

Diagnosis of left-ventricular non-compaction in patients with left-ventricular systolic dysfunction: time for a reappraisal of diagnostic criteria?

Sanjay K. Kohli¹, Antonios A. Pantazis¹, Jaymin S. Shah¹, Benjamin Adeyemi², Gordon Jackson³, William J. McKenna¹, Sanjay Sharma³, and Perry M. Elliott^{1*}

¹The Heart Hospital, University College, 16–18 Westmoreland Street, W1G 8PH London, UK; ²North Middlesex Hospital, London, UK; ³University Hospital Lewisham, London, UK

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Aims

Left-ventricular non-compaction (LVNC) is characterized by excessive and prominent left-ventricular (LV) trabeculations and may be associated with systolic dysfunction in advanced disease. We sought to determine the proportion of patients fulfilling LVNC criteria in an adult population referred to a heart failure clinic using current diagnostic criteria.

Methods and results

One hundred and ninety-nine patients [age 63.5 ± 15.9 years, 124 (62.3%) males] with LV systolic impairment were studied. All underwent clinical examination, electrocardiography, and 2-D echocardiography. The number of patients fulfilling diagnostic criteria for LVNC was retrospectively determined using three published definitions. Results were compared with 60 prospectively evaluated normal controls (age 35.7 ± 13.5 years; 31 males, 30 blacks). Forty-seven patients (23.6%) fulfilled one or more echocardiographic definitions for LVNC. Patients fulfilling LVNC criteria were younger ($P = 0.002$), had larger LV end-diastolic dimension ($P < 0.001$), and smaller left atrial size ($P = 0.01$). LVNC was more common in black individuals (35.5 vs. 16.2%, $P = 0.003$). Five controls (four blacks) fulfilled one or more LVNC criteria.

Conclusions

This study demonstrates an unexpectedly high percentage of patients with heart failure fulfilling current echocardiographic criteria for LVNC. This might be explained by a hitherto underestimated cause of heart failure, but the comparison with controls suggests that current diagnostic criteria are too sensitive, particularly in black individuals.

Keywords

Left ventricular non-compaction • Echocardiography • Diagnosis • Race

Introduction

Left-ventricular non-compaction (LVNC) is a myocardial disorder characterized by excessive and prominent trabeculations associated with deep recesses that communicate with the ventricular cavity but not the coronary circulation.^{1,2} Prominent trabeculations are a normal feature of the developing myocardium *in utero* and LVNC is thought to result from a failure of trabecular regression that occurs during normal embryonic development.³ Echocardiographically, left-ventricular (LV) trabeculations are defined as structures with similar echogenicity to the myocardium that move synchronously with ventricular contraction.^{2,4}

Clinical studies suggest that LVNC is often familial with predominantly autosomal dominant inheritance. It has been linked to mutations in several genes including ZASP,⁵ α dystrobrevin,⁶ and tafazzin.^{6,7} The disease can present throughout life with progressive LV systolic dysfunction and may be associated with an increased incidence of thrombo-embolism and ventricular arrhythmia^{1,8,9}.

Although the diagnosis of LVNC is usually made using echocardiography and increasingly magnetic resonance imaging there is no universally accepted definition of LVNC at present. Some criteria require a double-layered appearance of the myocardium on two-dimensional echocardiography¹⁰ and cardiac magnetic resonance (CMR) imaging¹¹ and others require only prominent or numerous LV trabeculations.^{4,12} Data from retrospective analyses of

* Corresponding author. Tel: +44 207 573 8888/ext. 4801, Fax: +44 207 573 8838. Email: pelliott@doctors.org.uk

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echocardiographic databases using different criteria suggest that LVNC is an extremely rare condition.^{1,13} However, the exponential rise in the number of reports describing LVNC suggests that its prevalence may have been underestimated (Pubmed, unpublished data). In addition, preliminary data in children suggest that racial origin may influence prevalence.¹⁴ In this study, we sought to determine the frequency of LVNC diagnosed using current echocardiographic criteria in a racially mixed population of patients with heart failure referred to a district hospital clinic.

Methods

Patient population

The study population comprised all patients referred by local primary care and hospital physicians to a dedicated heart failure clinic at the University Hospital Lewisham, London, UK between April 2004 and March 2005.

Controls

The control population consisted of 60 normal healthy volunteers (30 blacks) recruited from unrelated staff at The Heart Hospital, Lewisham Hospital and the North Middlesex Hospital. All were asymptomatic, normotensive, and had no family history of premature cardiovascular disease. None of these individuals were taking medications.

Study procedures

All patients and controls were evaluated by medical history, physical examination, 12-lead electrocardiography (ECG), 2-D and Doppler echocardiographic examination. Where clinically indicated, 24 h Holter monitoring was performed. Echocardiographic data were acquired using a System Five or Vivid 7 echocardiographic scanner (GE Medical Systems) following the recommendations of the American Society of Echocardiography for transthoracic studies. All images were stored digitally on magnetic optical disks or a computer hard drive. Retrospective (heart failure patients) and prospective (control group) analysis of echocardiographic studies were performed by two independent observers (SK and AP) blinded to individual clinical and demographic details. Studies were analysed on a dedicated workstation using commercially available software (GE Medical Systems, Echo-pacPC, version 4.0.1 and System Five workstation). LV end-diastolic cavity dimensions were measured from the 2-D images and indexed to body surface area.

On the 2-D echocardiographic images, trabeculations were defined as localized protrusions of the ventricular wall ≥ 3 mm in thickness¹⁵ associated with intertrabecular recesses filled with blood from the LV cavity (visualized by colour Doppler).¹ When two myocardial layers could be identified, the presence of numerous small cavities within the inner myocardial layer was confirmed using colour flow Doppler.

Three echocardiographic definitions were used for the identification of LVNC in the heart failure and control groups (Table 1). The size and number of trabeculations were evaluated on the apical views in diastole^{4,9} and the thickness of the non-compacted layer was measured on parasternal short-axis views in systole.¹⁰ Only cases identified as LVNC by both observers were considered as positive. The distribution of trabeculation in patients with LVNC was determined using the 16-segment model recommended by the American Heart Association.¹⁶ Patients fulfilling one or more criteria for LVNC were classified into three morphological groups using previous descriptions^{17–20} (Figure 1):

Table 1 Diagnostic criteria for left-ventricular non-compaction

1. Chin et al. ⁹ LVNC is defined by a ratio of $X/Y \leq 0.5$ X = distance from the epicardial surface to the trough of the trabecular recess Y = distance from the epicardial surface to peak of trabeculation These criteria focus on trabeculae at the LV apex on the parasternal short axis and apical views, and on left-ventricular free-wall thickness at end-diastole
2. Jenni et al. ¹⁰ (i) A two-layer structure, with a thin compacted layer and a thick non-compacted layer measured in end systole at the parasternal short-axis views LVNC is defined by a ratio of $N/C > 2$ where N = non-compacted layer of myocardium C = compacted layer of myocardium (ii) Absence of co-existing cardiac structural abnormalities (iii) Numerous, excessively prominent trabeculations and deep intratrabecular recesses (iv) Recesses supplied by intraventricular blood on colour Doppler
3. Stollberger et al. ⁴ (i) More than three trabeculations protruding from the left-ventricular wall, apically to the papillary muscles, visible in a single image plane (ii) Intertrabecular spaces perfused from the ventricular cavity, visualized on colour Doppler imaging

- (1) Spongy: Defined by an inner myocardial layer demonstrating numerous small cavities on 2-D echocardiography without the appearance of well defined discrete recesses.
- (2) Meshwork: Trabeculations and pseudotendons interwoven in a meshwork.
- (3) Prominent trabeculations only: Localized protrusions of the ventricular wall defining deep recesses filled with blood from the LV cavity in the absence of (1) and (2).

Statistical analysis

Statistical analysis was performed using SPSS (version 12.0) statistical software (SPSS Inc., Chicago, IL, USA). All continuous data are expressed as mean \pm SD. Continuous variables were compared using the Student t-test and non-continuous variables were compared using the χ^2 test. To account for multiple testing and the subsequent inflation in type I error, we used a Bonferroni correction and thus only P -values ≤ 0.0025 were considered to be statistically significant. All statistical tests were two-sided.

Results

The patient population comprised 202 consecutive patients. Three patients were excluded from the analysis due to poor echocardiographic windows. The characteristics of the final study cohort ($n = 199$) are summarized in Tables 2 and 3. One hundred and forty-three patients had an ejection fraction $< 40\%$ and 156 (78.4%) were in NYHA functional class II or more at their first assessment. No patient had symptoms or signs of neuromuscular disease.

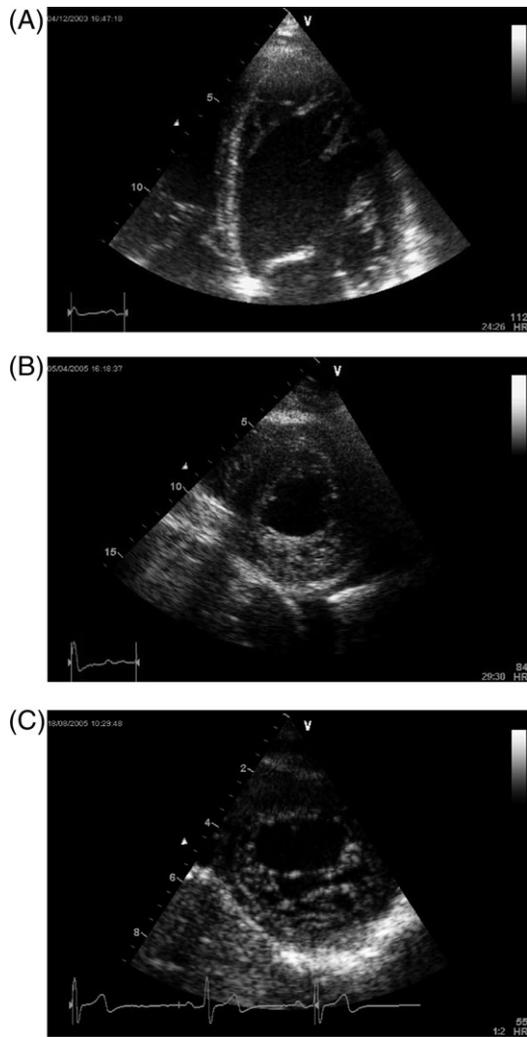


Figure 1 Examples of the different morphologies used to describe left-ventricular non-compaction. (A) Isolated trabeculations; (B) Spongy pattern of non-compaction; (C) Meshwork of tendons and trabeculations where despite the obvious manifestation of the disorder, it is difficult to define either a discrete layer or discrete trabeculations. As these images show, there is considerable subjectivity in defining such patterns and the interpretation is heavily influenced by the imaging plane

Proportion of patients fulfilling criteria for left-ventricular non-compaction

Trabeculations were identified in the left ventricle in 69 (34.7%) patients; 47 patients (23.6% of the total population; 95% CI = 18.3, 30.0) fulfilled one or more criteria for LVNC. There were seven cases that the independent reviewers disagreed on with respect to the diagnosis of LVNC. This translated to a kappa (measure of agreement)=0.9 ($P < 0.001$). These patients were included in the non-LVNC cohort.

Thirty-seven (78.7%) patients fulfilled the diagnostic criteria suggested by Chin *et al.*, 30 (63.8%) the criteria proposed by

Table 2 Clinical characteristics of the heart failure population

Smoker (%)	53 (26.6)
Hypertension	79 (39.7)
Systolic blood pressure (mmHg)	130.9 ± 21.2
Diastolic blood pressure (mmHg)	75.1 ± 14.0
History of diabetes (%)	47 (23.6)
History of ischaemic heart disease (%)	65 (32.7)
Family history of heart failure (%)	14 (7)
Family history of cardiomyopathy (%)	6 (3)
NYHA II (%)	119 (59.8)
NYHA III (%)	35 (17.6)
NYHA IV (%)	2 (1)
Syncope (%)	2 (1)
Chest pain (%)	38 (19.1)
Sinus rhythm (%)	159 (79.9)
Left bundle branch block (%)	49 (24.3)
Atrial fibrillation (%)	37 (18.6)
Paced rhythm (%)	2 (1)
Pacemaker/defibrillator (%)	13 (6.5)
NSVT (Holter monitor) (%)	15 (7.5)

All values shown as number (%) or mean ± one standard deviation. NYHA, New York Heart Association functional class; NSVT, non-sustained ventricular tachycardia.

Table 3 Demographic and echocardiographic characteristics of study population and controls

	Controls, n = 60	Patients, n = 199	Significance
Age (years)	35.7 ± 13.5	63.5 ± 15.9	<0.001
Male (%)	31 (51.7)	124 (62.3)	0.2
Black (%)	30 (50%)	76 (38.2)	0.1
White (%)	30 (50%)	116 (58.3)	0.1
Other ^a (%)	0 (0%)	7 (3.5)	0.1
Body mass index (kg/m ²)	21.2 ± 3.8	29.1 ± 6.5	0.03
Ejection fraction (%)	64.9 ± 0.7	33.7 ± 13.9	<0.001
Left-ventricular end-diastolic dimension indexed to body surface area (mm/m ²)	26.5 ± 2.7	30.3 ± 6.5	<0.001
A-wave duration (ms)	122.8 ± 27.5	138.1 ± 27.2	0.001
E-wave deceleration time (ms)	174.6 ± 49.5	174.4 ± 61.4	1.0
E/A ratio	1.2 ± 0.8	1.2 ± 0.7	0.5

All values shown as number (%) or mean ± one standard deviation. ^aSubjects from South Asia subcontinent.

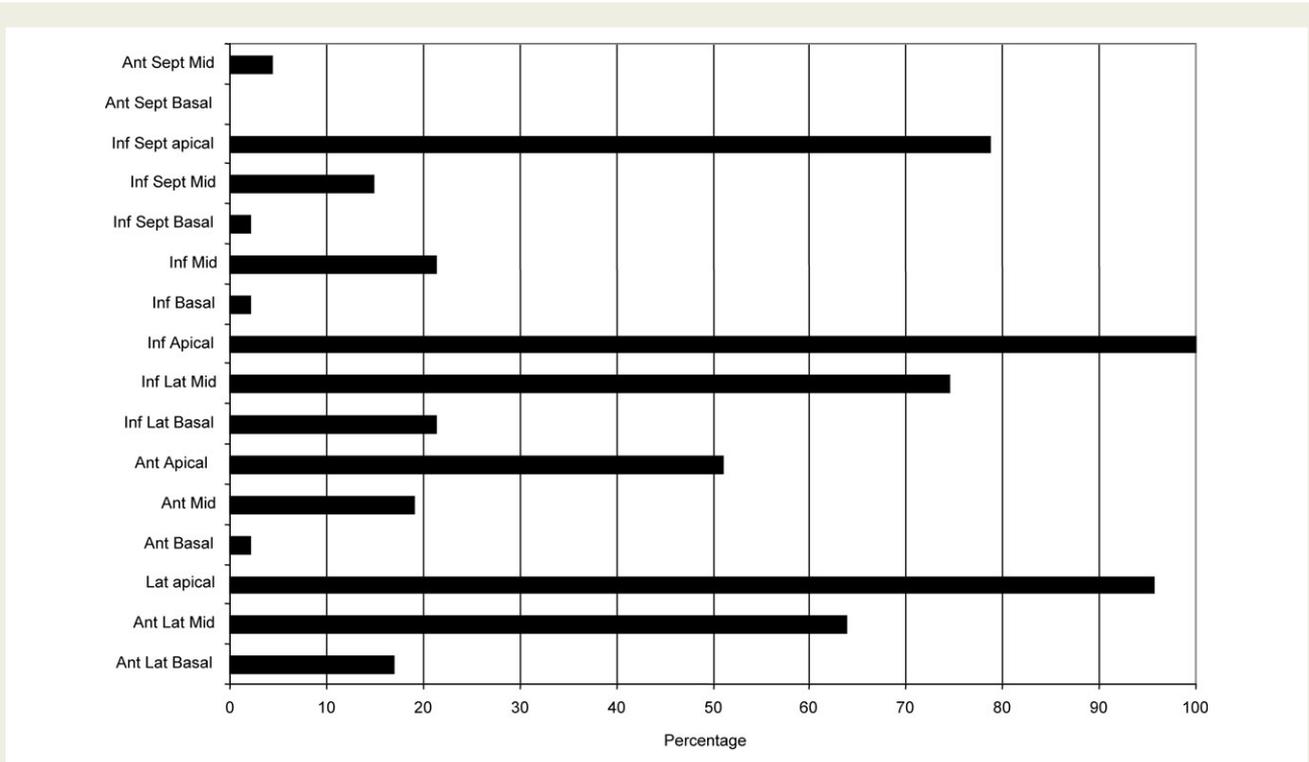


Figure 2 Location of trabeculations according to the 16-segment left-ventricular echocardiographic model

Jenni *et al.*, and 25 (53.2%) the criteria suggested by Stöllberger *et al.* Seventeen of the LVNC patients (36.2%) fulfilled only a single definition. There was an overlap of all three diagnostic approaches in 29.8% on stratified analysis. If only one definition had been used for the diagnosis, the prevalence of LVNC would have ranged from 12.1 to 18.6%, depending on the definition used.

Morphology and distribution of left-ventricular non-compaction

The distribution of trabeculation in patients fulfilling LVNC criteria is shown in Figure 2. The most frequently involved segments were apical followed by the inferior and lateral mid-segments. Nine (19.1%) patients had a spongy trabecular pattern, 23 (48.9%) a meshwork, and 15 (31.9%) had prominent trabeculations only. The relation between diagnostic criteria and the morphological categorization is shown in Figure 3.

Clinical characteristics

Table 4 demonstrates the clinical and echocardiographic features of patients fulfilling LVNC criteria compared with the remainder of the cohort. Patients with LVNC were younger ($P = 0.002$) and had a larger LV end-diastolic dimension ($P < 0.001$) and smaller left atria ($P = 0.01$). This difference in the LV end-diastolic dimension persisted after the measurement was corrected for body surface area (Table 4). The frequency of LVNC in black patients was higher than in whites (35.5 vs. 16.2% respectively, $P = 0.003$). There was no statistically significant difference in any other echocardiographic parameter between black and white

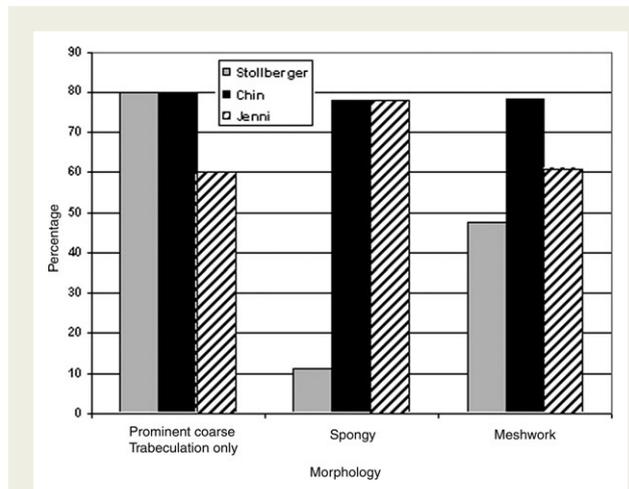


Figure 3 Relationship between morphologies and diagnostic definitions. The study cohort was divided into groups according to the appearance of the non-compacted myocardium. Within each group the percentage of patients diagnosed with each of the definitions was calculated. This showed that the likelihood of fulfilling specific criteria is influenced by morphology

patients with LVNC. Similarly there were no differences in clinical characteristics between the three criteria. The frequency of hypertrabeculation consistent with LVNC declined with advancing age in white but not black patients (Figure 4). There were no significant

Table 4 Univariate analysis for clinical and echocardiographic predictors of left-ventricular non-compaction

	Non-diagnostic for LVNC, n = 152	Diagnostic for LVNC, n = 47	Significance
Age (years)	65.4 ± 15.6	57.4 ± 15.4	0.002
Blacks (%)	49 (32.2)	27 (57.4)	0.003
Males (%)	94 (61.8)	30 (63.8)	0.9
Hypertension (%)	60 (39.5)	19 (40.4)	1.0
Systolic blood pressure (mm Hg)	130.1 ± 21.0	133.7 ± 22.0	0.3
Diastolic blood pressure (mm Hg)	74.2 ± 13.5	77.9 ± 15.1	0.1
Ischaemic heart disease (%)	57 (37.5)	8 (17.0)	0.01
History of atrial fibrillation (%)	44 (28.9)	5 (10.6)	0.01
Family history of cardiovascular disease (%)	55 (36.2)	12 (25.5)	0.2
Family history of heart failure (%)	9 (5.9)	5 (10.6)	0.3
NYHA class	2.0 ± 0.7	1.9 ± 0.7	0.2
Syncope (%)	0 (0.0)	2 (4.3)	0.055
Chest pain (%)	30 (19.7)	8 (17.0)	0.8
Left-ventricular hypertrophy (%)	21 (13.8)	1 (2.1)	0.03
Left-ventricular ejection fraction (%)	34.1 ± 13.0	32.3 ± 16.3	0.4
Left-ventricular end-diastolic dimension (mm) indexed	29.2 ± 6.0	33.9 ± 6.7	<0.001
Left atrium size (mm)	47 ± 8	43 ± 7	0.01

All values shown as number (%) or mean ± one standard deviation.
LVNC, left-ventricular non-compaction.

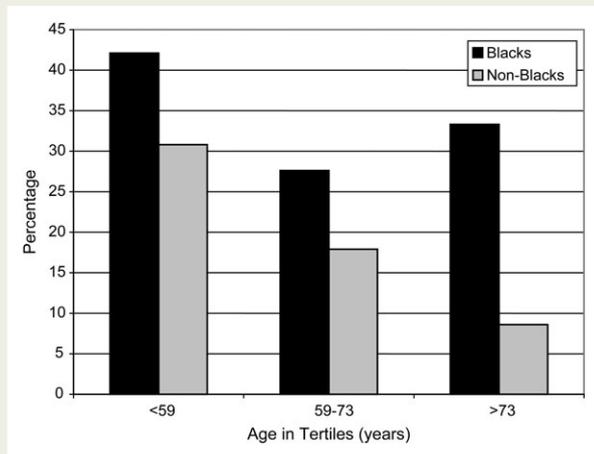


Figure 4 The frequency of left-ventricular non-compaction in relation to age in blacks and non-blacks, using the three existing criteria; $\chi^2=1.5$ ($P=0.5$) for blacks and $\chi^2=6.6$ ($P=0.04$) for non-blacks

differences in LV ejection fraction, LV end-diastolic dimension, and number of wall segments involved between patients fulfilling different criteria.

Table 3 shows the demographic and echocardiographic data for the controls compared with the study population. The controls were younger, but were matched for gender and ethnicity. All controls had normal LV dimensions and function; four (13.3%) black and one (3.3%) white control fulfilled one or more criteria for LVNC; (three Chin, three Jenni, and two Stöllberger).

Discussion

LVNC is defined by the presence of prominent trabeculations on the luminal surface of the ventricle in association with deep recesses that extend into the ventricular wall but which do not communicate with the coronary circulation.¹ Histologically, the findings in LVNC are non-specific, with areas of normal myocardium and fibrosis.^{10,21} In some cases, LVNC occurs in association with other congenital heart defects, including atrial and ventricular septal defects, congenital aortic stenosis, and aortic coarctation;^{14,22–25} when no other congenital heart lesion is present, LVNC is said to be isolated. Until recently, isolated LVNC was thought to be extremely rare with a prevalence in adults of <0.3%^{1,8,13} and an annual incidence in children of <0.1 per 100 000.^{14,26} However, the exponential rise in the number of reports of patients with LVNC suggests that an increased awareness and the use of modern ultrasound technology have resulted in an increased detection of the morphological features of LVNC in routine clinical practice. The findings in this study lend further support to this hypothesis and raise a further question; namely, is LVNC currently being overdiagnosed?

Diagnostic criteria for left-ventricular non-compaction

A number of echocardiographic definitions for the diagnosis of LVNC have been proposed. Two are based on an analysis of fewer than 45 patients with what appeared to be a common phenotype; the third is extrapolated from a post-mortem study examining the number of prominent trabeculations.^{4,9,10} Although all definitions attempt to describe the morphology of the condition, they differ substantially in their approach. The method proposed originally by Chin *et al.*⁹ evaluates the size of trabeculations in

relation to the thickness of the compacted wall in different echocardiographic views and at different levels of the left ventricle in end-diastole. Jenni and coworkers^{10,20} have proposed a method that relies on the detection of two myocardial layers, compact and non-compact, in short-axis views of the left ventricle in end-systole. LVNC, in this instance, is defined by the ratio between the two layers. The third definition, proposed by Stöllberger et al.,^{4,12} determines the number of prominent trabeculations visible in apical views of the left ventricle in diastole.

In this study, we used all three echocardiographic definitions to identify LVNC, assessing the number and size of trabeculations, as well as the relative thickness of the non-compacted layer when possible. There was a poor correlation between the three echocardiographic definitions, with only 29.8% of patients fulfilling all three criteria. This is, perhaps, not surprising as the criteria differ not only in the definition of abnormal trabeculation, but also in the echo planes and phase of the cardiac cycle in which they are applied. It has been suggested that the specificity of the echocardiographic criteria for LVNC can be improved by applying additional morphologic parameters^{20,27} such as the presence of an extensive meshwork of trabeculae. As can be seen in Figure 3, inclusion of these patterns failed to increase the level of agreement between the criteria. This probably is explained by the fact these additional parameters are also highly subjective and as dependent on imaging plane as the other criteria.

Increasingly, CMR imaging is also being used to detect LVNC. CMR has the advantage of good spatial resolution at the apex and lateral wall of the left ventricle and, in a recent study, has been used to quantify the ratio of non-compacted and compacted layers in patients with LVNC and in normal controls.¹¹ However, most CMR studies have used an adapted version of existing echo criteria with all the same limitations. Moreover, direct comparison with echo is not always possible as the detection of the non-compact layer using CMR is performed in diastole, whereas the echocardiographic definition applies to systole (in the case of the Jenni criteria).

Clinical implications

Fine trabeculations are a feature of the normal left ventricle, but it is only quite recently that technical advances such as harmonic imaging,¹⁵ contrast echocardiography,²⁸ and CMR imaging¹¹ have permitted their detection in normal individuals. The most important question posed by this study is whether the remarkably high proportion of patients fulfilling current diagnostic criteria for LVNC is explained by a genuine congenital abnormality or an exaggeration of normal trabeculation patterns. Evidence from developmental studies, individual case reports and small clinical series support the concept of LVNC as a real disease entity that may in some cases have an association with other cardiac and somatic abnormalities. In this study, patients fulfilling LVNC criteria had subtle phenotypic differences compared with other individuals with heart failure (younger age and larger LVEDD) but the fact that 8.3% of normal controls also fulfilled LVNC criteria suggests that prominent trabeculations in patients with heart failure could be no more than an incidental finding. Similar arguments apply to the high prevalence of LVNC in black individuals. Recent data from paediatric cohorts^{14,26} report a higher incidence of LVNC in black children with cardiomyopathy presenting to a referral

centre, but the fact that the majority of normal controls fulfilling the LVNC criteria in the present study were black suggests that the present diagnostic criteria are too sensitive and need to be re-evaluated in individuals of different racial backgrounds.

Early reports suggested that LVNC is associated with severe LV dysfunction and a high incidence of ventricular arrhythmias and thrombo-embolic complications.⁸ More recent studies describe a much lower incidence of death, stroke, or documented sustained ventricular arrhythmia.²⁹ This could reflect the inclusion of pre-clinical or mild cases, but this study suggests that some patients may not have LVNC at all. Only longitudinal studies can determine the additional thrombo-embolic and arrhythmic risk posed by the presence of prominent trabeculae in dilated ventricles.

Limitations

This study was conducted to investigate the frequency of the diagnosis of LVNC in a heart failure population using current diagnostic criteria. We accept that our findings are challenging and are likely to be controversial. The prevalence of LVNC is very high when compared with prevalence rates reported from historic echo registries. However, in a recent report, LVNC was diagnosed in 5% of patients with hypertension and 3% of patients with dilated cardiomyopathy.²⁰ While these numbers are lower than those reported in this study, they are substantially higher than in the previous echo registries and are, we believe, consistent with our hypothesis that current diagnostic criteria are too sensitive.

The major limitations of this study are its retrospective design and the fact that echocardiographic data in patients were collected without a specific focus on LVNC. This is important as the morphologic appearance of increased trabeculations can be produced if oblique views of the ventricle are used for quantification. However, all echo studies were performed in accordance with the American Society of Echocardiography guidelines and the control group were studied prospectively with the specific aim of detecting features consistent with LVNC. We believe, therefore, that this study is representative of real-life clinical practice and that the results highlight the limitations of current diagnostic criteria for LVNC.

The control group was not age matched to the LVNC cohort but if LVNC results from a developmental abnormality during embryogenesis, its frequency should be independent of age. Importantly, the controls and patients were matched with respect to gender and race, both of which might conceivably influence the prevalence of LVNC.

Conclusions

The findings in this study raise several important questions concerning the diagnosis of LVNC in patients with LV systolic dysfunction. While it is certain that the presence of prominent ventricular trabeculation can be caused by a disorder of ventricular morphogenesis, this study suggests that current echocardiographic diagnostic criteria are too sensitive and result in over-diagnosis of LVNC in patients with LV systolic dysfunction. This seems particularly true in black individuals. In order to avoid unnecessary investigations and treatment in patients and their relatives, large and detailed studies of normal individuals of different racial origin are required to determine the upper limits of normal trabecular patterns.

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