Isolated left ventricular non-compaction controversies in diagnostic criteria, adverse outcomes and management

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ABSTRACT

Isolated left ventricular non-compaction (LVNC) is a morphological abnormality of excessive trabeculation of the LV, often complicated by ventricular dysfunction, arrhythmias and cardioembolism. Advances in cardiovascular imaging and widespread availability of imaging technology have led to an increase in the diagnosis of LVNC imposing a need for evidence-based imaging diagnostic criteria. Although recent studies have addressed the utility of newer diagnostic methodologies and the incidence of adverse events in this condition, the diagnosis and management remain controversial. In this review, we provide an overview of the current controversies in the clinical diagnosis of LVNC, and suggest a management approach.

INTRODUCTION

Isolated left ventricular non-compaction (LVNC) is a myocardial disorder characterised by prominent ventricular trabeculations and deep recesses extending from the LV cavity to the subendocardial surface of the LV wall with or without LV dysfunction.[1 2] LVNC can be diagnosed in childhood or only recognised later in life. In childhood, the classic description of a distinctive 'non-compacted' spongy appearance of the myocardium was associated with congenital heart diseases in earlier literature, but has been identified as a distinct entity over the past few decades.[3 4] When the disease is first recognised later in life, it is often not clear whether this represents late recognition of long-standing non-compaction or delayed morphological manifestation of an underlying cardiomyopathy. Association between LVNC and neuromuscular disorders has also been demonstrated.[2]

Although the American Heart Association has classified LVNC as a primary genetic cardiomyopathy,[5] the European Society of Cardiology refers to LVNC as an 'unclassified cardiomyopathy'[6] based on the fact that LVNC may be a morphological manifestation of several distinct cardiomyopathies. At present, there is no consensus on whether LVNC is a distinct cardiomyopathy, an epiphenomenon or a phenotypic variant of other cardiomyopathies. However, the absence of specific genotype-phenotype association, the occurrence of LVNC morphology in various metabolic diseases and other cardiomyopathies, and the illustration that the LVNC phenotype is not necessary for development of cardiomyopathy, all suggest that it is unlikely a distinct cardiomyopathy.[7–9]

Advances in cardiovascular imaging and its widespread availability have led to increased diagnosis of LVNC. However, there exists poor agreement between the various diagnostic criteria[10] with a preponderance towards overdiagnosis.[11–13] The field is further challenged by rarity of the disease, the publication of only small studies, the lack of international/multicentre collaborations, and the absence of a non-pathological gold standard for diagnosis. Furthermore, since older case series were affected by limitations in imaging techniques and the use of evidence-based therapies, patients were generally diagnosed with advanced disease and had more adverse outcomes. In this paper, using a structured literature search, we provide a comparison of the different imaging-based diagnostic criteria along with discussion of newer approaches, provide an update to the adverse outcome data with comparison of older and newer studies, and suggest a management approach for patients with LVNC. Other recent publications have provided a comprehensive review of the epidemiology, pathogenesis, genetic considerations, clinical presentation and natural history of LVNC,[9 14–16] and are, hence, not discussed in this review.

LITERATURE REVIEW

A MEDLINE search (from 1970 to June 2012) was performed using 'non-compaction', 'diagnostic criteria', 'outcomes', 'management' and their variations as keywords on the OVID search engine. The search was limited to records in humans and in the English language. All citations were screened for inclusion by using a hierarchical approach of assessing the title, abstract and manuscript. For case series, those that provided data on more than one adverse event in *prospective follow-up* in at least 10 adult patients with LVNC were included. In studies with duplicated cohorts of patients, the latest publication was used. Studies that included patients with non-compaction associated with congenital heart disease, and did not provide separate data on patients with isolated non-compaction were excluded. References of all selected articles and relevant reviews were screened to identify additional studies.

CARDIOVASCULAR IMAGING CRITERIA

Echocardiographic diagnostic criteria

Traditionally, the diagnosis of LVNC is based on 2D echocardiography. Although three different diagnostic criteria exist (table 1, figure 1), there is no universally accepted definition of LVNC. All

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Table 1 Published echocardiographic and CMR diagnostic criteria

	Echo			CMR	
Criteria	**Chin[17]**	**Jenni[1]**	**Stollberger[2]**	**Petersen[35]**	**Jacquier[37]**
Patients, n	8	7	–	7	16
Criteria	1. Numerous, excessively prominent trabeculations with deep intertrabecular recesses2. Progressive decrease in the ratio of myocardial thickness from epicardial surface to trough (X) and epicardial surface to peak (Y) of the trabeculations at the mitral valve and papillary muscle level (PLAX view) and apex (subcostal or apical four-chamber view)*3. A progressive increase in the LV free-wall thickness(Y) from the mitral valve level to apex	1. No coexisting cardiac abnormalities2. Two-layered myocardial structure with a compacted (C) thin epicardial band and a thicker non-compacted (NC) endocardial layer of trabecular meshwork with deep endomyocardial spaces. Measurement of maximal NC/C layer ratio.3. Non-compaction predominantly in mid-lateral, mid-inferior, and apical segments.4. Colour Doppler evidence of deep perfused intertrabecular recesses	1. >3 trabeculations protruding from LV wall, apical to the papillary muscles, visible in one image plane†2. Perfused intertrabecular spaces by colour Doppler3. Two-layered myocardial structure with the non-compacted endocardial layer usually but not necessarily thicker than the compacted layer in end-systole[19]‡	1. Two-layered myocardium2. Compacted and non-compacted segments measured from long-axis SSFP cines at a site with the most prominent trabeculations3. Measurement should be perpendicular to compacted myocardium (apical segment 17 should not be used)	1. Short-axis SSFP cines used to obtain total LV mass (tips of trabeculae to epicardium – red and yellow lines below) 2. Same used to obtain compacted myocardial mass (epicardium to compacted endocardium, green and yellow lines below)3. Difference between first and second measurement provides trabecular mass4. Papillary muscles should be included in the *compacted myocardial* mass
Cardiac phase	End-diastole	Systole	Not stated	Diastole	End-diastole
Ratio/ other	None suggested*	NC/C>2.0	None suggested	NC/C>2.3	Trabecular mass >20%

Figure 1 accompanies this table.
*A mean±SEM X/Y ratio of 0.92±0.07 (base), 0.59±0.05 (papillary muscle), and 0.20±0.04 (apex) was seen in LVNC. The apical measurements had the lowest measurement reproducibility.
†Trabeculations=structures with the same echogenicity as the myocardium and moving synchronously with ventricular contractions.
‡This criteria was suggested in a subsequent publication, and no non-compacted:compacted segment ratio is suggested.
C Compacted, CMR Cardiac MR, LV Left ventricular, NC Non-compacted, SSFP Steady-state free precession.

criteria are based on morphological findings, and require the presence of prominent trabeculations with deep intertrabecular recesses communicating with the ventricular cavity, and a two-layered appearance to the myocardium (trabecular myocardium as one layer, and compacted myocardium as the second layer).[1 2 17–19]

Despite similarities in the diagnostic criteria, there are several important differences. Chin *et al*[17] calculated the depth of the intertrabecular recesses relative to the posterior wall thickness, by comparing the distance between epicardial surface and trough of the intertrabecular recesses (X) with distance between epicardial surface and peak of trabeculations (Y) (table 1, figure 1) in end-diastole. A progressive decrease in the X:Y ratio, and an increase in total LV posterior wall thickness (Y) from the base to the apex was seen in LVNC but not in controls[17] (table 1). The measurements were obtained from the parasternal long-axis view for the basal and mid-papillary levels, and from the subcostal or apical 4-chamber view for the apical segments. The original paper *did not* provide a cut-off for the X:Y ratio to diagnose LVNC. Interestingly, subsequent publications making reference to Chin *et al*'s work suggest an X:Y ratio of ≤0.5 from short-axis view to diagnose LVNC.[9] This may have been an extrapolation from the original publication which suggests that the X:Y ratio at the papillary muscle level in patients with LVNC was 0.59±0.05 (mean±SEM). Chin *et al* also did not describe the specific location of the non-compacted segments, the minimal number of trabeculations necessary, or the need to illustrate perfusion of the intertrabecular spaces. Their criteria were based on eight patients (mostly paediatric) and eight controls (table 1).

Chronologically, Jenni *et al* published their criteria for LVNC a decade later[1] consisting of four components (table 1, figure 1)

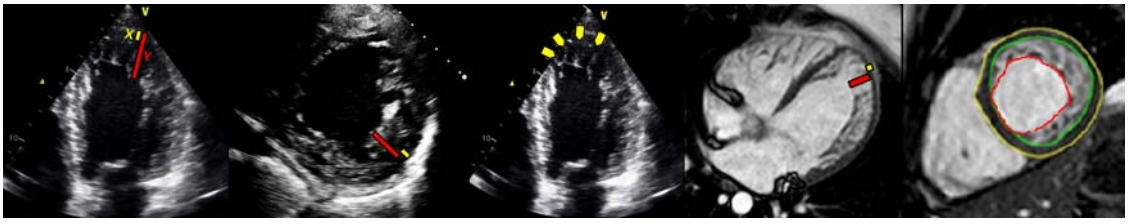

Figure 1 Graphic representation of the left ventricular non-compaction criteria ordered left to right in the same order as table 1 (accompanies table 1).

that evolved over several publications.[1 20 21] In the absence of other cardiovascular disease, a two-layered myocardium with intertrabecular spaces filled by blood from the ventricular cavity visualised by colour Doppler was required. The mid-lateral and inferior walls and the apex were shown to be most commonly involved. A non-compacted:compacted segment ratio measured at the site of maximal wall thickness of >2.0 at any level at end-systole using a short-axis view was suggested as a parameter that differentiated LVNC from patients with LV hypertrophy or dilated cardiomyopathy. This ratio was based on seven patients with LVNC, and no sensitivity or specificity data were provided. Also, the original publication included regional hypokinesia of the non-compacted or other segments in the diagnostic criteria.[1] However, when subsequently validated in a cohort of 139 patients with various cardiovascular disorders,[22] hypokinesia was found to have low specificity and appears to have been removed from the criteria.[9] Unfortunately, the *overall* sensitivity and specificity of Jenni's criteria was not reported in this validation study.[22]

The third criteria by Stollberger *et al* was extracted from a large postmortem study,[23] and required the presence of more than three trabeculations located apical to the insertion of the papillary muscles as visible in one apical image plane. This location criterion was an attempt to ensure clear distinction between trabeculations and papillary muscles. They were the first to clearly define trabeculations as structures with the same echogenicity as the myocardium, and moving synchronously with the ventricle.[2] The initial publication did not require the presence of a two-layered myocardium, and did not suggest a ratio, as it was felt that this measurement was inaccurate.[18] Their subsequent publications, however, have suggested the presence of a two-layered myocardium.[19] Also, they referred to this entity as 'LV hypertrabeculation' as opposed to non-compaction, although the word non-compaction has been added in their more recent publications.[19] One of the concerns about Stollberger's criteria is that it may be describing a different entity, as a significant proportion of their patients had neuromuscular disorders. This finding has not been confirmed by other groups[12 13 24–27] but may reflect the lack of a thorough neurological examination and objective testing of at-risk tissues in other studies.

More recently, Belanger *et al* have also assessed the utility of the LV trabecular area as measured by echocardiography using a four-chamber view to identify LVNC.[28] They used trabecular area cut-offs of $<2.5\ cm^2$, 2.5–4.9 cm^2 and $\geq 5.0\ cm^2$ to define mild, moderate and severe LVNC. These criteria, however, correlated poorly with a modified version of Jenni *et al*'s criteria, and further validation has not been performed.

Limitations of current echocardiographic criteria

None of the three criteria were generated prospectively in a large patient cohort, or have been rigorously validated in an unbiased manner. The validity of these criteria was questioned by the work of Kohli *et* al,[10] where an unexpectedly high percentage (23.6%) of patients with heart failure (HF) fulfilled one or more of the diagnostic criteria for LVNC in addition to 8.3% of healthy controls (majority of the controls who met the criteria were African–Americans). This raised concern that the current criteria were overly sensitive due to the use of morphologic descriptions that lack specificity, especially in the African–American individuals. Also, other studies have shown a poor correlation among the three criteria.[27] In addition, the reproducibility of the measurement of non-compacted:compacted segment ratio, or even of the enumeration of trabeculations, has been shown to be poor.[29] Therefore, consensus with respect to the diagnostic criteria and additional criteria that extend beyond morphological features is still needed for a definitive diagnosis of LVNC.

Additional echocardiography methods to aid diagnosis

First of all, refinements to current morphological criteria should be considered. One potential consideration is the derivation of a numerical proportional increase in the non-compacted: compacted segment ratio from the base to the apex, as opposed to using a single cut-off to diagnose LVNC. Advanced echocardiography methods, such as 3D echocardiography (3DE) and LV opacification with contrast administration,[30 31] may also improve diagnostic accuracy. 3DE allows a more comprehensive assessment of the LV for trabeculations postacquisition and measurement of trabecular volumes, which may further aid with the diagnosis.[30] Contrast administration can improve the visualisation of the trabeculations[26 31] and the compacted myocardium, and illustrate intertrabecular perfusion (figure 2A); however, this must be used with caution as it can actually reduce overall image quality in inexperienced hands.

Beyond morphology, it is important to include a functional component for the diagnosis of LVNC. Although Frischknecht *et al*[22] showed that the presence of hypokinesis of myocardial segments was not helpful in differentiating LVNC from other cardiomyopathies, it may be important to look at the distribution of hypokinetic segments (more in the apex than at the base) as opposed to its presence or absence—particularly in patients with reduced LV function. Also, regional dysfunction may be important for diagnosing LVNC in patients with preserved systolic function as shown in comparison with patients with mitral regurgitation in Frischknecht's study.[22] Additional tools, such as myocardial strain, may provide a better assessment of regional variability in myocardial function in LVNC than visual assessment. Recently, myocardial strain values have been shown to be abnormal in patients with LVNC even in the context of preserved systolic function[32] (see supplement movie 1, figure A) suggesting subclinical LV dysfunction. Also, a pattern of relative basal sparing (ie, higher proportional reduction in strain in the apex compared with the base) has been shown to differentiate LVNC from dilated cardiomyopathy[33] (figure 2B1,B2). In addition, more advanced mechanical parameters, such as basal and apical twist both occurring in the same direction, have also been shown to help differentiate LVNC from DCM[34] (figure 2B3).

Finally, although diastolic function abnormalities have been described in patients with LVNC,[20 25] this has not been used to differentiate patients with LVNC from those with prominent trabeculations or other forms of cardiomyopathy, and may merit further investigation.

While echocardiographic criteria can be refined, whether improved specificity of the echocardiographic diagnosis of LVNC may provide incremental insights into clinical phenotypes and natural history remains to be determined.

Cardiac magnetic resonance imaging criteria

Cardiac MR (CMR) with its superior contrast-to-noise (CNR) and signal-to-noise ratio (SNR) has had an emerging role in the diagnosis of LVNC, especially when echocardiographic image quality is limited. Currently, two CMR diagnostic criteria exist (table 1). The first criteria published by Petersen *et al*[35] included the presence of a distinct two-layered appearance of the myocardium, with a non-compacted:compacted myocardial ratio of >2.3 measured using steady-state free precession (SSFP)

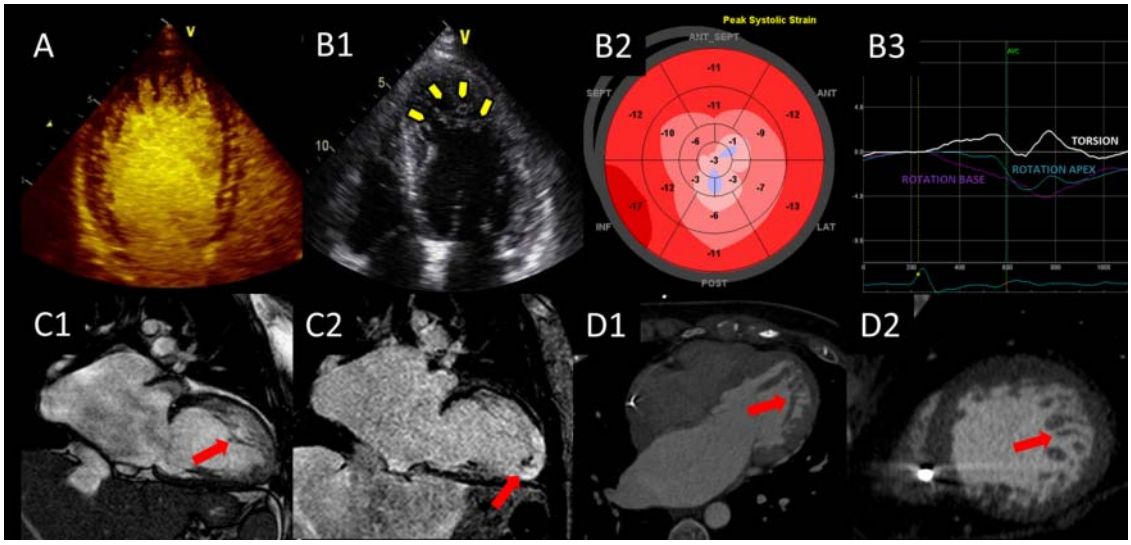

Figure 2 Methods to improve the diagnosis of left ventricular non-compaction (LVNC). (A) Use of echo contrast agent can aid visualisation of deep recesses in the trabeculated myocardium. Patient with LVNC suggested on 2D echocardiography (B1), demonstrated reduction in longitudinal strain at the site of greatest trabeculation (apex) on a 2D speckle-tracking polar map (B2) and absent LV torsion as a result of unidirectional rotation of the base and apex (B3) (normally, basal rotation is clockwise while apical rotation is counter-clockwise). The apical versus base strain difference has been previously validated with tissue Doppler-based strain analysis.[33] We have demonstrated the same with speckle tracking-based strain in panel B2. Example of LV trabeculation seen on steady-state free precession cardiac MRI (cardiac MR (CMR)) (C1, red arrow) with an apical thrombus (C2, red arrow) and myocardial fibrosis/scar (C2, bright area, red arrow) noted on late gadolinium enhancement imaging (C2). (D1, 2) Clearly delineated LV trabeculation on cardiac CT images (red arrows), demonstrating its superior signal-to-noise ratio and contrast-to-noise ratio in comparison with echocardiography and CMR.

acquisitions, in diastole (exact part of diastole not specified), perpendicular to the compacted myocardium in one of the three long-axis views at a location with the most prominent trabeculations. The maximal ratio should be used for the diagnosis. This ratio based on seven patients with LVNC had a sensitivity and specificity of 86% and 99%, respectively, to differentiate LVNC from a comparison group of healthy volunteers, patients with other cardiomyopathies, hypertension, aortic stenosis or athlete's heart. Contrary to Jenni *et al*'s criteria, the location of non-compaction was not shown to be useful in the diagnosis of LVNC in this study. Interestingly, when Petersen's criteria were recently applied in a multiethnic study of atherosclerosis, among 323 patients without cardiac disease or hypertension, a ratio >2.3 was seen in at least one region in 43% of the patients, and in at least two regions in 5% of the patients, suggesting that these morphological criteria have reduced specificity[11] when used in a population with low pretest probability of LVNC. Therefore, when the pretest probability of LVNC is high, as in Petersen *et al*'s original work, a cut-off of 2.3 is appropriate, however, if the pretest likelihood is low, a higher cut-off may be necessary.

Originally, Korcyk *et al*,[36] and more recently Jacquier *et al*,[37] proposed an alternate diagnostic criteria using CMR. Using SSFP short-axis acquisitions, the LV trabecular mass was calculated as the difference between the global LV mass (including the trabeculae) and the compacted LV mass (excluding the trabeculae) in end-diastole (table 1). In comparison with patients with DCM, hypertrophic cardiomyopathy and controls, an LV trabecular mass >20% of the total LV mass was predictive of LVNC, with a sensitivity and specificity of 93.7% (for both) in patients with known (n=12) or suspected (n=4) LVNC. Each group had 16 patients. Although the interobserver reproducibility of the trabecular mass measurement was reported to be high, the reproducibility of the trabecular mass percentage was not reported. Work by Fernandez–Golfin *et al* in controls and various other cardiomyopathies has, however, shown that the interobserver reproducibility of the percentage trabecular mass was poor.[38]

Additional MRI features to aid diagnosis

As with echocardiography, current CMR criteria are based solely on morphological features (figure 2C1) and, hence, there are opportunities for improvement as suggested with echocardiography above. Additional morphological consideration for diagnosis of LVNC that we have consistently noted in our lab, although not formally published, includes *thinned* compacted epicardial layers at the sites of non-compaction as previously described[39] (Jenni *et al*'s criteria), as well as an abrupt transition from normal to 'non-compacted' segments (figure 2, C1–2). However, beyond morphology, CMR provides opportunities for more comprehensive myocardial characterisation. Several studies have shown the presence of myocardial fibrosis in the trabecular and compacted myocardium in up to 55% of patients with LVNC using late gadolinium enhancement imaging (LGE) (figure 2C2).[40 41] Although suggestive of advanced disease (defined as worse New York Heart Association (NYHA) class, more likely to be receiving HF therapy, more dilated ventricles, and lower ejection fraction (EF)), LGE may be present in asymptomatic patients and those with preserved systolic function.[41] In addition, LGE imaging can be used to detect the presence of intertrabecular thrombus (figure 2C2). CMR can also provide a high spatial resolution assessment of myocardial perfusion at rest.[42] Since disturbance of microcirculation has been described in patients with LVNC,[42 43] presence of perfusion abnormality in the absence of epicardial coronary disease in areas of non-compaction and in 'normal' myocardium may be an additional feature in LVNC. Also, use of CMR to assess myocardial mechanics, such as strain and torsion, has not been evaluated, and may illustrate subclinical LV dysfunction in patients with preserved systolic function, or unique patterns of abnormality in

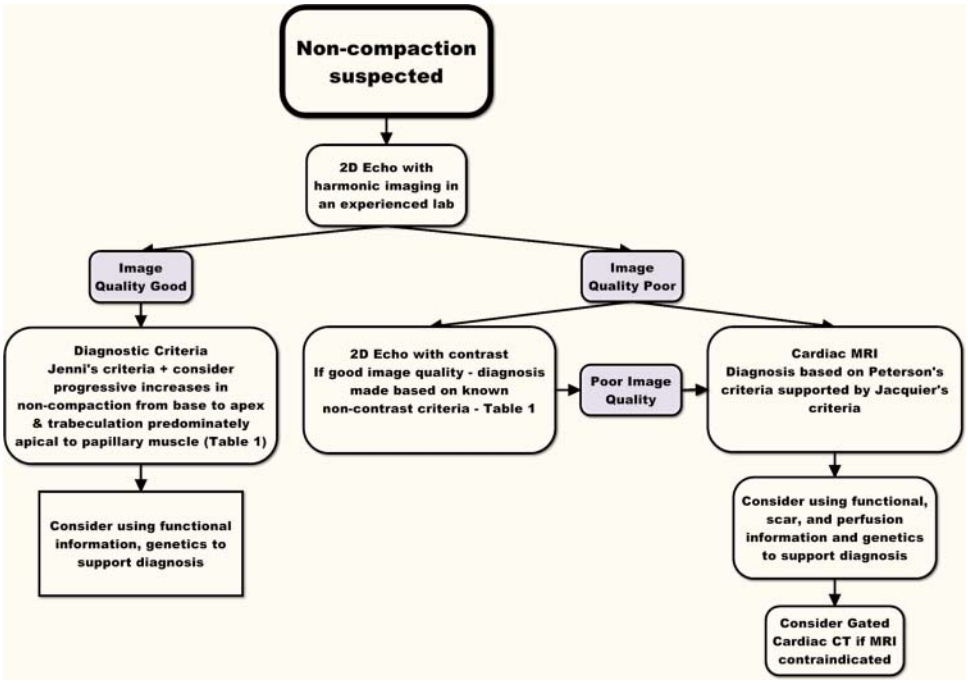

Figure 3 Suggested diagnostic algorithm for patients with suspected left ventricular non-compaction.

those with LV dysfunction. Therefore, more comprehensive diagnostic criteria consisting of a multiparametric approach may improve the diagnostic utility of CMR.

Finally, the role of CT in LVNC has not been established, despite the fact that it has the highest spatial resolution of all the imaging methods, and has the potential to optimally delineate trabeculations (figure 2D1, D2), although at the cost of radiation exposure.

DIAGNOSTIC APPROACH

Based on the current literature, we have suggested a multimodality diagnostic approach for the diagnosis of LVNC (figure 3). Despite its pitfalls, echocardiography should remain the first imaging modality as it is widely available, portable and likely more cost-effective. With respect to the echocardiographic criteria, we suggest the use of Jenni's criteria with additional consideration of progressive increase in non-compacted:compacted segment ratio from the base to the apex, with the trabeculations being predominantly apical to the papillary muscles. We also suggest the use of the functional parameters that we have discussed to aid with the diagnosis. CMR is, however, likely the best imaging modality for LVNC assessment due to superior SNR, CNR, unlimited imaging planes and the ability to use tissue characterisation in the diagnosis. We suggest the primary use of Petersen's criteria with additional confirmation with Jacquier's criteria. It is however, important to be mindful that Petersen's criteria may result in overdiagnosis in low pretest probability population, and that the trabecular mass percentage measurement can have low reproducibility.[38]

CLINICAL PHENOTYPES IN PATIENTS WITH LVNC

Most patients identified as having LVNC are asymptomatic; however, when symptoms occur, the most common presentations include HF, arrhythmias and embolic events. The existing published data on these clinical outcomes (summarised in table 2) are subject to huge selection bias, as the majority of enrolled patients had advanced disease at enrolment, as illustrated by a high proportion of patients with symptoms and LV dysfunction. Furthermore, the lack of data on patient comorbidities in most studies is a substantial impediment to understanding the natural history of LVNC. Also, patients with LVNC likely have a long preclinical phase of disease before LV dysfunction or symptoms develop, and if detected early, overall prognosis may not be as dismal as portrayed. In fact, the true prevalence and incidence of LVNC is largely unknown, leading to difficulties in characterising true risks of incident-adverse cardiac events.

Heart failure

Comparing all published adult case series, the incidence of HF decompensation requiring hospital admission during follow-up ranges from 53%[20] to 30%[13] over 2.3–3.8 years, although all later studies illustrate a prevalence close to the lower end of this range. These differences may be explained by several important factors. Chronologically, the incidence of HF admission was the highest in the earliest study by Oechslin *et al*[20] (table 2), where use of evidence-based HF therapy was not described. In all subsequent studies, the use of HF therapy in patients was greater than 50%. Also, the mean EF at diagnosis of LVNC was lower in Oechslin *et al*'s study compared with three of the later studies.[12 13 25] In addition, the majority of patients were symptomatic at enrolment in Oechslin *et al*'s *study*, while in the remaining studies, between 12% and 31% were asymptomatic with minimal or no events occurring in the asymptomatic group. Another important difference is the higher prevalence of advanced diastolic dysfunction (pseudonormal and restrictive patterns) in Oechslin *et al*'s study, compared with the study by Aras *et al* (65% vs 38%).

Although there are some discrepancies in the HF admission rates, the data based on mostly symptomatic patients with LV dysfunction (Stage C HF) suggests that the admission rate is similar to that reported for other forms of cardiomyopathy,[44] and that it can be reduced with evidence-based HF therapy. The data also suggest that in asymptomatic patients, the incidence of HF admission is minimal.

Table 2 Baseline clinical characteristics and outcomes of LVNC during follow-up in adult patients in large case series or registries*

	Oechslin [20]	Murphy[27]	Aras [25]	Stollberger[53]	Lofiego[26]	Stanton[12]	Habib[13]
Year of publication	2000	2005	2006	2007	2007	2009	2011
Patients, n	34	45	67	86	65	30	105
Men, %	74	62	66	76	37	60	66
Age at diagnosis mean±SD, years	42±17	37±17	41±18	52±15	45±16	39±19.5	45±17
Diagnostic criteria used	Jenni	Chin + Jenni	Jenni	Jenni+Stollberger	Jenni	Jenni	Jenni
Follow-up, mean (range), mos	44 (0.7–139)	46 (6–179)	30 (9–50)	51 (3–106)	46 (6–193)	30†	28†
EF at inclusion, mean±SD %	33±13	–	43.5±14.4	–	31±11	41‡	46±18
EF<50% at inclusion, %	86§	67	66	–	>90¶	77	84§
Diastolic dysfunction at inclusion, %	100§	–	71§	–	>32**	–	>50**
NYHA 3–4 at inclusion, %	35	36	30	44	32	17	48
Asymptomatic at inclusion, %	Minimal	31	12	30	26	–	17
Adverse events in asymptomatic, %	–	0	0	–	6	–	–
Familial occurrence, %	18	19	33	–	31	–	8
AF during f/u, %	–	–	–	–	9	7	7
VT during f/u, sustained/non-sustained, %	8.8/32	0/20	2.2/33	–	6/–	0/27	6/–
CHF admission during f/u, %	53	–	34	–	34	–	30
Thromboembolism during f/u, %	21	4	9	–	5	0	5
ICD implantation during f/u, %	12	7	1.5	–	12	–	28
Transplant, %	12	–	0	1	14	–	9
Death, %	35	2	15	22	11	10	11
Sudden death, %	18	2	9	4	5	–	1

*Data from Chin *et al*'s[17] and Ritter *et al*'s[21] publication are not included as they did not meet inclusion criteria (paediatric patients, lack of prospective follow-up, or data included in subsequent publication).
†Range not provided.
‡SD not reported.
§Data only in a subgroup of patients.
¶Defined as EF<45%.
**Data only presented for advanced diastolic dysfunction.
AF Atrial fibrillation, CHF Congestive heart failure, EF Ejection fraction, F/U Follow-up, LVNC Left ventricular non-compaction; mos Months, NYHA New York Heart Association, VT Ventricular tachycardia.

Arrhythmias

The two most common, clinically significant arrhythmias in patients with LVNC are ventricular tachycardia (VT) and atrial fibrillation (AF). The incidence of sustained VT has been similar among all published studies ranging from 0% to 9%, while the incidence of non-sustained VT (NSVT) had ranged from 20% to 33% over 2.3–3.8 years (table 2). The highest incidence of sustained VT (9%) again was in the study by Oechslin *et al*[20] likely due to the same reasons provided above for HF admission. The study that had the lowest incidence of sustained and NSVT, had the greatest proportion of patients who were asymptomatic and preserved EF.[27] Given that the high prevalence of reduced EF in all studies (table 2) the incidence of NSVT (20%–33% over 2.3–3.8 years) is not surprising, and is much lower than reported in patients with other forms of dilated cardiomyopathy (~60%).[45] Furthermore, NSVT has not been shown to provide additional prognostication of sudden cardiac death above that provided by routine clinical parameters.[45] Scar assessment by CMR is prognostically useful in predicting likelihood of serious arrhythmia in other cardiomyopathies,[46] but its role in this regard remains to be defined in LVNC.

With respect to AF, the incidence during follow-up was 7%–9% in the three studies that reported this outcome. However, the incidence of AF at the time of enrolment in all the studies described (table 2) was higher ranging from 6% to 26%.[13 20] Although the occurrence of AF during the follow-up period was higher than that reported in the general population, it is still lower than that seen in symptomatic patients with other forms of cardiomyopathies.[47]

Systemic thromboembolism

Thromboembolism may include the cerebrovascular, peripheral vascular and mesenteric systems. Although Oechslin *et al* reported an embolic incidence of 21%, later studies only show an incidence of 0%–9% with most reporting a 5% incidence over a follow-up period of 2.3–3.8 years. The lower incidence in the later studies is a reflection of the higher use of anticoagulation (aspirin and warfarin), as well as the larger population reflecting a more accurate estimate.[12 25–27] Interestingly, when patients with LVNC were matched with controls with a similar degree of LV systolic dysfunction, there was no difference in the rates of systemic thromboembolism.[48] In addition, registry data suggests that in patients with LVNC without AF, the incidence of ischaemic stroke over a mean follow-up period of 7.3 years was only 1.7%.[49] Therefore, it appears that the main risk factor for thromboembolic events in patients with LVNC is the severity of the underlying systolic dysfunction, the presence of AF and previous thromboembolic events rather than non-compaction itself.[50 51] Also, the overall annualised event rate of thromboembolism in patients with LVNC is not different from that described in patients with HF from other cardiomyopathies.[52] Finally, in the studies that presented data on asymptomatic patients with preserved systolic function, no thromboembolic events were reported during follow-up.[25 26]

MORTALITY

In patients with LVNC Oechslin *et al*[20] reported mortality of 35% over a mean follow-up period of 3.7 years. However, recent studies with similar mean follow-up periods report

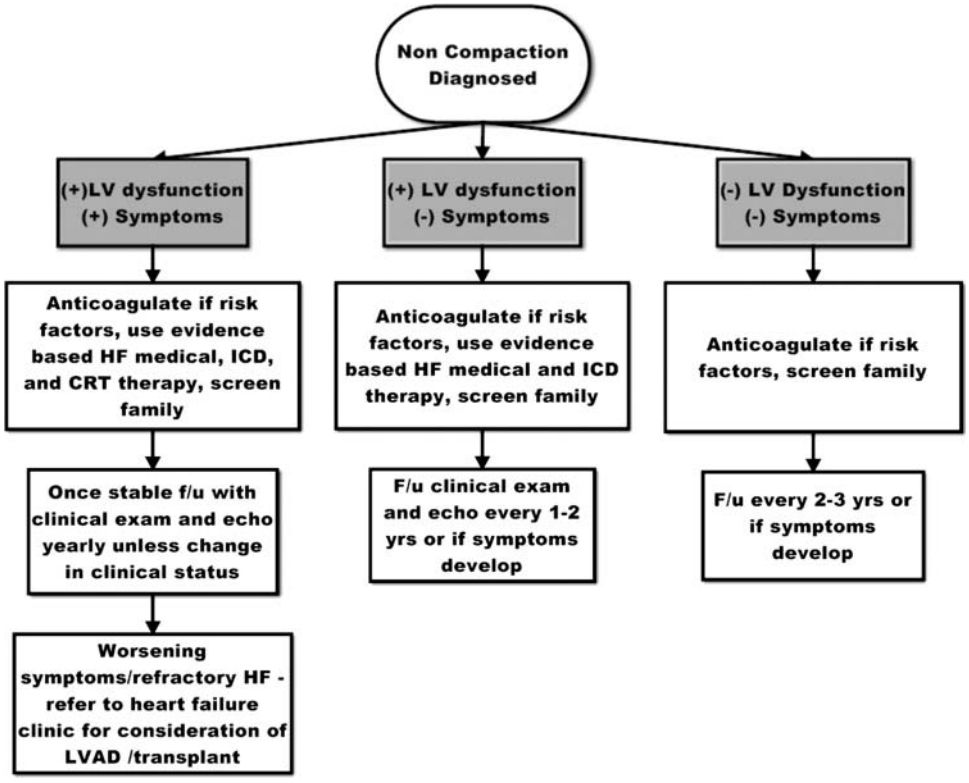

Figure 4 Suggested management algorithm for patients with left ventricular non-compaction.

mortality in the range of 2%–15%, suggesting that although the prognosis may be bad it is not as poor as originally described.[25 27] The study by Stollberger *et al*[53] showed a slightly higher mortality among the contemporary studies, however, this was driven by a significantly higher proportion of patients with neuromuscular disorder. The rationale for the marked difference between Oechslin *et al* and subsequent studies is multifactorial involving, possibly, milder phenotype of the disease detected due to improvement in imaging techniques, higher incidence of asymptomatic patients enrolled, higher prevalence of implanted cardiac defibrillator use, and better use of evidence-based HF medical therapy. In addition, Oechslin *et al*, as well as several of the recent studies, do not provide data on the prevalence of coronary artery disease in their patients.[12 13 27] The one study that performed cardiac catheterisation in patients with LVNC showed 29% of the patients had significant CAD,[25] which may be an important confounder in estimates of mortality. Also, in the studies that present data on asymptomatic patients, none died during follow-up. Therefore, with earlier identification of LVNC, guideline-based HF and device therapy, and accounting for comorbidities, such as CAD, the mortality rates may not be as poor as originally reported. Also, the current annualised mortality rates reported in patients with LVNC are comparable with those seen with other cardiomyopathies.[44 45]

MANAGEMENT

Since no guidelines for the management of patients with LVNC exist, we have suggested a strategy based on case series, registry data, previous reviews and local experience (figure 4). Patients who are asymptomatic and have normal LV systolic function may be followed every 2–3 years with clinical assessment and echocardiography, as their prognosis is usually good.[25–27] Clinical visits should comprise history, physical examination, echocardiography as well as Holter monitoring, to identify silent arrhythmias. Patients who are asymptomatic, but have echocardiographic LV systolic and/or diastolic dysfunction should be treated with evidence-based HF therapy,[54] and followed every 1–2 years, and undergo the original investigations at subsequent visits. Symptomatic patients should be managed based on their clinical presentation based on the respective consensus guidelines.[54] Neurological referral at the time of diagnosis of LVNC is also appropriate.[14 53] In the correct clinical context, when regional wall-motion abnormalities or LV dysfunction is present, an elective coronary angiogram could be considered to rule out obstructive coronary disease. There is, however, no evidence that LVNC is associated with increased risk of coronary artery disease.

There is controversy regarding the routine use of anticoagulation in patients with LVNC. Some in the past have argued that all patients should be anticoagulated with warfarin,[20] while others recommend anticoagulating only those with any of the following: LV dysfunction (fractional shortening <25% or EF <40%), AF, previous history of embolic events,[9 25 27 50] or those with known ventricular thrombi.[48] There is, however, no robust data to support either approach. We support the use of the second approach, which has been shown to reduce the incidence of thromboembolic events in one study.[26]

The issue of ICD implantation in all LVNC patients has been proposed due to the high risk of sudden cardiac death, but is also highly controversial.[20] Implantation of an ICD is indicated for secondary prophylaxis in patients with sustained ventricular arrhythmia with haemodynamic compromise, and those with aborted sudden cardiac death.[55] However, for the purpose of primary prevention, current guidelines for non-ischaemic CM should be considered (EF≤35%, NYHA 2–3, optimal medial therapy, life expectancy with good functional status for >1 year).[54] It is also important to realise that although the incidence of SCD (table 2) in LVNC is high (1%–9% in recent

studies), it is still significantly lower than that seen in ICD trials of patients with ischaemic and non-ischaemic CM.[25]

FAMILIAL SCREENING AND FOLLOW-UP

Comprehensive clinical screening is recommended in asymptomatic first-degree relatives of patients diagnosed with LVNC.[56] The screening should consist of genetic history extending to at least three generations, symptom history, physical examination and the diagnostic tests recommended above for follow-up of patients with LVNC. Some of the genetic mutations associated with LVNC include the G4.5 gene, DTNA (α-dystrobrevin), Cypher/ZASP, lamin A/C cardiac troponin T (TNNT2), myosin heavy-chain gene (MYH7), cardiac actin (ACTC1), SCN5A and MYBPC3.[9 14 15 57] The role of routine genetic screening of family is undefined.[56 58] Family screening with clinical evaluation beginning in childhood should be repeated every 3–5 years, unless a known genetic mutation is present (in the index case), where it should be repeated every 1–3 years.[56]

CONCLUSIONS AND FUTURE DIRECTIONS

There are many unanswered clinical questions in LVNC, and despite the increase in case reports in this area, the overall knowledge base of this condition remains limited. Current diagnostic criteria alone may be inadequate to make or refute the diagnosis, and emphasises the need to look beyond just morphological criteria. We propose the need for incorporation of functional criteria in the diagnosis of LVNC. Furthermore, a multimodality imaging approach capitalising on the strength of each modality may improve diagnostic accuracy. Also, patients with LVNC are at risk for many adverse clinical outcomes, and need to be followed closely by clinicians with adequate familiarity with the disease and its consequences. However, based on limited published data, the adverse event rates are not significantly different from patients with other forms of cardiomyopathy of the same functional status. Asymptomatic patients with incidental diagnosis of LVNC have overall good prognosis. Therefore, management of adverse outcomes, such as HF, arrhythmia and cardioembolism should be based on current respective practice guidelines, and screening of first-degree relatives is warranted. Due to the rarity of LVNC, national or international registries of patients and multicentre collaborations are needed to assess the utility of functional diagnostic criteria, better define the disease, provide a more accurate estimation of clinical adverse outcomes, and determine appropriate therapy. Specific therapies other than generic treatment for HF remain to be defined in this interesting and unusual clinical entity.

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Isolated left ventricular non-compaction controversies in diagnostic criteria, adverse outcomes and management

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Notes