

Left Ventricular Non-Compaction: Current Controversy and New Insights

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Abstract

Left ventricular non-compaction is an increasingly recognized familial cardiomyopathy characterized morphologically by deep myocardial trabeculations and a highly variable, but potentially aggressive clinical course leading to cardiac death or cardiac transplantation. Great controversy exists regarding the pathophysiology, diagnostic approach, clinical characteristics, and management of the condition. To date, there are no universally accepted precise diagnostic criteria or management guidelines. Recent clinical studies and basic science research have significantly added to our understanding of LVNC in all of these aspects. This article reviews the literature to date on LVNC and addresses current controversies surrounding the pathophysiology, diagnosis, clinical features, and management.

Keywords: Left ventricular non-compaction; Left ventricular hypertrabeculation; Cardiomyopathy; Genetics of cardiomyopathy; Familial cardiomyopathy; Sudden cardiac death; Heart failure

Abbreviations and Acronyms: LVNC - Left Ventricular Non-Compaction; ILVNC - Isolated Left Ventricular Non-Compaction; ECG - Electrocardiogram; PET - Positron Emission Tomography; VSD - Ventricular Septal Defect; TTE - Transthoracic Echocardiography; EF - Ejection Fraction; MRI - Magnetic Resonance Imaging; VAD - Ventricular Assist Device; VT - Ventricular Tachycardia

Introduction

First described in 1969, Left Ventricular Non-Compaction (LVNC) is an increasingly recognized familial cardiomyopathy characterized morphologically by deep myocardial trabeculations and a highly variable, but potentially aggressive clinical course leading to cardiac death or cardiac transplantation [1-12]. Grant et al. is often cited as first describing LVNC in 1926 [13-15]. However, this group in fact described the autopsy findings of a 14 month old subject with pulmonary atresia, a patent ductus arteriosus, and a single ventricle demonstrating numerous trabeculations and blood filled spaces which communicated with both the left ventricular cavity and the coronary vessels [1,16]. This finding of trabeculations with recesses that communicate with the coronary vessels is more accurately termed persistent sinusoids, a separate phenomenon associated with pulmonary atresia with intact ventricular septum [1,17]. In fact, the first case of LVNC was described by Feldt et al. in a 3 month subject with cyanotic congenital heart disease and dextrocardia in whom they noted the presence of bizarre trabecular patterns and a two layered myocardium comprised of a thick spongy inner layer and a compact outer layer [2]. Great controversy exists regarding the pathophysiology, diagnostic approach, clinical characteristics, and management of the condition. To date, there are no universally accepted precise diagnostic criteria or management guidelines. Recent clinical studies and basic science research have significantly added to our understanding of LVNC in all of these aspects. This article will review the literature to date on LVNC and address current controversies surrounding the pathophysiology, diagnosis, clinical features, and management of this fascinating disease. A literature review was performed using PubMed to identify articles and case reports in the English literature between 1926 and May 2014 on the clinical description, molecular mechanism, genetics, and treatment of Left ventricular non-compaction. Combinations of medical subject heading terms including 'Left ventricular non-compaction', 'Left ventricular hypertrabeculation', 'Non-compaction of ventricular myocardium', 'Isolated left ventricular non-compaction',

and 'Familial cardiomyopathy' were used. Identified articles and case reports were reviewed and the related reference lists were also searched to include any potential additional studies.

Clinical Features

Epidemiology

Estimating the prevalence of LVNC is significantly limited by the fact that the best available data comes from studies which used varying diagnostic criteria and included a low number of patients. Furthermore, the data is retrospective and potentially affected by selection bias of patients being referred to tertiary echocardiography labs. Current estimated prevalence of isolated LVNC (ILVNC) is 0.014-0.26% based on this data [4,6,10,18-20]. The mean age of diagnosis is approximately 40 years of age for adults and 7 years of age for children [4,6-10]. Men are more commonly affected, accounting for 56-82% of cases [4,5,7-10,21-23]. Disease is familial in nearly half of patients diagnosed during childhood and 20-33% of patients diagnosed during adulthood [2,3,5,6,9,18,23,24]. The lower familial occurrence in adults may partially be due to less rigorous screening in this population. LVNC is more common in patients with congenital heart disease with one study of 200 patients demonstrating a prevalence of 12% in this population [25]. The most common congenital diseases associated LVNC are bicuspid aortic valve, aortic coarctation, Ebstein's anomaly, and Tetralogy of Fallot [18,25].

Heart failure

Clinical presentations of LVNC are widely variable ranging from asymptomatic patients to aggressive cardiomyopathy symptoms resulting in cardiac death or transplantation [3,4,6-12,18-20]. Clinical heart failure is a common presentation and has been shown to occur in 33-73% of adult patients and in 22-54% of children across multiple

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studies [3-9,20-22]. There is limited data explicitly analyzing the correlation between symptoms of heart failure and LV dysfunction; however, the few studies which include this data demonstrate significant overlap of patients with clinical heart failure and LV systolic dysfunction [3,12,22]. Four case series have documented predictors of LV dysfunction. One case series of 67 patients found advanced age, a high number of affected LV segments, and a high non-compaction/compaction (NC/C) ratio to predict LV dysfunction [6]. Another study of 42 patients showed that a high NC/C ratio on MRI predicted LV dysfunction [12,23,24]. Additionally, 2 small studies found Late Gadolinium Enhancement (LGE) on MRI to predict LV dysfunction [23,24]. Historically, LVNC has been thought to confer a particularly high risk of malignant arrhythmia and embolic events based on the early sentinel studies; however, more recent data calls into question whether LVNC patients carry a higher risk of these events compared to dilated cardiomyopathy controls matched in other clinical parameters [3-10].

Arrhythmia

The occurrence rate of VT in adults with LVNC has been highly variable across studies (6-63%) which include a small number of patients, a high percentage of whom also have LV dysfunction as a strong risk factor for VT [3-6,10,22,25,26]. Thus, whether or not LVNC is an independent risk factor for VT is not known. One observational study to date documents an association between VT and LV dysfunction in patients with LVNC [6,27]. The rate of VT in pediatric populations is generally lower ranging from 0-23% in most studies [8,9,11,20,21]; however, one study comprising 8 pts demonstrated VT in 5 (63%) of them [7].

Wolff-Parkinson-White (WPW) Syndrome has been well described in pediatric patients with LVNC occurring at a rate of 9-17% in the five largest case series [8,9,11,14,20]. Such an association has not been clearly established in adults with occurrence rate varying from 0-3% [4-6,10,12,22,28].

Atrial Fibrillation (AF) has been observed at a widely variable rate in adult LVNC with several studies demonstrating an occurrence of 3.8-29% [3-6,10,22,29]. The largest patient series showing this data included 228 patients who were periodically followed with Holter monitoring demonstrated a rate of 3.8% and AF was only observed in patients with dilated cardiomyopathy [29]. Whether or not there is higher rate of AF in adults patients with LVNC compared to age and comorbidity matched controls is not clear. AF is rarely seen in children with LVNC [7-9,20].

Complete Atrioventricular (AV) block has been observed in 4-13% of pediatric patients [7,8,21,30]. Adults studies show a wider range with most large studies demonstrating a rate of 0-3%; however, one study of 18 patients by He et al showed a rate of 22% for unclear reasons [3-6,10,19,22,28]. Steffel et al. found complete AV block to be associated with LV dysfunction in their series of 78 patients [22].

12-lead ECG in the vast majority of cases is abnormal demonstrating many non-specific abnormalities including left ventricular hypertrophy, inverted t-waves, ST segment changes, axis shifts, intraventricular conduction delays, q-waves, premature ventricular contractions, first degree AV block, and prolonged QTc, [3-9,11,12,20-22,27]. Invasive Electrophysiologic (EP) study has been performed in a small number of patients with two studies showing 13/28 adult patients having inducible ventricular arrhythmias [21,28]. Both studies are retrospective and likely strongly affected by selection bias. Ability to induce VT with invasive EP study was also predictive of

sudden cardiac death in the study by Steffel et al; however overall, there is not sufficient data to validate this finding [22].

Embolization

A high rate of systemic embolization ranging from 21-38% is a classically described complication of LVNC in adults thought in part to be due to thrombus formation in the deep intertrabecular recesses [4,27]. However, subsequent adult studies have shown both a lower total rate of systemic embolism (0-15%) and a strong association of embolic events with presence of AF and LV dysfunction [3,6,10,12,19,25,26,31]. One case series of adults compared 30 patients with LVNC to dilated cardiomyopathy control patients and found a lower rate of stroke in the LVNC group [10]. These studies were all retrospective and thus a large proportion of patients were anti-coagulated at the discretion of the treating physician and this likely affects the results. Based on this data, a higher rate of embolic events in patients without AF or LV dysfunction has not been established. Systemic embolization events in children are generally rare (0-2%); however, one outlier study with 8 patients showed systemic embolization in 3 (38%) patients [7-9,20,30].

Pathology

The pathophysiology of LVNC remains controversial. In particular, it is not known whether the condition is a distinct cardiomyopathy or a phenotypic manifestation of other cardiomyopathies [3,18,32-38]. In normal development, the early heart tube forms at week four of gestation and trabeculations subsequently emerge. At week eight, trabecular remodeling and compaction of the LV myocardium occur simultaneously with invasion of the developing coronary circulation [39]. Failure of the compaction process in utero is a longstanding proposed mechanism for development of LVNC and was initially thought to account for the phenotype of these patients [4,35-38,40]. This hypothesis is supported by new evidence of an autosomal dominant form of LVNC in humans caused by a mutation in the mindbomb homolog1 (MIB1) gene encoding a protein which regulates cell proliferation and compaction of fetal myocardium [41]. Several lines of evidence, however, suggest that failure of compaction may not completely explain the finding of LVNC in many patients. Fetal echocardiographic studies attempting to demonstrate prenatal non-compaction in patients who later developed pediatric disease have yielded equivocal results [42-44]. Furthermore, the majority of mutations in patients with familial LVNC are in sarcomeric, cytoskeletal, z-line, or mitochondrial proteins, most of which are also associated with dilated and hypertrophic cardiomyopathies [34,45-51]. These data suggest that in some patients ventricular non-compaction may be a phenotypic consequence of another primary cardiomyopathy.

Some experts suggest that pediatric LVNC is likely a distinct, primary condition and that adult onset LVNC is a phenotypic variation of other cardiomyopathies [52]. This theory is supported by the fact that mutations in the G4.5 gene result in a severe, infantile, X-linked form of LVNC with a poor prognosis [42]. In contrast, adult LVNC shows autosomal dominant inheritance and is associated with various other mutations most of which as previously stated are associated with dilated and hypertrophic cardiomyopathies [34,41,45-49]. Additionally, families with adult LVNC demonstrate marked variation in phenotype [34,41,45,46,48]. Thus, it appears that infantile LVNC from G4.5 mutation is both genetically and phenotypically distinct from adult LVNC. However, many autosomal dominant inherited forms of LVNC from other mutations can still result in severe symptom onset during infancy, so it is not conclusive that pediatric LVNC is a distinct disease entity [34,41,45,46,48].

Microvascular ischemia has been suggested as an additional factor in the pathophysiology of LVNC. Junga et al found that areas of non-compaction in pediatric patients with isolated LVNC corresponded to areas of hypoperfusion on PET scan [53]. Case study with MRI has also shown areas of perfusion deficits which correspond to areas of non-compaction [54]. These findings are thought to potentially explain the development of arrhythmia and pump failure in LVNC. Whether microvascular ischemia contributes to the development of non-compaction is less clear.

Autopsy study of LVNC has been performed on a small number of patients demonstrating gross findings of numerous tendons and filaments of various thickness, large trabeculations, and deep recesses within the left ventricle most prominently toward the apex [42,55-58] (Figure 1). Extensive endocardial fibroelastosis can be seen on gross inspection as well [42,55-57]. One study of 14 patients categorized recesses into 3 patterns: 1) anastomosing broad trabecular, 2) coarse trabecular resembling multiple papillary muscles, and 3) interlacing smaller muscle bundles with a smooth endocardial surface with compressed invaginations [55]. Microscopic analysis consistently confirms the presence of large trabeculations, endocardial recesses, and marked endocardial fibroelastosis [8,42,55-58]. Other microscopic features which have been reported, but occur with varying frequency in small autopsy studies include loose arrangement of fascicles, myocyte hypertrophy, coarse myocyte vacuolization, increased perivascular and interstitial space, reduced intracellular filaments, central cytoplasmic clearing, small patches of sub-endocardial fibrosis, increased glycogen in sub-endocardial cells, and presence of fat cells [8,42,55-58]. Electron microscopy performed on a few patients occasionally demonstrates elongation of mitochondria and variation in mitochondrial shape with

rare branching and minimal vesiculation of cristae [52,56]. Increased perinuclear glycogen has been reported on electron microscopy as well [52].

Genetics

Familial LVNC has been linked to various mutations in genes encoding for sarcomeric, cytoskeletal, z-line, and mitochondrial proteins; however, these mutations collectively only account for a small fraction of patients with LVNC and rigorous linkage analysis to determine statistical significance of these polymorphisms is lacking in many reports [34,45,46,48,50]. Furthermore, animal models of these mutations failed to establish genotypic-phenotypic correlation. Genetic variants in both myosin heavy chain 7 (MYH7) and troponin T (TNNT2) have been found in families with inherited forms of the disease, but linkage analysis failed to solidify clear linkage and genetically modified mice with these mutations do not recapitulate disease [34,45]. Hence, overall evidence to date that mutations in MYH7 and troponin T causing LVNC is only suggestive and hypothesis generating. Other genetic variants in a variety of genes, including Z line protein ZASP and alpha dystrobrevin have been found in patients with non-compaction, but linkage analysis is lacking as well [46,48] (Table 1).

The mitochondrial bound protein tafazzin is encoded by the G4.5 gene on the X chromosome. G4.5 mutation is known to cause Barth syndrome, an X-linked cardioskeletal myopathy with abnormal mitochondria leading to a phenotype in infant males of neutropenia, 3-methylglutaconic aciduria, and dilated cardiomyopathy [47]. A family has been described with a loss of function mutation in the G4.5 gene causing X-linked LVNC without other signs of Barth syndrome, indicating that it may be a severe allelic variant of Barth syndrome with specific effects on the heart [52].

More recently, variants in the mindbomb homolog 1 gene have been associated with LVNC in autosomal dominant pedigrees. Targeted inactivation of MIB1 in mouse myocardium causes reduced NOTCH1 activity, expansion of compact myocardium to proliferative, immature trabeculae, resulting in LVNC phenotype [41]. To date this is the only genetic mutation found in human pedigrees that reliably causes LVNC phenotype in animal models with targeted inactivation. Mindbomb encodes an ubiquitin ligase critical to Notch signaling, a master regulator of myocyte proliferation and differentiation [41]. This is the first mutation discovered that directly affects cell proliferation during embryologic myocardial compaction and adds validity to the theory that some forms of LVNC may represent a distinct, primary cardiomyopathy (Table 1).

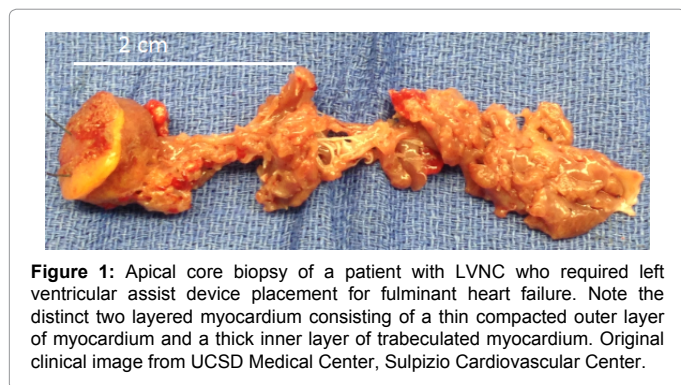


Figure 1: Apical core biopsy of a patient with LVNC who required left ventricular assist device placement for fulminant heart failure. Note the distinct two layered myocardium consisting of a thin compacted outer layer of myocardium and a thick inner layer of trabeculated myocardium. Original clinical image from UCSD Medical Center, Sulpizio Cardiovascular Center.

GENE/PRODUCT	FUNCTION	INHERITANCE PATTERN	AGE OF PRESENTATION	ANIMAL MODELS EXHIBIT	ASSOCIATIONS	SOURCES
MIB1/E3 ubiquitin- protein ligase	Regulates myocardial cell proliferation	Autosomal Dominant	Adult and late childhood	LVNC	None	Luxan
G4.5/tafazzin	Acetyl-transferase in mitochondria	X-linked	Early childhood	None	Barth Syndrome, DCM	Towbin, Bleyl
DTNA/ α -dystrobrevin	Stabilizes plasma membrane	Autosomal dominant	Adult and childhood	DCM	None	Ichida, Grady, Towbin
ZASP/Z-line associated protein	Cytoskeletal	Autosomal dominant	Adult and childhood	DCM	DCM	Vatta
TNNT2/TroponinT Type II	Sarcomeric	Autosomal dominant	Adult and childhood	DCM	DCM	Luedde, Hershberger
MYH7/ β -myosin heavy chain	Sarcomeric	Autosomal dominant	Adult and childhood	HCM, DCM	HCM	Klaassen
MYBPC3/Myosin binding protein C	Sarcomeric	Autosomal recessive	Adulthood	HCM	HCM	Ripoll

MIB1 = Mindbomb Homolog 1, HCM = Hypertrophic cardiomyopathy, DCM = Dilated cardiomyopathy

Table 1: Genes Associated With LVNC.

Associations

Association between LVNC and neuromuscular disorders has been well established. Recent study by Stollberger et al. demonstrated that of 106 patients with LVNC who underwent a complete neurologic evaluation, 22 (21%) patients were diagnosed with a well-defined neuromuscular disorder and 68 patients (64%) a neuromuscular disorder of unknown etiology [5]. The rate of neuromuscular disease in this study is higher than previously described in other studies; however, patients in these previous studies were not routinely referred for neurologic evaluation [4,6,26,27]. The presence of a neuromuscular disorder in conjunction with LVNC was found to be associated with a higher mortality rate in this case series, 15% versus 0% [5]. The authors offer the presence of respiratory muscle involvement and disqualification for transplant as possible explanations for this finding [5]. Additionally, the reciprocal finding was reported in a case series of 113 patients with mitochondrial disorders showing that patients with an associated cardiomyopathy had an 18% survival rate at age 16 as compared with a 95% survival rate of age matched patients without cardiomyopathy [59]. Neuromuscular disorders which have been observed in conjunction with LVNC include Becker muscular dystrophy, metabolic myopathy, myotonic dystrophy type 1, infantile glycogenosis type II (Pompe's disease), myoadenylate-deaminase deficiency, Leber's hereditary optic neuropathy, Friedreich ataxia, Charcot-Marie-Tooth, Barth syndrome, dystrophinopathy, dystrobrevinopathy, laminopathy, zaspopathy, and various mitochondrial disorders [49]. LVNC is additionally associated with a high rate of facial dysmorphisms in children characterized by a prominent forehead, low set ears, strabismus, high-arching palate, and micrognathia [7-9,60].

Diagnosis

Diagnosis of LVNC is based on imaging criteria with TTE being the most commonly used modality. The qualitative findings of multiple, prominent ventricular trabeculations and deep intertrabecular recesses communicating with the ventricular cavity as demonstrated by color Doppler imaging (Figure 2) are widely accepted requirements to make the diagnosis [3,6,7,10,60-64]. However, to date there are no universally accepted, precise diagnostic criteria. Three commonly cited quantitative TTE criteria credited to Chin et al., Jenni et al., and

Stollberger et al. have been described (Table 2) [7,32,60,64]. Notably, the Chin quantitative diagnostic criteria was never proposed by Chin et al., but rather by other authors based on the echocardiographic findings reported in their study [7,32,65,66]. The utility of these quantitative criteria or superiority of any one is not well established as each is limited by validation in very small studies and unknown sensitivity/specificity (Table 2) [7,60,64]. In particular, there is concern that application of these criteria using newer, higher quality TTE imaging techniques results in poor specificity. A study by Kohli et al., found that 8.3% of control patients and 23.6% of patients with heart failure fulfilled one or more of these quantitative diagnostic criteria for LVNC [65]. The majority of control patients who fulfilled criteria for LVNC were African American raising particular concern of poor specificity of the criteria in this population [65]. There is also concern about the reproducibility of these criteria as shown in a study of 104 patients by Saleeb et al. demonstrating poor inter-observer agreement in both the determination of the NC/C ratio and the number of trabeculations [67]. Given these limitations, Transesophageal echocardiography (TEE), 3-dimensional (3D) echocardiography, and contrast echocardiography may be considered to enhance imaging of trabeculations and aid in the diagnosis [68-70]. There is interest and ongoing research in assessment of functional parameters to assist in diagnosis of LVNC as well. Recent study by Belavia et al. demonstrated abnormal myocardial strain in patients with LVNC and preserved EF [71]. Additionally, a study by Frishknecht et al. showed that regional wall motion abnormality differentiated LVNC from the myocardium of patients with mitral regurgitation and aortic stenosis [72].

Trabeculations are found at the apex in nearly all reported cases and also commonly seen in the mid-lateral and mid-inferior walls [4-6,8,10-12,22,27]. Right ventricular (RV) involvement of non-compaction pathology is difficult to determine due to the frequent presence of trabeculations in normal subjects and is seldom used to aid in the diagnosis [6-11,60,63,64]. Left ventricular dysfunction has been demonstrated in approximately 50-75% of patients across multiple adult and pediatric studies [3-6,8-11,20,26,27,29]. Left ventricular dilation has also been reported in up to 43-67% of adults with LVNC [3,4,6,18]. Diastolic dysfunction may also be present as well demonstrated by one study of 57 adult patients showing 19% of subjects to have a restrictive

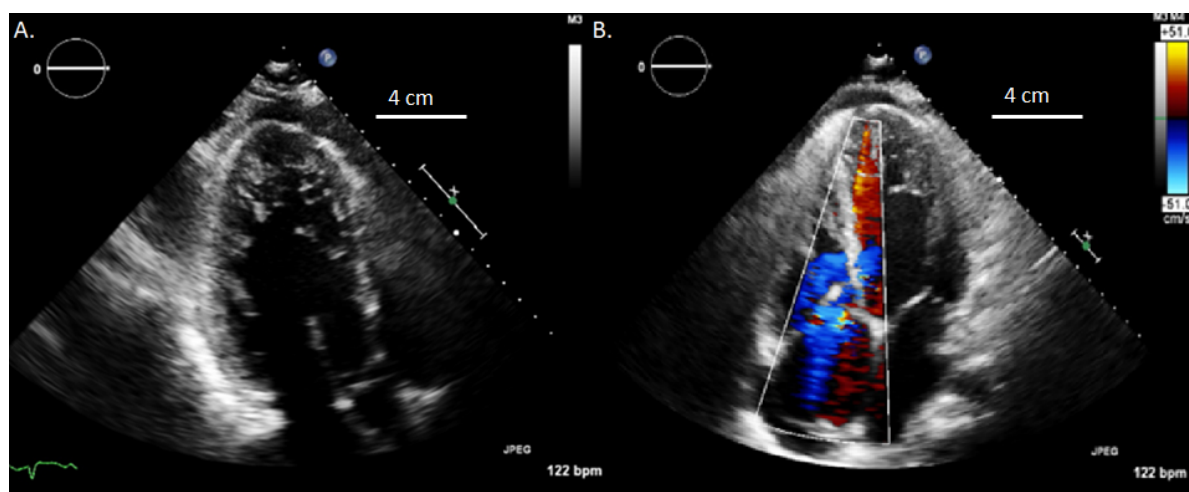


Figure 2: A. Apical 3-chamber transthoracic echocardiographic image of patient with LVNC demonstrating prominent ventricular trabeculations and deep intertrabecular recesses predominately in the apical and distal posterior walls. B. Apical 4-chamber echocardiographic view of same patient with color Doppler demonstrating communication of intertrabecular recesses with the ventricular cavity. Original clinical image from UCSD Medical Center, Sulpizio Cardiovascular Center.

	CHIN ET AL	JENNI ET AL	STOLLBERGER ET AL	PETERSEN ET AL	JACQUIER ET AL	STACEY ET AL
Imaging modality	TTE	TTE	TTE	Cardiac MRI	Cardiac MRI	Cardiac MRI
Quantitative criteria	Quotient of the distance from epicardial surface to trough of trabecular recess (X) and distance from epicardial surface to peak of trabeculation (Y) ≤ 0.5	Non-compacted to compacted segment ratio > 2.0	> 3 trabeculations from apex to papillary muscle in 1 imaging plane	Non-compacted to compacted segment ratio of >2.3	LV trabecular mass $>20\%$ of total LV mass	Non-compacted to compacted ratio of >2
Qualitative features	No co-existing cardiac anomalies, progressive increase in Y from base to apex	No co-existing cardiac anomalies, 2 layered myocardium, intertrabecular recesses communicate with LV cavity demonstrated by color flow Doppler	Intertrabecular recesses communicate with LV cavity by color flow Doppler, 2 layered myocardium	2 layered myocardium	2 layered myocardium	2 layered myocardium
Anatomic focus of measurement	Base, papillary muscles, and apex	Mid-lateral, mid-inferior, apex	Apex, lateral, inferior walls	All of LV	All of LV	All of LV
Views	Parasternal long axis, apical 4-chamber, subxyphoid	Parasternal short axis	Various	Long axis	Short axis	Short axis
Cardiac phase	End-diastole	End-systole	Not applicable	Diastole	End diastole	End systole
Supporting data	8 patients with LVNC compared to 8 controls found to differ significantly	7 patients with LVNC, TTE correlated to autopsy findings, differentiated patients from 19 LVH and/or DCM controls	No rigorous validation	7 patients with LVNC differentiated from 125 subjects with HCM, DCM, hypertensive heart disease, aortic stenosis, and athletes	16 patients with LVNC differentiated from 48 HCM, DCM, and healthy controls	Associated with higher hazard ratio of clinical events than Petersen, Jacquier criteria
Sensitivity/Specificity	None documented	None documented	None documented	86%/99%	93.7%/93.7%	None documented
Limitations	No sensitivity/specificity data, few patients studied	No sensitivity/specificity data, few patients studied	No rigorous validation	May lack specificity in lower pretest probability patients	Interobserver reproducibility of LV trabeculated mass is potentially poor	New criteria, unknown reproducibility of findings

Table 2: Diagnostic Criteria for LVNC.

pattern [6]. Additionally, in 2 pediatric studies of 36 and 10 children respectively, 30-42% exhibited restriction on TTE [9,11].

Cardiac MRI is an emerging modality in the diagnosis of LVNC carrying the advantage of high spatial resolution and image quality [73-75] (Figure 3). Three diagnostic criteria have been developed by Petersen et al., Jacquier et al., and Stacey et al. (Table 2). The criteria by Petersen et al. require the presence of a 2-layered myocardium with an NC/C ratio of >2.3 on Steady State Free Precession (SSFP) imaging in diastole using the maximal ratio found in long axis views [73]. The criteria was validated by differentiating 7 patients with LVNC from controls which included athletes, normal subjects, HCM, DCM, hypertensive heart disease, and aortic stenosis patients [73]. This study showed a sensitivity of 86% and specificity of 99%. However, when applied in a Multi-Ethnic Study of Atherosclerosis cohort 43% of 323 patients without cardiac disease had a NC/C ratio of >2.3 in one region and 6% in two regions indicating that the criteria lack specificity in a lower pre-test probability population [74]. The Jacquier criteria requires the presence of a 2-layered myocardium and quantifies the LV trabecular mass compared to the total LV mass finding that an LV trabecular mass $>20\%$ diagnosed LVNC with 93.7% sensitivity and 93.7% specificity in 7 patients with LVNC compared to HCM, DCM, and healthy controls [75,76]. The chief limitation of this technique is the concern that inter-observer reproducibility of trabecular mass quantification is poor as demonstrated in a study by Fernandez-Golfin et al. [77]. Most recently, Stacey et al. have proposed measuring the NC/C ratio in end systole to improve upon the specificity of the diastolic criteria [78]. Their retrospective study of 122 patients with LVNC demonstrated that an NC/C ratio of >2 in end systole was associated with higher

hazard ratios for clinical events of Congestive Heart Failure (CHF) and a composite end point of death, CHF readmission, embolism, and ventricular arrhythmia than the Petersen and Jacquier criteria [78]. The study additionally found that an NC/C ratio in end systole had better correlation with reduced EF and reduced myocardial thickening than the Petersen and Jacquier criteria [78]. MRI also offers functional information about fibrosis in trabeculated segments and microvascular perfusion. One study of 42 patients with LVNC found that LGE in trabeculated segments was present in 55% of patients [23]. The degree of LGE in trabeculated segments correlated with adverse clinical outcomes and LV systolic dysfunction in this and other another study of 9 patients [23,24]. MRI study has also demonstrated sub-endocardial perfusion deficits in areas of non-compaction lending credence to the hypothesis that microvascular dysfunction and ischemia may play a role in the development of LVNC [54].

To navigate these different multi-modality diagnostic criteria, an algorithm has been proposed by Thavendiranathan et al. They advocate using the Jenni criteria for TTE with additional consideration of progressive increase in NC/C ratio from base to apex, followed by consideration of functional information on TTE discussed above. In the case of suboptimal TTE image quality they recommend use of contrast TTE or, if still not suitable, MRI with primary application of Petersen's criteria, confirmation with Jacquier's criteria and consideration of functional MRI data [66]. Given the data available at this time, we find this to be a reasonable diagnostic approach; however, special attention to the limitations of each criteria summarized in Table 2 must be applied and we caution against the strict use of quantitative criteria as cut off values when diagnosing LVNC.

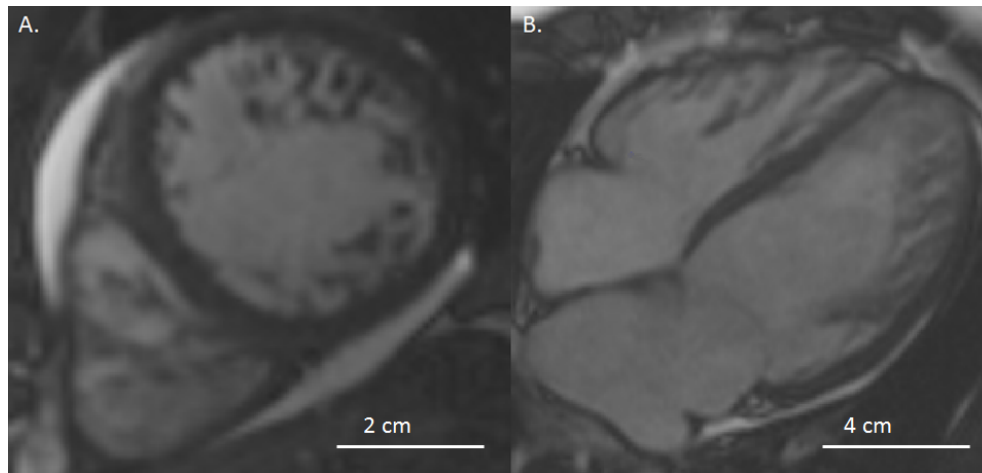


Figure 3: Steady state free precession (SSFP) MRI still frame images at end diastole in a patient with LVNC. Short axis (A) and apical 4-chamber (B) views show clear delineation of a thick inner layer of non-compacted ventricular myocardium with deep trabeculations and outer compacted layer of myocardium. Original clinical image from UCSD Medical Center, Sulpizio Cardiovascular Center.

Prognosis

The prognosis of adult patients with LVNC is uncertain and highly variable across studies that include only a small number of patients with earlier case series suggesting a 5 year mortality/transplant rate of nearly 60% [4,27]. However, several more recent studies indicate a mortality/transplant rate of 3-15% over an average 3 year follow up period [3,5,6,10,19,25,26]. The reason for this discrepancy is unclear. It has been postulated that newer imaging techniques and heightened provider awareness have resulted in earlier diagnosis of patients with LVNC [3]. Clinical heart failure, LV dilatation, advanced age, and ECG abnormalities at time of diagnosis have been shown to predict mortality in some studies [4,5,10,26]. LV dysfunction, atrial fibrillation, and greater extent of non-compaction have also been associated with higher mortality rate in some studies with a notable exception in a 65 patient case series by Lofiego et al. [5,6,10,19,24,26]. Ventricular arrhythmia has been associated with higher mortality in 2 studies [18,26], but not in a 34 patient series by Oechslin [4]. The most common causes of death are advanced heart failure and sudden cardiac death occurring in nearly equal frequency [3,6,10,12,18,19,25,26]. Whether or not patients with LVNC experience higher morbidity and mortality compared to dilated cardiomyopathy controls is not well established; however, one 39 patient study demonstrated no difference in 3 year survival between adult LVNC patients and a dilated cardiomyopathy control cohort [10]. Pediatric studies show a wide 3 year survival range of 6-37.5% [7-9,11,20]. LV dilatation and extent of non-compaction were associated with higher mortality in one very small study of 10 patients [11]. A larger study with 46 patients demonstrated that earlier age of presentation was associated with a higher mortality rate. This study did not show any association of EF or extent of non-compaction with mortality [20].

Management

There are no guidelines for specific management of LVNC due to limited data. Therapy focuses on treatment of known clinical complications at discretion of the clinician. Patients with LVNC are managed with neurohormonal blockade, diuretics, and cardiac resynchronization/defibrillator therapy according to standard clinical guidelines for systolic and diastolic dysfunction though there has been limited study validating their efficacy in this population. One case study

found that carvedilol improved EF, left ventricular dimensions, and left ventricular mass in an infant with isolated LVNC [79]. In another study of 10 children, carvedilol was associated with stabilization or improvement in ventricular function in 7 patients [11].

Given the possibly elevated risk of ventricular arrhythmia in LVNC, remote outpatient arrhythmia monitoring is strongly recommended. Retrospective study of 12 patients with isolated LVNC and low EF who underwent Intracardiac Defibrillator (ICD) implantation for primary and secondary prevention showed a 50% rate of appropriate firing for secondary prevention and a 25% rate for primary prevention [80]. Data is lacking in patients with normal EF and thus, unlike hypertrophic cardiomyopathy, there are no strong recommendations for the prophylactic placement of ICDs in LVNC with preserved EF. Currently, implantation of an ICD for LVNC is a Class IIb recommendation according to ACC/AHA guidelines [81]. We recommend maintaining a high degree of suspicion for arrhythmia and getting diagnostic testing when appropriate.

Prevention of systemic embolization is a therapeutic priority in LVNC, however, the risk of systemic embolization in patients without AF and with normal EF is unclear. Regardless, there remains suspicion that the deep intertrabecular recesses may represent an independent risk of thrombus formation in these patients. Oechslin et al. have advocated anticoagulation for patients with an LV EF <40% [32]. Given the lack of data on this matter, risk of bleeding should be especially considered in the decision to anti-coagulate these patients.

Referral for genetic counseling and clinical screening of first-degree relatives up to three generations is recommended. Clinical screening that includes history, physical examination, ECG, and TTE should be performed every 3 years beginning in childhood if genetic testing and/or clinical family screening is negative [82]. Due to the fact that the presence of mutations known to be associated with LVNC is rare and their significance unclear, the role of genetic testing remains undefined [82]. However, if a suspected causative mutation is present, then screening should be performed yearly in childhood and every 1-3 years in adulthood [82]. A neurologic evaluation is recommended for all patients as there is a high prevalence of associated neuromuscular disorders.

Perspective

LVNC is a familial cardiomyopathy with potential for high morbidity and mortality that poses a great clinical challenge due to lack of precise diagnostic criteria or management guidelines. The pathophysiology of LVNC continues to be a point of great controversy and multiple recent genetic studies still do not answer the question as to whether the condition is a primary cardiomyopathy or a phenotypic variation of other cardiomyopathies. While early studies indicated that patients with LVNC experienced high mortality and a uniquely high risk of malignant arrhythmia and systemic embolism, more recent study has demonstrated a better prognosis and the elevated risk of arrhythmia and embolism compared to comorbidity matched controls has not been confirmed. However, LVNC has been shown to have a strong association with neuromuscular disorders in multiple studies where patients were referred for routine neurologic screening and presence of a neuromuscular disorder has been shown to convey a worse prognosis. Further basic science and clinical research are greatly needed to refine the understanding of the origin, clinical characteristics, diagnostic approach, and management of this unique disease.

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