dysfunction with LVNC cardiomyopathy. In our case-control study, we compared a cohort of patients fulfilling the Petersen criterion for LVNC with LV dysfunction to a cohort of age- and sex-matched controls with LVNC but no LV dysfunction. We tested the hypothesis that the underdevelopment of the compact layer, rather than the excessive trabeculation of the noncompact layer, impacts on the contractile performance of the LV by a disease-specific pathophysiologic mechanism.

2. Methods

The study cohort consisted of a single-center population of patients who underwent contrast-enhanced CMR and received a diagnosis of "isolated" LVNC. Isolated LVNC was diagnosed based on a positive Petersen criterion (noncompacted (NC) to compacted (C) myocardium ratio in diastole >2.3) in the absence of other diseases such as hypertrophic and dilated cardiomyopathy, valvular heart disease, or congenital heart disease [3].

The study was approved by the local institutional review board and because of its retrospective nature no consent was required. The datasets analysed during the current study are available from the corresponding author on reasonable request.

2.1. Cardiac magnetic resonance protocol

All CMR images were performed on a 1.5 T scanner (Magnetom Avanto Siemens AG, Germany) using a protocol including postc-ontrast sequences accordingly with SCMR current recommendations [8,9]. Biventricular morpho-functional assessment was performed by a set of steady-state free precession sequence cine loops in sequential short-axis views and long-axis views as previously reported [10]. After 10 min since administration of gadolinium-based contrast agent (gadobenate dimeglumine, Multihance or gadobutrol, Gadovist, typically 0.2 mmol/kg of body weight), 2-dimensional segmented fast low-angle short inversion recovery sequences were acquired in the same views of the cine images, covering the entire ventricles (repetition time, 5.4–8.3 ms; echo time, 1.3–3.9 ms; average in-plane spatial resolution, 1.4–1.5 × 2.2–2.4 mm; 6-mm slice thickness; 2-mm gap; and flip angle, 20°–25°). Inversion times were adjusted to null normal myocardium using a Look-Locker sequence, and images were repeated in 2 separate phase-encoding directions to exclude artefacts.

Global ventricular volumes, systolic function were calculated from the short-axis cine images, excluding papillary muscles from the myocardium, using a computer-aided analysis package (CMR42; Circle International ®) [11]. In all patients, the end-diastolic thickness of the compact and noncompact layers was measured according to a previously reported protocol [3]. The 2 layered wall thickness was systematically measured in long-axis view for all LV segments according to the AHA-17-segments model (with the exclusion of the 17th segment i.e., the apex). The number of segments with a NC/C ratio > 2.3 and the minimum value of thickness of the compact layer were assessed at basal, mid and apical level.

2.2. Follow-up

All patients underwent annual clinical evaluation, including medical history, physical examination, basal 12-lead ECG and 24-h Holter monitoring, and control echocardiographic examination; a control CMR was performed in those patients showing a worsening of echocardiographic LV systolic function during follow-up.

2.3. Statistical analysis

Data are expressed as median with 25th to 75th percentiles because normality could not be assumed for any variable. Categorical differences among groups were evaluated by the $\chi 2$ test or the Fisher exact test, as appropriate. Differences among continuous variables were compared using the two-sample Z Kolmogorov-Smirnov test. Linear regression analysis was performed to study the correlation between median thickness of mid-ventricular free wall segments and left ventricular ejection fraction.

Receiver operating curve characteristics were used to generate the most accurate cut-off values of compact layer thickness and its segmental extent for LV systolic dysfunction.

A 2-tailed probability value of 0.05 was considered statistically significant. All analyses were performed using SPSS 23 (SPSS Inc., Chicago, IL).

3. Results

Of 2454 CMR studies performed at the University Hospital of Padua during the study period 2017–2022, 196 (11%) fulfilled the Petersen criterion for LVNC. Of these 196 patients, 11 (5,6%) index patients fulfilled the Petersen criteria for LVNC and had a reduced LV ejection fraction LVEF (< 50%) (LVNCrEF). The final study population, included a total of 33 patients with isolated LVNC which consisted of the 11 index patients with LVNCrEF and 22 age-and gender matched controls fulfilling the Petersen index for LVNC with a preserved LVEF (LVNCpEF). Baseline clinical characteristics of the entire study population and subgroups of patients with reduced LVEF and those with preserved LVEF are reported in Table 1.

Seventy-three percent were male with a median-age of 25 years (IQ 19–42). Median LVEF and LV EDV were 55% (IQ 48–58) and 100 ml/m2 (IQ 89–104), respectively. Median LV EF in the index patients was 45% (42–48%) and 57% (55–59%) in the control subjects. Baseline clinical and imaging characteristics of the study population are reported in Table 1.

3.1. Correlation between thickness of compaction layer and LV EF

On standard CMR, patients with LVNCrEF had a statistically significantly higher value of the Petersen's criterion compared with patients with LVNCpEF [median NC/C ratio 3.5 (IQ 2.8–3.7) versus 2.5 (IQ 2.4–3.0); $p = 0.01$].

Segmental analysis of thickness based on the AHA17-segments model is reported in Table 2. There was no statistically significant difference between patients with LVNCrEF and those with LVNCpEF with regard to the number of the involved myocardial segments fulfilling the Petersen's NC/C thickness ratio > 2.3 [6 (IQ 3–7) vs 4 (IQ 1–5)

Table 1
Baseline clinical characteristics

	Overall ($n = 33$)	LVNCrEF ($n = 11$)	LVNCpEF ($n = 22$)	P value
Age (years)	25 (19–42)	25 (18–44)	24 (19–42)	1.00
Male, n (%)	24 (73)	8 (73)	16 (73)	1.00
Caucasian ethnicity	33 (100)	11 (100)	20 (100)	–
Body surface area (mq)	1.75 (1.66–2.03)	1.71 (1.61–1.8)	1.8 (1.66–2.07)	0.45
Family history of SCD, n (%)	4 (12)	2 (18)	2 (9)	0.58
Family history of CM, n (%)	7 (21)	3 (27)	4 (18)	0.66
Symptoms				
Chest Pain, n (%)	4 (12)	3 (27)	1 (5)	0.10
Dyspnea, n (%)	7 (21)	4 (36)	3 (14)	0.14
Palpitation, n (%)	15 (45)	7 (63)	8 (36)	0.13
ECG				
Interventricular conduction defect, n (%)	8 (24)	4 (36)	4 (18)	0.39
Repolarization abnormalities, n (%)	4 (12)	1 (9)	3 (14)	1.00
Echocardiographic criteria for LVNC, n (%)	33 (100)	11 (100)	22 (100)	–
24-h-ECG Holter				
Atrial arrhythmias, n (%)	0 (0)	0 (0)	0 (0)	–
NSVT, n (%)	3 (9)	2 (18)	1 (5)	0.25
Standard CMR analysis				
LV EF (%)	55 (48–58)	45 (42–48)	57 (55–59)	<0.01
LV EDV (ml/mq)	100 (89–104)	100 (90–104)	101 (87–103)	0.97
RV EF (%)	54 (51–58)	53 (47–58)	55 (51–59)	0.84
RV EDV (ml/mq)	87 (80–98)	81 (75–92)	88 (84–98)	0.29

LVNCrEF: Left ventricular non compaction with reduced ejection fraction; LVNCpEF: Left ventricular non compaction with preserved ejection fraction; SCD: sudden cardiac death; CM: cardiomyopathy; ECG: electrocardiogram; CMR: cardiac magnetic resonance; EF: ejection fraction; EDV: end diastolic volume; LV: left ventricle; NSVT: non-sustained ventricular tachycardia; RV: right ventricle.

Table 2
Segmental analysis of thickness

Thickness of LV segments	LVNCrEF	LVNCpEF	*P* value
Segments with ratio of noncompaction/compaction thickness > 2.3 (n)	6 (3–7)	4 (1–5)	0.29
Thickness of basal segments			
Compact layer (mm)	5.6 (4.7–7.2)	6.5 (6–7.3)	0.10
Non-compact layer (mm)	0	0	
Thickness of mid-ventricular segments			
Compact layer (mm)	4.9 (4.2–5.2)	5.6 (5–6.6)	0.09
Non-compact layer (mm)	7.9 (3.3–9.5)	5 (0–8.9)	0.65
Thickness of apical segments			
Compact layer (mm)	3.4 (2.8–4.3)	5.1 (3.8–5.7)	0.01
Non-compact layer (mm)	12 (9.5–13.7)	11.8 (9.8–13.8)	1.00
Thickness of compact layer of mid-ventricular segments			
Septal mid ventricular segments (mm)	6 (5–6.5)	5.9 (5.1–6.9)	0.84
Free wall mid-ventricular segments (mm)	4.3 (3.9–4.9)	5.5 (5–6.5)	<0.01
Mid ventricular segments of free wall with thickness of compact layer <5 mm (n)	3 (3–4)	1 (0–4)	0.01
Patients with ≥2 mid ventricular segments of free wall with thickness of compact layer <5 mm (n, %)	11 (100)	9 (41)	<0.01
Papillary muscles			
Papillary muscles mass (g/mq)	1.2 (0.8–1.4)	1.6 (1.1–1.8)	0.08
Well-formed Papillary muscles (n, %)	5 (46)	13 (59)	0.48

LVNCrEF: Left ventricular non compaction with reduced ejection fraction; LVNCpEF: Left ventricular non compaction with preserved ejection fraction; C: compact layer; NC: non compact layer; FW: left ventricle free wall.

segments, $p = 0.29$].

The two patients groups did not differ with regard to the thickness of the noncompact and the compact layers in the basal LV segments [median 5.6 mm (IQ 4.7–7.2) in LVNCrEF patients versus 6.5 mm (IQ 6–7.3) in LVNCpEF patients; $p = 0.10$]. The overall value of thickness of the compact layer (both septal and free wall segments) in LVNCrEF patients was significantly lower than that of LVNCpEF patients at apical level [3.4 mm (IQ 2.8–4.3) vs 5.1 mm (IQ 3.8–5.7), $p = 0.01$] and was of borderline statistical significant at mid-ventricular level [4.9 mm (IQ 4.2–5.2) vs 5.6 mm (IQ 5–6.6); $p = 0.09$]. The wall thickness of non-compact layers at both apical and mid-ventricular level (both septal and free wall segments) did not show any statistically significant difference among the two patients subgroups (Figs. 1, 2).

A subanalysis of the association between wall thickness and systolic dysfunction at mid-ventricular segments, showed that the thickness of the compact layer in the four free-wall mid-ventricular segments was significantly lower in patients with LVNCrEF than in those with LVNCpEF [median 4.3 mm (IQ 3.9–4.9) vs 5.5 mm (IQ 5–6.5), $p < 0.01$]; by comparison, the thickness of the two septal mid-ventricular segments did not show any significant association with reduced LV ejection fraction [median 6.0 mm (IQ 5–6.5) in LVNCrEF vs 5.9 mm (IQ 5.1–6.9) in LVNCpEF;$p = 0.84$].

On linear regression analysis, there was a linear correlation between median thickness of mid-ventricular free wall segments and left ventricular ejection fraction ($r = 0.51$, $p = 0.005$) (Fig. 3).

On the ROC curve analysis, a thickness of the compact layer <5 mm

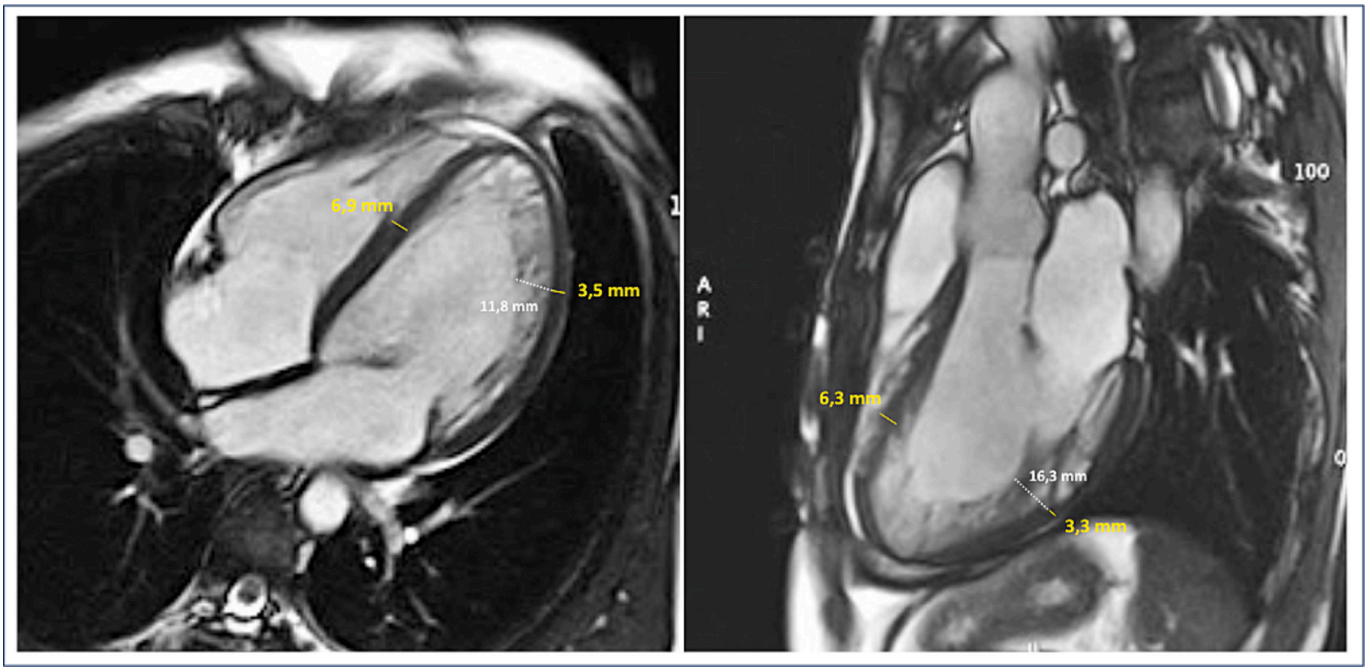


Fig. 1. A representative example of a patient with LVNCrEF. Diastolic frames of kinetic images in both four-chamber long axis and three-chamber long axis views showing a thinned compact layer with a thickness < 5 mm of the free-wall mid-ventricular segments. Note the free-wall to septum asymmetry of thickness.

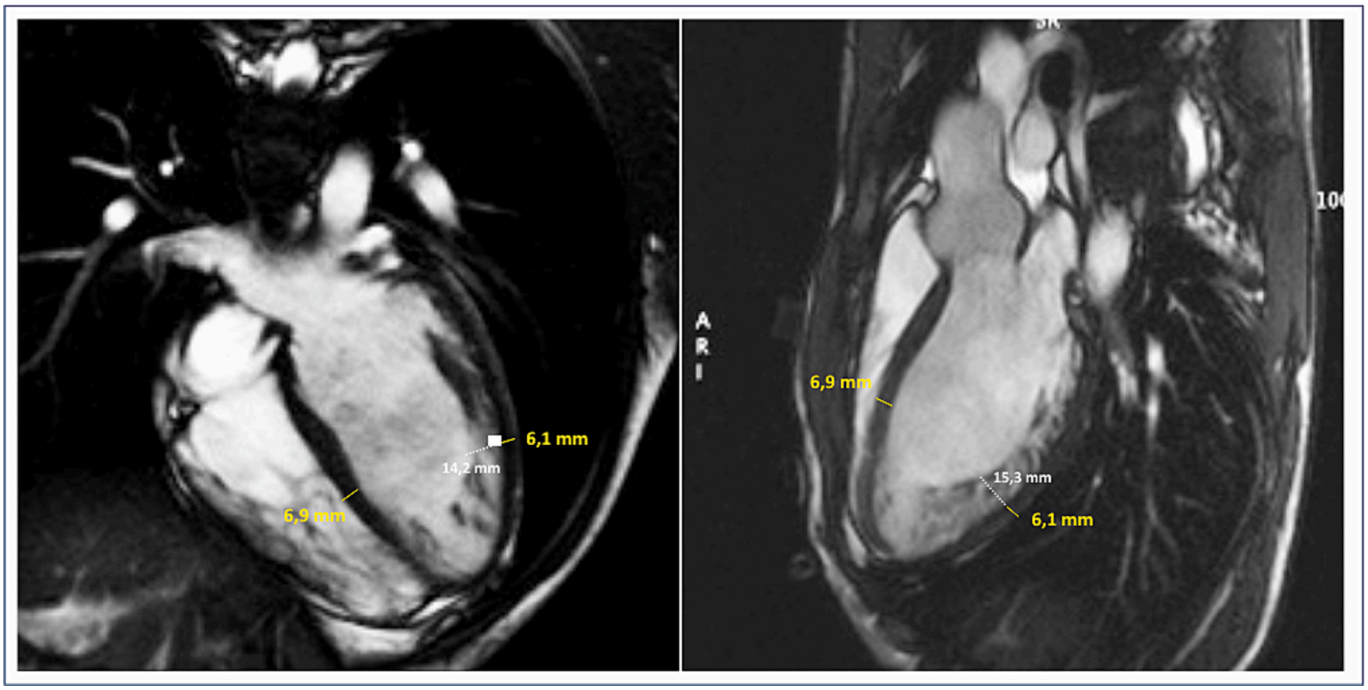


Fig. 2. A representative example of a patient with LVNCpEF. Diastolic frames of kinetic images in both four-chamber long axis and three-chamber long axis views showing a thickness of compact layer ≥5 mm.

in the free-wall mid-ventricular segments showed the best accuracy for differentiating between LVNCrEF patients versus LVNCpEF patients (AUC 0.83, $p = 0.02$) (Supplemental online Fig. 1). Patients with LVNCrEF had a greater number of free-wall segments with a thickness of compact layer <5 mm compared to those with LVNCpEF [3 (IQ 3–4) versus 1 (IQ 0–4) segment(s); $p = 0.01$]. On the ROC curves analysis, ≥2 segments with thickness of compact layer <5 mm in the free wall mid-ventricular segments showed 100% sensitivity (11/11 patients) and 60% specificity for reduced LVEF (AUC 0.81, $p < 0.01$) (Supplemental online Fig. 2). The presence of <2 segments with thickness of compact layer <5 mm in the free wall mid-ventricular segments had a 100% negative predictive value for LV systolic dysfunction.

3.2. Mass of papillary muscles

On quantitative analysis, the mass of papillary muscles was lower in patients with LVNCrEF than in those with LVNCpEF [1.2 (IQ 0.8–1.4) versus 1.6 (IQ 1.1.-1.8) g/mq], although the difference was of borderline

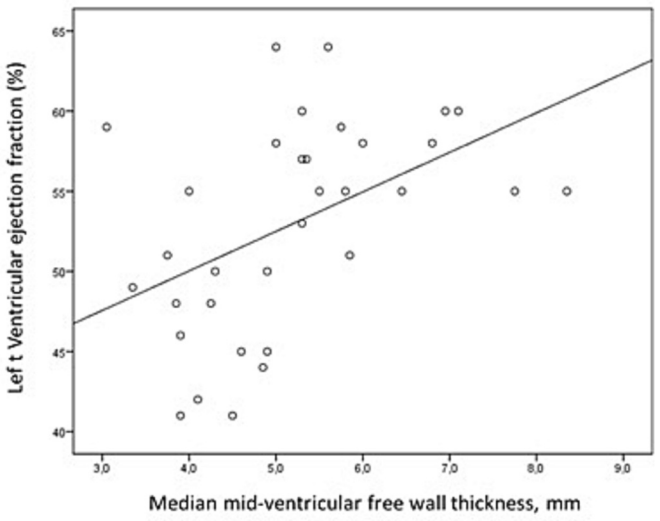


Fig. 3. Relationship between thickness of mid-ventricular free wall segments and left ventricular systolic function. Linear regression analysis plot showing the correlation between thickness of mid-ventricular free wall segments and LV ejection fraction (r = 0.51, p = 0.005).

statistical significance ($p = 0.08$).

3.3. Follow-up

All patients underwent a clinical evaluation and control echocardiographic examination during a mean follow-up period of 46 ± 8 months. No patients experienced overt heart failure, ventricular tachycardia or thromboembolic events during the follow-up period. Among the 11 patients with LVNCrEF associated with ≥2 segments with a compact myocardial layer <5 mm in the free wall mid-ventricular segments, in 9 patients the mild systolic LV dysfunction on baseline echocardiography remained unchanged on control echocardiographic examinations (mean 3.2); in the remaining 2 patients there was a further reduction of LV ejection fraction on control echocardiographic examinations (from 49% and 47% to 44% and 43%, respectively) during follow-up. All 22 patients with LVNCpEF associated with a thickness of compact myocardial layer ≥5 mm in the free wall mid-ventricular segments showed a LV systolic function within normal limits on both baseline and repeat echocardiographic tests (mean 2.8) during follow-up.

A control CMR was performed in the 2 patients with worsening of echocardiographic LV systolic function over follow-up and confirmed the further reduction of LV ejection fraction.

4. Discussion

Our study was designed to test the hypothesis that a critical underdevelopment of the compact layer represents a disease-specific determinant of the reduction of LV systolic function in isolated LVNC cardiomyopathy. The thickness of the compact layer of the LV Bull'eye segments was measured on CMR imaging studies and compared in a consecutive series of index patients with LVNCrEF versus age and gender matched controls with LVNCpEF. The results of our CMR study showed that an insufficient development of the compact layer, rather than the excessive trabeculation as evaluated by the NC/C ratio, was significantly associated with the impairment of LV systolic function which characterizes the LVNC cardiomyopathy.

The study findings are in keeping with those of previous studies showing that an excessive trabeculation in isolation (i.e., in subjects without phenotypic features of other heart muscle diseases or congenital malformations) has no clinical and prognostic significance. Previous large population studies reported that Petersen criteria for LVNC were fulfilled in approximately 20% of healthy individuals of the general population and that increasing values of NC/C thickness ratio were non associated with LV systolic dysfunction and poor clinical outcome over a long term follow up [5,7,12]. Previous CMR studies, demonstrated that a reduced LV ejection fraction (<50%) and the presence of LGE/myocardial fibrosis are predictors of poor clinical course in LVNC patients [6]. However, it remains unclear whether these prior studies enrolled patients with a "true" LVNC cardiomyopathy or patients with a variety of dilated cardiomyopathy (DCM) or other heart muscle diseases with an "excessive trabeculation" phenotype. To avoid confusion with overlapping diseases, by study design we enrolled only patients with "isolated" LVNC, excluding those patients who fulfilled the CMR Petersen criterion for excessive trabeculation (hypertrabeculation phenotype) in association with features diagnostic for other heart muscle disease including LV dilation or LGE/myocardial fibrosis. Our subset of patients with "isolated" LVNC had an expectedly low prevalence of clinically overt heart failure, ventricular tachycardia and thromboembolic events that instead represent relevant disease manifestations in patients with advanced cardiomyopathy [4].

In the context of "isolated" LVNC, the identification of cut-off values of the thickness of compact layer associated with a reduced LVEF, provided significant insights into the pathogenesis and CMR imaging diagnosis of true LVNC cardiomyopathy. Our study results indicated that the presence of >2 free wall mid-ventricular segments with a maximal thickness < 5 mm had a sensitivity of 100% for diagnosing patients with isolated LVNC and reduced LVEF. The absence of such reduced thickness values for critical under-development of the compact layer had a 100% negative predictive value for LVNC cardiomyopathy. Of importance, there was a free-wall to septal thickness asymmetry with thinning of mid-ventricular segments of the LV free wall (median 4.3 mm) and preserved thickness of mid-ventricular segments of the septum (median 5.5 mm). This free-wall to septal thickness asymmetry is a peculiar morphologic feature that may further characterize the isolated LVNC cardiomyopathy phenotype and help a differentiation from dilated cardiomyopathy with secondary excessive trabeculation, in which the wall thinning in the context of "eccentric hypertrophy" is expected to affect symmetrically septum and free wall.

It is noteworthy that patients without reduced thickness values of the compact layer maintained a preserved echocardiographic LV systolic function over time, whereas those with ≥2 free wall mid-ventricular segments with a maximal thickness < 5 mm showed during a long-term follow-up either persistent or worsened LV systolic function on serial echocardiographic examinations and, in some cases, on control CMR study.

Our CMR study results confirm and extend previous echocardiographic findings suggesting the potential pathophysiologic importance of the thinned LV compact layer. In a previous small case-control study, a thickness value of the compact layer <5 mm measured on echocardiography in diastole was more often observed in athletes with LVNC and reduced LVEF than in those with a LVNC and normal LVEF [13]. Among 36 athletes fulfilling echocardiographic criteria for LVNC, 3 with LV EF <50% were reported to have a thickness of compact layer <5 mm in systole and < 4 mm in diastole [14].

Failure of noncompaction layer thickness and noncompaction/compaction layer thickness ratio to predict LV systolic dysfunction, is in keeping with the current perspective that the excess of trabeculation does not represent a distinctive morpho-functional marker for LVNC cardiomyopathy, but a non-specific "phenotypic trait" observed even in association with other diseases and over-loading conditions. In this regard, current embryologic evidence does not support the old concept that the compact layer is the result of a compaction process of the trabeculated myocardium, but indicates that compact layer and trabeculated layers develop independently each other according to an "allometric growth" [12].

4.1. Study limitations

The study was limited by the relatively small sample of index patients because of the low prevalence of LVNC cardiomyopathy in isolation herein defined as LVNC with a reduced systolic function in the absence of LV dilatation or other phenotypic features of other known heart diseases.

To avoid possible overlap between isolated LVNC cardiomyopathy and dilated cardiomyopathy with a hypertrabeculation phenotype, we excluded patients with LV dilation systolic dysfunction and positive Petersen criterion for LVNC. Therefore, our study identified only the subset of patients with isolated LVNC cardiomyopathy with a reduced LV ejection fraction and no dilatation. Whether the free-wall to septal thickness asymmetry of segments at mid-ventricular level may help to differentiate advanced isolated LVNC cardiomyopathy with dilatation from dilated cardiomyopathy with a hypertrabeculation phenotype remains to be determined by future studies.

As per study design, we reported an association between the thickness of compact layer and the LV systolic dysfunction in isolated LVNC, but cause-effect relationships can not be provided.

Molecular genetic data were not addressed because this was not a genotype–phenotype correlation study, but a CMR imaging study aimed to delineate the phenotypic features of LVNC cardiomyopathy and the relationship between tinned compact layer and systolic dysfunction. Of note, a genetic aetiology is unlikely to impact the disease phenotype as shown by previous study reporting that LVNC patients with pathogenic variants of sarcomeric genes are phenotypically not distinct from those with a negative molecular genetic testing [15].

5. Conclusions

In conclusion, a thinned compact layer with a thickness < 5 mm of 2 or more segments of the LV mid wall in diastole was associated with a true LVNC cardiomyopathy, herein defined as LVNC in isolation with a reduced systolic function in the absence of LV dilatation. The excessive trabeculation in the absence of thinning of the compact layer appears as a “phenotypic trait” rather than a “cardiomyopathic morphologic marker” and is deprived of clinical and prognostic significance.

The results of the present study should be considered hypothesis-generating and are expected to stimulate future prospective investigations on larger patient populations with LVNC cardiomyopathy over a longer follow-up. Validation of our preliminary results by further studies focusing on the clinical and prognostic significance of the thinning of compact layer rather than the excessive trabeculation may impact future management of patients with LVNC.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2023.131614.

Fundings

None.

Author statement

The study was approved by the local institutional review board and because of its retrospective nature no consent was required. The datasets analysed during the current study are available from the corresponding author on reasonable request.

Declaration of Competing Interest

No disclosures.

References

[1] B.J. Maron, J.A. Towbin, G. Thiene, C. Antzelevitch, D. Corrado, D. Arnett, A. J. Moss, C.E. Seidman, J.B. Young, American Heart Association; Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; Council on Epidemiology and Prevention, 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. 113 (14) (2006 Apr 11) 1807–1816, https://doi.org/10.1161/CIRCULATIONAHA.106.174287.

[2] J. Finsterer, C. Stöllberger, J.A. Towbin, Left ventricular noncompaction cardiomyopathy: cardiac, neuromuscular, and genetic factors, Nat. Rev. Cardiol. 14 (4) (2017 Apr) 224–237, https://doi.org/10.1038/nrcardio.2016.207.

[3] S.E. Petersen, J.B. Selvanayagam, F. Wiesmann, M.D. Robson, J.M. Francis, R. H. Anderson, H. Watkins, S. Neubauer, Left ventricular non-compaction: insights from cardiovascular magnetic resonance imaging, J. Am. Coll. Cardiol. 46 (1) (2005 Jul 5) 101–105, https://doi.org/10.1016/j.jacc.2005.03.045.

[4] V. Vergani, D. Lazzeroni, G. Peretto, Bridging the gap between hypertrabeculation phenotype, noncompaction phenotype and left ventricular noncompaction cardiomyopathy, J. Cardiovasc. Med. (Hagerstown) 21 (3) (2020 Mar) 192–199, https://doi.org/10.2459/JCM.0000000000000924.

[5] F. Zemrak, M.A. Ahlman, G. Captur, S.A. Mohiddin, N. Kawel-Boehm, M.R. Prince, J.C. Moon, W.G. Hundley, J.A. Lima, D.A. Bluemke, S.E. Petersen, 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. 64 (19) (2014 Nov 11) 1971–1980, https://doi.org/10.1016/j.jacc.2014.08.035.

[6] C. Grigoratos, A. Barison, A. Ivanov, D. Andreini, M.S. Amzulescu, L. Mazurkiewicz, A. De Luca, J. Grzybowski, P.G. Masci, M. Marczak, J.F. Heitner, J. Schwitter, B.L. Gerber, M. Emdin, G.D. Aquaro, Meta-analysis of the prognostic role of late gadolinium enhancement and global systolic impairment in left ventricular noncompaction, JACC Cardiovasc. Imaging 12 (11 Pt 1) (2019 Nov) 2141–2151, https://doi.org/10.1016/j.jcmg.2018.12.029.

[7] D. Andreini, G. Pontone, J. Bogaert, A. Roghi, A. Barison, J. Schwitter, S. Mushtaq, G. Vovas, P. Sormani, G.D. Aquaro, P. Monney, C. Segurini, M. Guglielmo, E. Conte, L. Fusini, A. Dello Russo, M. Lombardi, P. Gripari, A. Baggiano, C. Fiorentini, F. Lombardi, A.L. Bartorelli, M. Pepi, P.G. Masci, Long-term prognostic value of cardiac magnetic resonance in left ventricle noncompaction: a prospective multicenter study, J. Am. Coll. Cardiol. 68 (20) (2016 Nov 15) 2166–2181, https://doi.org/10.1016/j.jacc.2016.08.053.

[8] J. Schulz-Menger, D.A. Bluemke, J. Bremerich, S.D. Flamm, M.A. Fogel, M. G. Friedrich, R.J. Kim, F. von Knobelsdorff-Brenkenhoff, C.M. Kramer, D.J. Pennell, S. Plein, E. Nagel, Standardized image interpretation and post-processing in cardiovascular magnetic resonance - 2020 update : Society for Cardiovascular Magnetic Resonance (SCMR): Board of Trustees Task Force on Standardized Post-Processing, J. Cardiovasc. Magn. Reson. 22 (1) (2020 Mar 12) 19, https://doi.org/10.1186/s12968-020-00610-6.

[9] C.M. Kramer, J. Barkhausen, C. Bucciarelli-Ducci, S.D. Flamm, R.J. Kim, E. Nagel, Standardized cardiovascular magnetic resonance imaging (CMR) protocols: 2020 update, J. Cardiovasc. Magn. Reson. 22 (1) (2020 Feb 24) 17, https://doi.org/10.1186/s12968-020-00607-1.

[10] M. De Lazzari, A. Zorzi, N. Bettella, A. Cipriani, K. Pilichou, M. Cason, T. Vessella, P. Sarto, M.R. Gualea, F. Chianura, L. Tardini, G. Ricci, I. Mazzanti, F. Ricci, R. Motta, M. Perazzolo Marra, D. Corrado, Papillary muscles abnormalities in athletes with otherwise unexplained T-wave inversion in the ECG lateral leads, J. Am. Heart Assoc. 10 (3) (2021 Feb 2), e019239, https://doi.org/10.1161/JAHA.120.019239.

[11] S.E. Petersen, N. Aung, M.M. Sanghvi, F. Zemrak, K. Fung, J.M. Paiva, J.M. Francis, M.Y. Khanji, E. Lukaschuk, A.M. Lee, V. Carapella, Y.J. Kim, P. Leeson, S. K. Piechnik, S. Neubauer, Reference ranges for cardiac structure and function using cardiovascular magnetic resonance (CMR) in Caucasians from the UK Biobank population cohort, J. Cardiovasc. Magn. Reson. 19 (1) (2017 Feb 3) 18, https://doi.org/10.1186/s12968-017-0327-9.

[12] S.E. Petersen, B. Jensen, N. Aung, M.G. Friedrich, C.J. McMahon, S.A. Mohiddin, R. H. Pignatelli, F. Ricci, R.H. Anderson, D.A. Bluemke, Excessive trabeculation of the left ventricle: JACC: cardiovascular imaging expert panel paper, JACC Cardiovasc. Imaging 16 (3) (2023 Mar) 408–425, https://doi.org/10.1016/j.jcmg.2022.12.026.

[13] B. Poscolieri, M. Bianco, T. Vessella, S. Gervasi, V. Palmieri, P. Zeppilli, Identification of benign form of ventricular non-compaction in competitive athletes by multiparametric evaluation, Int. J. Cardiol. 176 (3) (2014 Oct 20) 1134–1136, https://doi.org/10.1016/j.ijcard.2014.07.288.

[14] S. Caselli, C.H. Attenhofer Jost, R. Jenni, A. Pelliccia, Left ventricular noncompaction diagnosis and management relevant to pre-participation screening of athletes, Am. J. Cardiol. 116 (5) (2015 Sep 1) 801–808, https://doi.org/10.1016/j.amjcard.2015.05.055.

[15] S. Probst, E. Oechslin, P. Schuler, M. Greutmann, P. Boyé, W. Knirsch, F. Berger, L. Thierfelder, R. Jenni, S. Klaassen, Sarcomere gene mutations in isolated left ventricular noncompaction cardiomyopathy do not predict clinical phenotype, Circ. Cardiovasc. Genet. 4 (4) (2011 Aug 1) 367–374, https://doi.org/10.1161/CIRCGENETICS.110.959270.