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REVIEW

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The role of multimodality imaging in the diagnosis of left ventricular noncompaction

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Abstract

Left ventricular noncompaction (LVNC) is a heterogeneous entity and, in reality, a likely spectrum of disease which is clinically associated with arrhythmia, thromboembolic complications and sudden cardiac death. With the emergence of cardiac MRI (cMRI), the phenotype is increasingly more prevalent, resulting in clinical uncertainty regarding prognosis and management. The currently accepted hypothesis suggests an early embryonic arrest of the normal, sequential myocardial compaction process. LVNC is observed in isolation or in association with congenital heart disease, neuromuscular disease or a vast array of genetic cardiomyopathies. Definition of the entity varies among international society guidelines with differences both within and between imaging modalities, predominantly echocardiography and cMRI. Long-term prognostic data are emerging but due to the intrinsic variability in reported prevalence, selection bias and lack of pathological to prognostic correlation, there are many uncertainties regarding clinical management. This review seeks to clarify the role of multimodality imaging in diagnosis and management of the disease. We discuss the sensitivity and specificity of the current diagnostic criteria, as well as the nuances in diagnosis using the available imaging modalities.

KEYWORDS

cardiac magnetic resonance imaging, cardiomyopathy, computed tomography, echocardiography, left ventricular noncompaction

1 | INTRODUCTION

Left ventricular noncompaction (LVNC) is a distinct structural cardiac disease entity. It remains poorly understood and is difficult to characterise systematically due to the wide spectrum of clinical manifestations and genetic heterogeneity. Traditionally, LVNC is characterised by prominent recesses and regions of hypertrabeculation within the myocardium with associated impaired ventricular systolic function.[1] LVNC has also been linked with a number of other structural and functional cardiac abnormalities and associated conditions, including arrhythmias, systemic thromboembolism and sudden cardiac death. The current lack of a gold-standard diagnostic criteria for LVNC and the diversity in imaging-based definitions that do not consistently correlate with clinical outcomes pose unique challenges to the diagnosis, management and risk stratification of this condition. The European Society of Cardiology has categorised it as an unspecified familial cardiomyopathy,[2] whilst the American Heart Association considers it a primary genetic cardiomyopathy.[3] This review examines the role of the various different imaging modalities within the clinical setting in the diagnosis and prognostication of LVNC and its associated conditions.

2 | EPIDEMIOLOGY AND PATHOPHYSIOLOGY

The most common published hypothesis for the morphological abnormalities in LVNC is that of the inappropriate arrest of the normal compaction process of the primordial ventricular myocardium in the developing foetus which usually occurs between weeks 8 and 12 of gestation. This is thought to lead to a failure of the final phase of foetal cardiac development when compaction of the ventricular myocardium occurs. During normal development of the foetal heart, vascular endothelial growth factors[4] trigger the process of compacting primordial trabeculations, which occurs progressively from the epicardium inwards, from the base to the apex of the heart and from septal to lateral walls, in conjunction with the formation of the myocardial capillary bed.[5] Arrest of this process is believed to result in persistence of trabeculae that communicate with the left ventricular cavity, predominantly in the apical endocardium. Conversely, an alternate hypothesis is that of intrinsic proliferation of trabeculae occurs which is independent of the compaction process of the ventricular myocardium.[6] This hypothesis was proposed based on the findings of a large study which demonstrated a positive correlation between trabecular thickness and the thickness of the compacted wall.[7] The net effect is phenotypic deep trabeculation involving a variable extent of the ventricle from apex upwards resulting in the potential for thromboembolic disease due to stasis of blood between trabeculae and arrhythmia due to local heterogeneity in cardiac conduction. As the apex is the last to compact, it is invariably affected which results in impaired torsional contraction (apical twist) required for optimal ejection.[8] If the noncompaction is extensive and affects the mid to basal segments, further ventricular dysfunction occurs. The same process of noncompaction can also affect the right ventricle as well, resulting in isolated or biventricular noncompaction.

Interestingly, LVNC has been classified as a familial or genetic cardiomyopathy despite lack of a causal relationship with any specific genetic mutations.[9] In fact, Oechslin and Jenni propose that LVNC may be the resulting phenotype due to a spectrum of physiologic adaptations to a pathologic condition, with genetic mutations serving as a catalyst for the disease state.[10] Physiologic adaptation can include pressure/volume-loaded states, as well as in athletes[11] and pregnancy,[12] where pregnancy may have a reversible component. Higher rates of LVNC have been documented in particularly in patients with sickle cell anaemia (due to increased cardiac preload).[13] Furthermore, hypertrabeculation has been reported in those with hypertension and left ventricular hypertrophy.[14]

Several mutations have been identified in patients with LVNC and concomitant congenital and valvular heart disease; however, modes of inheritance are varied.[15] The likelihood of variable penetrance further complicates any potential genotype-phenotype correlations, making targeted genetic testing difficult. A large retrospective multicentre Dutch trial looked at 327 unrelated patients with LVNC and found genetics played a role in 48% of cases either through known mutations or familial disease without known mutation. The most common mutations (71% of cases) identified were *MYH7, MYBPC3 and TTN*.[16]

Genetic testing can assist in prognostication, especially in the paediatric population, where pathogenic mutations within a traditional cardiomyopathy panel were seen with earlier diagnosis, greater symptoms and systolic impairment and major adverse cardiac events (MACE). This trend was weakened in the adult subgroup due to a greater proportion of sporadic LVNC cases. Compound heterozygosity of the *MYBPC3* gene conferred a higher risk of MACE, whilst mutations in *MYH7* were had a lower risk.[16]

Few studies have captured the incidence and prevalence of LVNC, but current data indicate it is a rare condition. Prevalence in adults referred for echocardiography ranges from 0.01% to 0.30%,[17,18] with a higher prevalence in patients with heart failure (3%-4%).[19,20] There appears to be a higher prevalence in males[21] and a high variability in the age of presentation (median of 40-50 years in adults; 5-7 years in paediatric patients).[22] A recent meta-analysis concluded consistently higher prevalence rates in cohorts diagnosed by cardiac magnetic resonance imaging (cMRI) (14.79%) as compared to echocardiography (1.28%), suggesting that the higher spatial resolution associated with cMRI detects changes in LVNC more readily. This may also be affected by selection bias as patients with undiagnosed cardiomyopathy are more likely to undergo cMRI.

Athletes also consistently demonstrated higher pooled prevalence in both cMRI (27.29%) and echocardiography (3.16%) modalities.[23] In fact, given the relatively higher prevalence of hypertrabeculation in athletes, recommendations for competitive sport in individuals with LVNC have been incorporated into official guidelines,[24] with concurrent systolic dysfunction or documented ventricular arrhythmias as the primary factors preventing participation in competitive sport.

However, current cross-sectional data should be interpreted with caution, since many factors may contribute to potential bias. Given the relative rarity of noncompaction, large-scale epidemiological studies have spanned long periods, often preceding or transgressing the development of diagnostic criteria, which have evolved over time and newer imaging techniques with the potential for overdiagnosis. Additionally, LVNC often remains clinically silent for a significant period of time, and thus, the results of these studies are likely to be confounded by selection.

3 | CLINICAL SIGNIFICANCE

The diagnosis of LVNC is often triggered by a manifestation of one of three classic clinical presentations—heart failure, arrhythmia and thromboembolic disease.

3.1 | Heart failure

Over 60% of patients diagnosed with LVNC develop heart failure.[21] Beyond the aforementioned impact on rotational contractility of the left ventricle, the loss of the mechanical contribution of the subendocardial layers due to hypertrabeculation may contribute to systolic dysfunction. Impaired formation of the myocardial capillary bed and microcirculation further potentiates this systolic impairment,[25] evident as subendocardial perfusion defects on cMRI,[26] positron emission tomography (PET)[27] and thallium scintigraphy.[28] In a case series of 34 patients,[21] one of the largest of its time, almost 80% of patients presented with dyspnoea, with one-third having New York Heart Association (NYHA) Class III-IV symptom severity and a mean left ventricular ejection fraction of 33%.

Systolic dysfunction and ventricular remodelling with dilatation are purported to be manifestation of the true noncompaction cardiomyopathy phenotype.[29] The echocardiographic features can resemble those seen in dilated cardiomyopathy with relatively thin compacted myocardial wall thickness,[30] albeit with excessive trabeculations fulfilling the criteria for noncompaction. It is likely that diastolic dysfunction also exists, with a restrictive filling pattern arising from the abundance of intracavitary trabeculae.[31] However, the exact characteristics of left ventricular diastology are yet to be delineated.

The presence of right ventricular dysfunction appears to provide further prognostic insight. A retrospective study[32] retrospective study of 14 patients with LVNC on cMRI found that patients with a right ventricular ejection fraction (RVEF) <35% were more symptomatic and had lower LVEF and higher LV volumes. Interestingly, these patients had a higher ratio of noncompacted to compacted myocardium, a finding that was also seen in patients with impaired left ventricular function.

3.2 | Arrhythmia

Cardiac arrhythmias are common in noncompaction cardiomyopathy. Supraventricular tachyarrhythmias can occur in up to 25% of patients, including atrial fibrillation, atrial flutter and atrioventricular nodal re-entrant tachycardia.[33] Indeed, pre-excitation atrioventricular re-entrant tachycardias have been found in up to 15% of paediatric patients with LVNC, but only 3% of adults.[1] Concomitant noncompaction cardiomyopathy in patients with Ebstein anomaly may contribute to this increased prevalence. Conduction disease can range from sinus node dysfunction,[34] bundle branch block[1] and complete atrioventricular block; however, the exact incidence of these is unclear.

Ventricular arrhythmias are a particular cause for concern in any patient diagnosed with noncompaction cardiomyopathy, being documented to occur in almost 50% of cases[35] and sudden cardiac death occurring in up to 18% of adults.[1] Similar to LV systolic dysfunction, traditional markers used in the nonischaemic dilated cardiomyopathy phenotype appear to predict ventricular arrhythmias in LVNC, including increased LV size and lower LVEF.[36] However, several case reports and series have demonstrated sustained ventricular tachycardia even in patients with preserved LV systolic function.[37,38] Despite such a high prevalence, specific guidelines do not exist for implantable cardioverter-defibrillator (ICD) therapy in patients with LVNC, beyond general guidelines for all cardiomyopathies, which recommend insertion of an ICD where left ventricular ejection fraction is ≤35% and documented sustained ventricular arrhythmias. One of the few ICD-based studies by Kobza and colleagues followed 12 patients over 36 months and demonstrated that only 5 experienced appropriate device therapies, of which 4 cases had devices inserted for secondary prevention.[39] The mechanism of ventricular arrhythmias in the context of LVNC remains poorly understood. Re-entry, arising from subendocardial ischaemia in noncompacted segments, was presumed to be the likely aetiology.[21] However, more recent studies have shown a higher prevalence of ventricular arrhythmias arising from more idiopathic regions including outflow tracts, basal perivalvular regions and fascicles.[40]

3.3 | Thromboembolic disease

Cardioembolic disease is another phenomenon documented in patients diagnosed with LVNC and is postulated to arise due to altered hemodynamics within a hypertrabeculated myocardium, haemostasis in severe ventricular systolic dysfunction or paradoxical embolism in those with congenital atrial or ventricular septal defects.[15,41] LV thromboembolic sequelae may manifest as cerebral strokes, transient ischaemic attacks, mesenteric ischaemia, myocardial infarction, renal infarction and acute limb ischaemia.[1,15] Pulmonary emboli may also arise from noncompaction involving the right ventricle via a similar mechanism. Preventative anticoagulation, however, is currently only recommended for those patients with known independent risk factors, such as prior thromboembolism, severe systolic dysfunction or concurrent atrial fibrillation. A systematic review published in 2019 found LVNC alone was not directly linked to increased thromboembolic event rates in the absence of the aforementioned defined risk factors.[42]

3.4 | Association with systemic disease and congenital heart disease

With the aetiology of LVNC hypothesised to be related to embryological arrest of myocardial compaction, there is

TABLE 1 Major TTE criteria for the diagnosis of LVNC

Authors and Year	Chin (1990)[50]	Jenni (2001)[51]	Stollberger (2013)[52]
No. of Patients	8 with LVNC 3 with autopsy correlation	7 with LVNC and correlated with autopsy 9 with hypertensive LV hypertrophy 10 with DCM	115 with LVNC Retrospective postmortem study
Criteria	(I) Ratio of X/Y ≤ 0.5 in end-diastole *X* = distance from the epicardial surface to the trough of the trabeculation *Y* = distance from epicardial surface to the peak of the trabeculation Measure at LV apex in parasternal short-axis and apical views	(I) Two-layer myocardial structure with thin compacted and thicker noncompacted myocardium (II) Ratio of noncompacted to compacted myocardium >2 in end-systole (III) Absence of coexisting cardiac structural abnormalities (IV) Excessive prominent trabeculations and deep intertrabecular recesses, latter supplied by intraventricular blood on colour Doppler Measure in parasternal short-axis views	(I) Presence of >3 trabeculations located apical to the papillary muscles, within a distinct two-layered myocardium (end-systole) (II) Perfusion of intertrabecular recesses with either colour Doppler or echocardiographic contrast (end-diastole) Measure LV segments apical to papillary muscles in parasternal short-axis and apical views

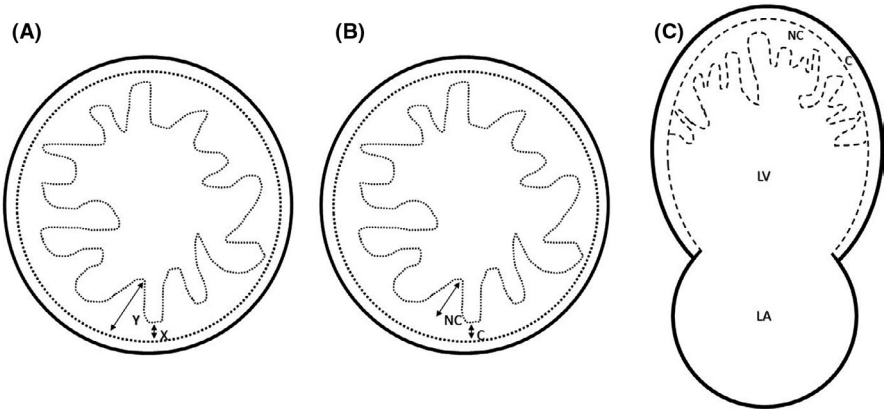

FIGURE 1 Schematic diagram illustrating the current most widely utilised echocardiographic diagnostic criteria for LVNC. A, Chin criteria: Parasternal short axis at the LV apex demonstrating the ratio of X/Y ≤ 0.5 in end-diastole. B, Jenni criteria: Parasternal short-axis view at the LV apex ratio of noncompacted (NC): compacted (C) is >2 in end-systole. C, Stollberger criteria: Apical window demonstrating greater than three trabeculae at the LV apex in a characteristic two-layered myocardium in end-systole

believed to be an association with other forms of congenital heart disease. A retrospective Swiss study of 202 patients aimed to assess the prevalence of congenital defects in patients diagnosed with LVNC on echocardiography. They found 12% patients had concurrent congenital heart defects,[43] the most common defect being a left ventricular outflow tract abnormality such as a unicuspid or bicuspid aortic valve or coarctation of the aorta.[43] The second most common was Ebstein anomaly, followed by Tetralogy of Fallot.[43] A recent retrospective assessment of congenital cases with single ventricle heart disease showed that the LVNC phenotype was only seen in 37% of those examined and was associated with reduced ejection fraction and increased ventricular volumes.[44]

Left ventricular noncompaction can also be associated with several congenital systemic disorders, most notably neuromuscular diseases, including mitochondrial disorders, myotonic dystrophy type 1 and Emery-Dreifuss muscular dystrophy due to mutations of the *LMNA* gene.[15,45] In particular, XLR Barth syndrome has a distinct association with the classic dilated hypokinetic phenotype of LVNC.[46] Given the potential for familial inheritance through both known and unknown mutations, clinical screening incorporating 12-lead ECG and at least echocardiography is suggested for first-degree relatives, especially in the setting of concomitant neuromuscular disorders.[15] Cascade genetic testing has also been suggested to screen family members that can avoid regular cardiac follow-up in those without mutations.[16] However, this strategy does not account for the many unknown mutations that may account for 16% of LVNC cases that are familial but without identifiable mutations on current cardiomyopathy panels. LVNC has also been demonstrated among patients with polycystic kidney disease with no obvious mechanistic link between the two pathological processes.[47-49]

4 | DIAGNOSIS

4.1 | Transthoracic echocardiography

Transthoracic echocardiography (TTE) is the most commonly used imaging modality in diagnosing LVNC due to its low risk, cost-effectiveness and accessibility. The three main echocardiographic diagnostic criteria were proposed by three groups (Table 1 and Figure 1),[50-52] although since then, there have been a few amendments and additions.

The initial case series by Chin et al[50] described prominent trabeculation and deep intertrabecular recesses within a pathognomonic two-layered myocardium in 8 patients. In this study, the morphological changes were reported to be best visualised in the parasternal short-axis and apical views in end-diastole. In this study, the ratio of distance measured from the epicardium to the trough of the trabeculation (*X*) and to the peak of the trabeculation (*Y*), with X/Y equal to or <0.5 was proposed to be diagnostic for LVNC (Figure 1).

A subsequent study[51] sought to refine these diagnostic criteria. Imaging features in 7 cases with LVNC diagnosed both on TTE and autopsy were compared to patients with hypertensive hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM). Whilst concurring with the previously proposed criteria by Chin and colleagues regarding the requirement of a distinct two-layered myocardium,[50] the Jenni criteria proposed a maximal ratio of noncompacted (NC) to compacted (C) myocardium > 2, as diagnostic of LVNC. The measurements in this study were obtained in the parasternal short-axis view (Figure 1) in end-systole.[51] Currently, this remains the most widely accepted and clinically applied echocardiographic criteria for diagnosing LVNC. An amendment to the Jenni criteria was proposed by Gebhard and colleagues,[30] who retrospectively compared the myocardium of patients with LVNC to patients with at least moderate aortic stenosis, and suggested compacted myocardium with an absolute value less than 8mm could further differentiate LVNC.

Another retrospective analysis[53] of 380 possible cases of LVNC used digital planimetry for accurate quantification of myocardial noncompaction area and proposed that in the apical four-chamber view (systole or diastole), total noncompaction area of up to 2.5 cm^2 was deemed to be mild, and 2.5-5 cm^2 was moderate and greater than 5 cm^2 suggestive of severe noncompaction.[53] Whilst this has not been pathologically and prospectively validated, it is the first criteria to consider the diagnosis and grading of LVNC using area, rather than length ratios.

The third major criteria were proposed by Stollberger and colleagues[52] and involved the quantification and morphology of trabeculae within myocardial layers in a large postmortem analysis of 115 patients with LVNC, with measurements taken across the full cardiac cycle. In end-diastole, after identifying the characteristic dual-layered myocardium, they proposed the presence of greater than three trabeculae apical to the papillary muscles, as specific for LVNC. This was done to prevent mistaking the papillary muscles for trabeculae. These criteria[52] also require demonstration of either flow by colour Doppler imaging or the presence of echo enhancing agent within the intertrabecular recesses (Figure 2). Likewise, Paterick and colleagues[54] suggested imaging through the entire cardiac cycle for better characterisation, although they did also propose measuring trabeculation size as a fraction of compacted myocardial thickness to improve specificity. In addition to the quantification of trabeculae size, Oechslin and colleagues[21] found the anatomic distribution of trabeculae of LVNC to be helpful, as they tend to be apical, inferior and lateral in LVNC.

Advanced echocardiographic techniques may improve the sensitivity and specificity of diagnosing LVNC. The use of 3D echocardiography has been shown to have higher spatial resolution, and accuracy hence has a significant advantage over standard 2D echocardiography in determining the extent of noncompacted myocardium.[55,56] The use of echocardiographic contrast such as Definity® or Optison can further improve diagnostic accuracy, by improving endocardial definition and allowing for better visualisation of the myocardial segments, particularly the commonly affected apical and mid-ventricular LV segments (Figure 2).[57] Contrast can also better detect the low blood flow velocity in intertrabecular recesses, which may be missed if relying solely on colour Doppler flow imaging.[57]

Several studies have[58-60] reported reduced global longitudinal strain in LVNC and have identified impaired LV apical rotation and LV torsion rates. Furthermore, LV apical rotation and VL torsion rates were also shown to be superior and sensitive discriminators of LVNC, even with a normal LVEF. Segmental strain analysis may also assist with differentiating between the idiopathic dilated cardiomyopathy phenotype and LVNC, with a significant basal-to-apical gradient in noncompaction.[61] Finally, whilst diastology has not been extensively studied in patients with LVNC, one study[62] found tissue Doppler velocities in children, particularly lateral mitral annulus "*E*" velocity, to be significantly reduced in LVNC compared to controls, and at a cut-off of 7.8 cm/s was proposed to be able to predict children at risk of death and need for cardiac transplantation at 1 year.

Echocardiographic markers of left ventricular function also appear to have prognostic associations, similar to those seen in the idiopathic dilated cardiomyopathy phenotype. One retrospective analysis of 67 LVNC patients found that those who died during their follow-up period had higher left ventricular end-diastolic diameter (LVEDD) (6.7 ± 1.1 cm vs 5.6 ± 0.8 cm, $P = .006$) and lower biplane LVEF (28 ± 5% vs 46 ± 14%, $P = .001$) compared to survivors.[36] A lower LVEF was also found to be associated with more symptoms and carried an increased risk of mortality on multivariate analysis.

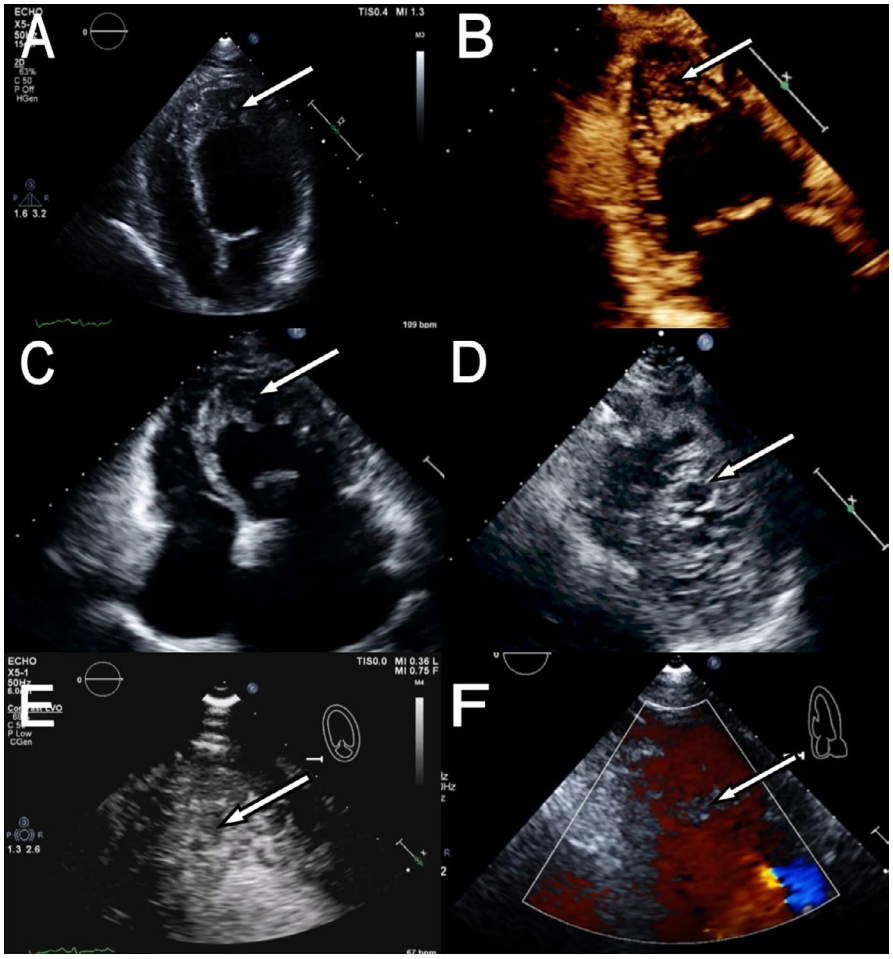

FIGURE 2 (clockwise from top left) A, Apical four-chamber view demonstrating characteristic apical noncompaction (arrow). B, Apical two-chamber view demonstrating apical noncompaction (arrow). C, Apical four-chamber view demonstrating LVNC (arrow) with resulting severe left atrial enlargement. D, Parasternal short-axis view at the level of the LV apex demonstrating noncompaction. E, Magnified view of LV apex demonstrating noncompaction, further highlighted by use of echocardiographic contrast. F, Colour Doppler flow within intertrabecular recesses seen in LVNC

Serial echocardiographic analysis also demonstrated both progressive LV impairment and improvement in LVEF in a small subset of patients. However, it is unclear whether this was influenced by optimal medical therapy or a reversible variant LVNC.

4.1.1 | Limitations of echocardiographic criteria

There have been a number of proposed criteria but there is a lack of consensus for a universally accepted "gold-standard" parameter for echocardiographic diagnosis of LVNC. Current diagnostic criteria are based on different parameters derived from small case series,[63] which have been shown to have low reproducibility when applied by two specialist reviewers.[64] A number of other studies have had similar conclusions. One retrospective study,[65] which applied the three major LVNC diagnostic criteria (Chin, Jenni and Stollberger) to 190 patients with LV systolic impairment, found an overall LVNC prevalence of 23.6% in Caucasian patients and 35.5% in Black patients. Application of the diagnostic criteria to Caucasian and Black controls revealed that 8.3% and 13.3%, respectively, also fulfilled the diagnostic criteria. Another study of 1146 asymptomatic control athletes by Gati and colleagues[11] also concluded oversensitivity of the Chin and Jenni criteria, with 8.1% fulfilling both criteria.

Furthermore, there is often poor visualisation of the LV apex which is the region most commonly involved in LVNC, due to operator dependence and patient variables including body habitus and chest wall deformity. Current criteria also require optimal visualisation of the LV endocardium and myocardium in multiple planes, and as LVNC is often segmental, suboptimal image quality can miss areas of significance. Poor visualisation of the LV apex, the region most commonly involved in LVNC, along with the anterior and lateral walls, can also limit diagnosis. The morphology of trabeculation, which is best examined in the parasternal short-axis views, may result in overestimation of trabecular morphology if not absolutely perpendicular to the long axis of the LV. Finally, whilst isolated right ventricular noncompaction is rare, poor visualisation with standard echocardiographic views further limits application of the current criteria.[63] The current criteria have only been validated in the left ventricle and hence may not be suitable for use in diagnosing right ventricular noncompaction, particularly since the right ventricle characteristically has more prominent trabeculation. Case reports of isolated right ventricular noncompaction in the literature

suggest correlation with cardiac MRI,[66,67] transoesophageal echocardiography[68] or relying on standard transthoracic apical views.[69,70]

The role of TTE in monitoring and prognosticating LVNC remains limited. Whilst one study suggests that deeper intertrabecular recesses may be associated with a greater risk for thrombus formation,[21] the use of TTE following initial diagnosis remains primarily to quantify and monitor the LV ejection fraction, which has been shown to be have a linear correlation with morbidity and mortality.[21] Whilst TTE, with contrast enhancement, is widely used as the first-choice imaging modality for diagnosis of LV thrombus primarily to its comparatively low cost and availability, a recent systematic review found that cMRI with LGE was the superior method for LV thrombi detection (sensitivity 88% and specificity 99%) compared to contrast TTE (sensitivity 23%-61% and specificity 96%-99%).[71]

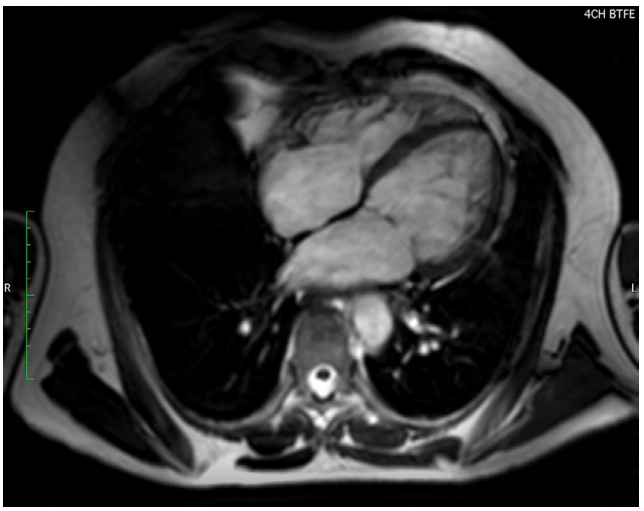

FIGURE 3 Axial cardiac MRI image demonstrating biventricular myocardial noncompaction

4.2 | Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging (cMRI) provides superior spatial resolution of the mediastinum (Figure 3) and, unlike echocardiography, can help accurately evaluate congenital heart disease and extra-cardiac thoracic pathology, which is often associated with LVNC. The advent of balanced steady-state free procession (SSFP) sequencing has reduced acquisition times and improved image quality.[72] Whilst it may not be used as the initial diagnostic modality due to the cost and limited availability, it is widely considered more sensitive than standard TTE in characterising myocardial trabeculation, detecting ventricular thrombi and imaging the most commonly affected apical and lateral LV segments.[73,74] Furthermore, the identification of myocardial fibrosis using late gadolinium enhancement (LGE) and correlation to the risk of ventricular arrhythmias has allowed prognostication.[75-77] Table 2 summarises the current major cMRI criteria used to diagnose LVNC.

The most widely accepted criteria for cMRI diagnosis of LVNC was proposed by Petersen and colleagues,[72] who studied seven patients with LVNC on the basis of imaging features, but with at least one supporting clinical feature: either family history; an associated neuromuscular disorder; or history of systemic embolisation, LV dysfunction or ventricular arrhythmia, in order to increase the pretest probability of recruited patients. Imaging findings were compared across normal and athlete controls, patients with HCM, DCM and aortic stenosis. Using cMRI, they highlighted the high prevalence (70%) of trabeculae and noncompaction, even in healthy hearts. They found apical and lateral segments to be most greatly affected across all study groups, but the key difference in pathological LVNC was a higher ratio of NC:C. In particular, they suggested increasing the ratio (>2.3 NC:C) and making the measurements in diastole to better appreciate the dual-layered myocardium and to improve accuracy. They found this cut-off to have 86% sensitivity and 99% specificity for LVNC. The major limitations of these criteria are that they were derived from small studies and were biased for LVNC patients that had clear supporting features which increased pretest probability. Furthermore, the diagnostic criteria remain subjective when interpreting the "most severely affected region" and thus require discretion in the planning and acquisition of relevant long-axis images using orthogonal planning scouts.

Jacquier and colleagues[78] proposed an alternative cross-sectional assessment approach by obtaining trabeculated LV mass. They proposed a trabeculated LV mass >20% of the total global mass as a reliable and reproducible definition of LVNC. However, the study population notably lacked ethnic diversity, since there was the absence of patients with African descent, who have previously been shown to have a higher prevalence of nonpathological LV trabeculation. Secondly, the LV mass calculations all included pooled intertrabecular blood within the noncompacted mass, which led to significant interpatient variability, and subsequent overestimation, a major limitation of this technique. Choi et al proposed a similar strategy but with volume[79] and suggested that a trabeculated LV myocardial volume >35% of the total LV myocardial volume is diagnostic of LVNC with high specificity (89.7%) against controls (but not for differentiation between LVNC and DCM).

Stacey and colleagues[80] subsequently compared the Petersen and Jacquier criteria with traditional end-systolic ratio of NC:C > 2 proposed in the Jenni criteria[51] and found the latter to have a stronger association with arrhythmias, clinical heart failure and subsequent hospital admissions.

In 2012, Grothoff and colleagues[81] described a method of measuring the LV myocardial mass index of noncompacted myocardium, both as an absolute value and as a percentage of total LV myocardial mass, proposing cut-offs of 15 g/m^2 and

TABLE 2 Major cardiac MRI criteria for diagnosis of LVNC

Author and Year	Petersen (2005)[72]	Jacquier (2010)[78]	Grothoff (2012)[81]
No. of Patients	177 patients (LVNC, healthy controls, healthy athletes, HCM, DCM, hypertension, aortic stenosis)	64 patients (LVNC, healthy controls, DCM, HCM)	57 patients (LVNC, healthy controls, DCM, HCM)
Criteria	(I) NC/C myocardial ratio >2.3 in end-diastole Note: apex excluded from measurement due to physiologically thinner compacted myocardium	(I) Trabeculated LV mass >20% of global LV mass in end-diastole	(I) LV myocardial mass index on noncompacted tissue ($LVMMI_{NC}$) >15 g/m^2 (II) $LVVMI_{NC}$ as a percentage of total LV myocardial mass index >25% (III) Increased trabeculation in LV basal segments and NC/C ratio ≥3:1 (end-diastole in short-axis)

25%, respectively. In this study, LVNC diagnosis was made using the Jenni echocardiographic criteria,[51] with at least one clinical feature as suggested by Petersen cMRI criteria.[72] Similarly, Choudhary and colleagues[82] also aimed to quantify noncompaction, but used the large difference in relative signal intensity of myocardium and blood pool on SSFP imaging to allow quantification of NC:C ratio. A high NC mass correlated with the presence of arrhythmia and systolic dysfunction at time of scan; however, longitudinal data were not available. Another study used a novel method of quantifying trabeculae,[83] by using fractals to quantify the complexity of the endocardial contour. This included an ethnically diverse subject population, and they demonstrated a higher fractal dimension (FD) in Black patients. They propose FD (at a global cut-off of 1.26) could be an alternative and reproducible measure of abnormal trabeculation in LVNC.

A unique and significant advantage of cMRI is in the identification of myocardial fibrosis, which is known to be found in patients with LVNC, based on early postmortem analysis.[51] Whilst LV trabeculation alone was not shown to be prognostic in a prospective study,[84] Dodd and colleagues[76] proved that LGE, considered a surrogate to myocardial fibrosis, correlated with the extent and severity of LVNC, based on clinical parameters of ejection fraction, and history of heart failure symptoms, arrhythmia and thromboembolism. This has been corroborated with subsequent studies[75,85] which have also shown LGE to be an important predictor of future arrhythmia burden, independent to ejection fraction. A recent meta-analysis of four studies consolidated this by demonstrating LGE to be directly related to risk of sudden cardiac death and overall adverse cardiovascular outcome.[77] A higher ratio of noncompacted to compacted myocardium on cMRI has also been associated with sustained ventricular tachycardia on Holter monitoring.[82]

4.2.1 | Limitations of cardiac magnetic resonance imaging criteria

The significantly higher cost of cMRI, compared to TTE, greatly limits widespread usage. Whilst patient factors affect image quality, they are not as influential as with echocardiography, although acquisition times are still long and the prolonged breath-holding required may not be tolerated. cMRI also remains contraindicated in many patients with cardiac devices and in end-stage kidney disease due to the risk of nephrogenic systemic fibrosis associated with gadolinium.

Finally, despite the multiple criteria published for cMRI in diagnosing LVNC, like echocardiography, there remains an absence of a globally accepted framework. In fact, much of the current diagnostic criteria were derived through receiver operator characteristic (ROC) curves of the respective studies with no formal validation.

The difference in accuracy of the various cMRI criteria was explored in a large case series[86] of 700 consecutive LVNC referrals, where the utility of the four major diagnostic cMRI criteria was examined, that is Petersen, Stacey, Jacquier and Captur. The prevalence widely varied, 39%, 23%, 25% and 3%, respectively, with the Petersen criteria being the most sensitive. This study found no association with adverse cardiovascular outcomes at 7 years. Similarly, Zemrak and colleagues[7] followed asymptomatic patients diagnosed with LVNC using the Petersen criteria (25.7% of patients) over a 9.5-year period and found no deterioration in LV volumes or function, even in patients with excessive trabeculation. Incidentally, there are major criticisms of this study. The entire study population was recruited from an American Multi-Ethnicity Study of Atherosclerosis registry, which had an overall low clinical pretest probability of LVNC. Furthermore, generalisability was impaired by a significantly higher African American population, known to have a higher incidence of benign trabeculation.

Further limitations highlighted were the oversensitivity of the most widely used Petersen criteria. The study by Kawal et al[87] found 43% of 323 normal controls with low pretest probability fulfilled the criteria in at least one myocardial segment; and Amzulescu et al[88] who found prominent trabeculation or fulfilment of the Petersen criteria in a cohort of DCM patients had no influence on cardiovascular outcomes over a 3.4-year period. For this reason, it has been suggested that LVNC should not be formally diagnosed in the absence of

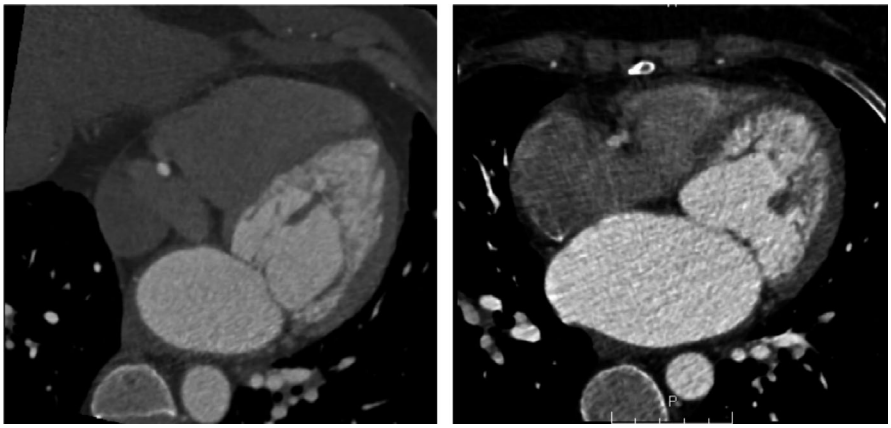

FIGURE 4 Axial CT coronary angiography images demonstrating left ventricular noncompaction

known associations, such as malignant arrhythmia, neuromuscular disorders, thromboembolic events or family history.[89]

4.3 | Computed tomography

Computed tomography (CT) is a novel imaging modality in diagnosing LVNC. Like echocardiography and MRI, CT is able to delineate the characteristic two-layered myocardium with prominent trabeculae (Figure 4). However, widespread use is limited by implications of radiation and iodine contrast, as well as its inferiority to MRI with regard to resolution and characterisation of myocardial tissue.

There have been two groups[90,91] that have proposed CT diagnostic criteria for LVNC. Both studies were relatively small (8 and 10 patients) and compared LVNC patients to healthy controls as well as other aetiologies of cardiomyopathy. Both studies were retrospective and examined patients who had undergone standard CT coronary angiography with electrocardiographic gating to rule out coronary artery disease. By measuring NC/C ratios in short axis in multiple ventricular levels, both groups concluded that LVNC could also be reliably diagnosed with similar NC/C cut-offs (used in cMRI) of 2.2 and 2.3, respectively, at end-diastole and in greater than 2 myocardial segments.[90,91] Unfortunately, the generalisability of these findings is limited by the small scale of their studies, and with a lack of a "gold-standard" for comparison, further work is required. Nevertheless, it remains unique as the only modality able to evaluate left ventricular architecture and coronary artery anatomy concurrently. It is also a viable alternative imaging modality in patients with equivocal echocardiograms and contraindications to MRI.

5 | CONCLUSION

Left ventricular noncompaction has been classified as a familial cardiomyopathy, with growing evidence towards certain associated genetic mutations. However, uncertainty remains with regard to its aetiology and prognostic significance. While echocardiography is likely to remain the first line investigation of choice in the majority of patients, better integration of advanced techniques such as contrast and speckle tracking imaging may improve the diagnostic framework in the future. cMRI can be used either as an initial modality or as an adjunct. It is considered superior to other modalities, with the potential to have more reproducible criteria, through semi-automated calculations, as well as the unique ability to detect myocardial fibrosis via LGE and better define sequelae such cardiac thrombus. Finally, whilst CT remains novel with limited data supporting routine clinical utility, its promise lies in the benefit of screening for coronary artery disease simultaneously.

Overall, the current imaging criteria are thought to overdiagnose LVNC—so much so that there has been a push for a change in nomenclature, from noncompaction to "excessive trabeculation" due to concerns regarding aetiology, overdiagnosis and a notable lack of longitudinal prognostic correlation. Thus, it is vital that patient pretest probability is considered when interpreting imaging results. Whilst individually each of the criteria reflect a poor level of specificity, a shift towards more automated measurements and an integrated clinical, electrocardiographic and multimodal imaging approach may be more likely to yield a clinically significant diagnosis.

CONFLICT OF INTEREST

None declared.

ETHICAL APPROVAL

This article does not contain any studies with human participants or animals performed by any of the authors. It is a narrative review of current literature.

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