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Left Ventricular Noncompaction

Ana G. Almeida

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Abstract

Left ventricular noncompaction (LVNC) is accepted as an unclassified (the American Heart Association) or a genetic cardiomyopathy (the European Society of Cardiology), but some argue that this phenotype may be a morphologic trait shared by different cardiomyopathies. This chapter covers the state of the art on the pathology, underlying mechanisms, its clinical manifestations, and diagnosis and treatment modalities of LVNC. LVNC may be defined as follows: an inner non-compacted layer with prominent left ventricular trabeculae and deep intertrabecular recesses and a thin outer compacted layer. Mechanisms are still debatable, with the hypothesis of compaction arrest during embryogenesis as the most accepted theory. Genetic data support LVNC as a distinct cardiomyopathy, although evidence for LVNC as a shared morphological trait is not ruled out, since LVNC may be associated with other cardiomyopathies, congenital heart diseases and in some cases may be acquired. Diagnosis is based on imaging and may be confirmed by the use of genetics. Clinical picture and prognosis and the management options are discussed.

Keywords: cardiomyopathy, Noncompaction, Echocardiography, cardiovascular magnetic resonance, prognosis

1. Introduction

Left ventricular noncompaction (LVNC) is a myocardial disorder that has been thought to occur due to the failure of left ventricle (LV) compaction during embryogenesis, leading to distinct morphological characteristics in the ventricular chamber [1]. In its first description, about 80 years ago, LVNC occurred in association with complex congenital heart diseases. More recently, an isolated form of LVNC was described [2], followed by many other reports. The involvement of the right ventricle in the noncompaction process has been increasingly

identified, and the condition is now included among the cardiomyopathies, but currently there is an intense debate whether LVNC is a distinct entity or a trait common to several cardiac conditions [3].

2. Anatomy and pathology

Left ventricular noncompaction (LVNC) is defined by essential markers: an inner noncompacted layer with prominent left ventricular (LV) trabeculae and deep intertrabecular recesses, and a thin compacted layer. There is a spectrum of morphologic variability, ranging from hearts with different degrees of noncompaction extension and amount, and right ventricular involvement.

From hearts obtained from autopsies or transplantation, LVNC diagnosis is based on the presence of a two-layered ventricular wall, comprising a thinner compact epicardial layer and an inner noncompacted layer, with prominent trabeculations associated with deep, intertrabecular recesses that communicate with the ventricular cavity but not with the coronary circulation [2, 3].

Noncompacted areas are commonly located at the LV apex and mid-apical wall segments, but typically spares the interventricular septum. When associated with hypertrophic cardiomyopathy phenotype (HCM), the hypertrophied septum coexists with the LVNC phenotype. Other described associations include dilated cardiomyopathy (DCM) and, more rarely, restrictive cardiomyopathy (RCM) or arrhythmogenic right ventricular cardiomyopathy (ARVC). Besides the relationship of LVNC with other cardiomyopathies, which may share the same genetic basis, there has been considerable controversy regarding the differentiation from normal LV trabeculation, which seems to occur in some normal asymptomatic individuals as found in analysis from the MESA study [4].

Histopathology has shown continuity between the endothelium of inter-trabecular recesses and that of the endocardium, distinguishing LVNC from persistent sinusoids. Other findings have included loosely organised myocytes and endocardial and subendocardial replacement fibrosis suggestive of ischaemic necrosis, which has been demonstrated by imaging techniques *in vivo* [5].

LV dilatation and ischemia are frequently present, and thrombus formation in the recesses may occur, which may be associated with possible thromboembolic events.

3. Aetiology and mechanisms

There are several etiologic hypotheses for LVNC. It may occur as an isolated disease (isolated LVNC) or in association with genetic diseases and congenital defects, as observed more commonly in infancy. The condition may also be sporadic and acquired, in physiological or pathologic conditions, and may also be permanent or transient. Thus, LVNC can originate during embryonic development or be acquired later in life.

The theory that supports the embryogenic hypothesis has been based in observational foetal studies showing the coexistence of LVNC with heart block and congenital heart diseases and from experimental studies on LVNC [6]. In humans, the embryonic myocardium is composed of a loose meshwork of interwoven fibres separated by deep recesses, which communicate with the LV cavity, allowing an increase in the myocardial surface area and the exchange diffusion from the cavity. From the 5th–8th weeks of embryogenesis, LV trabecular compaction occurs simultaneously with the invasion of the myocardium by the coronary vasculature coming from the epicardium. The LV compaction progresses from the heart base to the apex and from the epicardium to the endocardium [1]. LVNC is thus thought to result from the arrest of trabecular compaction during this phase of embryogenesis. A second embryogenic hypothesis suggests that LVNC results from the inhibition of the regression of embryonic structures that would maintain the looseness of cells or of cell bundles [7].

On the other hand, evidence supports the hypothesis that the pathogenetic mechanisms leading to noncompaction may occur in adult life, ending in acquired forms of LVNC and supporting a non-embryogenic theory. This is the case of young athletes, pregnant women, patients with sickle cell disease, and renal failure, which may present the phenotype of LVNC. In athletes, the phenotype seems to relate to intensive training, but in a small proportion of 0.9% has been found to develop ultimately LV dysfunction suggestive of a LVNC cardiomyopathy [8]. In pregnancy, an important proportion of women, described as up to 25% were found to develop LVNC phenotype *de novo*, which was reversible. This pattern was not shown to be associated with deleterious clinical events and has been proposed to result from a response to increased loading conditions [9]. Also, in sickle cell disease, this pattern has been found and hypothesised to result from chronic anaemia and increased preload, resulting in a stimulus for hypertrabeculation [10].

4. Genetics

The LVNC trait may be familial, inherited, or non-familial, sporadic. Non-familial forms are diagnosed when LVNC is proven absent in relatives. As presented above, sporadic LVNC can be acquired and may be transient, as in highly trained athletes, sickle cell anaemia patients, and pregnancy. Many familial cases identified to date are associated with mutations in the same genes that cause other types of cardiomyopathies but may also occur isolated.

In fact, several studies suggest that noncompaction of the LV myocardium is a genetically heterogeneous disorder [11], with a familial and a sporadic form. Studies of the familial form have shown that LVNC may be transmitted as an autosomal dominant inheritance with incomplete penetrance, as an autosomal recessive, and as X-linked traits. Sporadic cases of LVNC and *de novo* mutations have also been recognised. To date, several disease *loci* have been identified.

The Barth syndrome was the first recognised genetic LVNC, characterised by dilated cardiomyopathy associated with LVNC. It is an X-linked disease with mutations in the G4.5 gene, located at Xq28, which encodes the tafazzins (a family of proteins) with acetyltransferase

functions in the mitochondria. This mutation was also identified in an X-linked severe neonatal LVNC, allelic with the Barth syndrome.

Another mutation, located in the α -dystrobrevin gene, was identified subsequently in patients with LVNC and associated with congenital heart diseases. [12]; α -dystrobrevin is a cytoskeletal protein component of the dystrophin associated glycoprotein complex, which links the extracellular matrix to the dystrophin cytoskeleton of the muscle fibre. This mutation was associated with a significant phenotypic variability with variable severity.

Mutations in the Z-line protein Cypher/ZASP have been identified in association with LVNC and dilated cardiomyopathy. This protein appears to play an important role in the maintenance of the normal myocyte architecture of cardiac and skeletal muscle.

Another LVNC phenotype has been reported in association with a mutation in the Lamin A/C protein, which has been linked to dilated cardiomyopathy, conduction system diseases, and muscular dystrophy.

Recently, LVNC has been linked to sarcomere gene mutations, causing hypertrophic cardiomyopathy. In a study of 247 families with cardiomyopathy, a mutation in the α -cardiac actin gene, essential for cell maintenance, was associated with LVNC, apical hypertrophic cardiomyopathy, and septal defects. Moreover, in a large study of patients with phenotype of LVNC, nine heterozygous mutations were identified in a proportion of the probands in genes encoding α -myosin heavy chain (MYH7), β -cardiac actin (ACTC), and cardiac troponin T (TNNT2), with 100% penetrance in the family members [13]. Another study identified a mutation in the sarcomeric TPM1 gene, at 15q22.1, in a family with LVNC and a history of sudden death.

Some studies have suggested that the phenotype for isolated LVNC may appear during adult life in patients with muscular dystrophy and with myocarditis. Nevertheless, these cases were not followed serially clinically and with an imaging modality, and the significance of the LV hypertrabeculation described is still unclear.

Although, many genes associated with LVNC are associated with additional phenotypes, like hypertrophic or dilated cardiomyopathies or congenital heart defects, several mutations were described in association with isolated LVNC. For instance, mutations in gene MIB1 were identified in two families with LVNC and autosomal dominant inheritance [14]. Recently, an important role in trabeculation for endocardial expression of a Notch ligand, Fkbp1a, was reported, [15] which was confirmed in a mouse model, suggesting its direct involvement in the LVNC phenotype.

A large number of genes have been identified in relation with the LVNC phenotype in association with other cardiomyopathies, congenital and acquired heart diseases, as well as part of syndromes; specific genetic mutations have been related with the LVNC phenotype, and there is a need for large databases and systematic follow-up with clinical and imaging to obtain definite conclusions on the clinical and prognostic significance of LVNC phenotype in relation with the genotype.

The role of modifying genes or epigenetics and load changes may influence the relationship of genotype-phenotype and contribute to explain the phenotype variability.

5. Epidemiology

LVNC has been considered rare, and its incidence and prevalence are uncertain, but is commonly diagnosed, due to increased awareness and more accurate imaging methods.

LVNC has been described to occur in infants (0.81 per 100,000 infants/year), children (0.12 cases per 100,000 children/year), and adults (prevalence suggested as 0.014% of patients referred for echocardiography and 0.05% among all adult echocardiograms in a large institution) [16, 17]. In a large population of patients with LV ejection fraction <45%, the prevalence was 3.7% [18]. However, LVNC can occur as an isolated myocardial trait or be associated with cardiomyopathies (hypertrophic, restrictive, dilated, and arrhythmogenic), congenital heart diseases, and complex syndromes affecting multiple organs and tissues, including mitochondrial diseases caused by mutations in both nuclear and mitochondrial genes, leading to increased uncertainty on the prevalence.

In fact, given the variability of clinical presentation, the prevalence of LVNC is largely unknown.

6. Clinical manifestations

Heart failure, ventricular and atrial arrhythmias, and systemic embolic events comprise the typical complications in patients with LVNC and may occur at any age. However, the initial presentation is variable and the patient may be asymptomatic (frequently diagnosed during a family screening) or present any of the clinical features and complications, including sudden death.

In its severe neonatal form, LVNC may manifest as heart failure or ventricular arrhythmias, which may lead to sudden death [2]. Studies of older children and adults have reported a high incidence of severe manifestations [7, 17, 19–22] such as LV dysfunction, thromboembolic events, which probably originate in the deep intertrabecular recesses, arrhythmias, and sudden death. Other studies, however, have found a much lower incidence of complications, suggesting subclinical or milder cases [23]. **Table 1** presents clinical findings from published studies.

There is no agreement so far on the natural history and outcomes in LVNC because most studies are retrospective, populations are limited and use distinct study methods.

Heart failure seems to occur frequently, as over 50% of symptomatic patients, and most researchers also report ventricular arrhythmias, cardiovascular deaths, and sudden cardiac death. A recent registry of a large population of adult patients with LVNC found heart failure in 74%, LV systolic dysfunction in 88%, strokes in 10%, and syncope episodes in 9%, [20] suggesting the need for long term surveillance of LVNC patients. Other series have found a more benign prognosis [23]. A recent published series describe a mean freedom from death or transplantation of 97% at 46 months in adults with LVNC.

Author	Chin	Ichida	Oechslin	Murphy	Lofiego	Aras	Stanton	Greutmann
Patients (N)	8	27	34	45	65	67	30	132
Population	Paediatric	Paediatric	Adult	Adult	Adult	Adult	Adult	>14 years-old
Follow-up	≤5 years	≤17 years	44 months	46 months	46 months	30 months	2.5 years	2.7 years
Family history (%)	50	44	18	51	31	33	–	23
Embolic events (%)	38	0	21	4	5	9	0	4
Ventricular tachycardia (%)	38	0	41	20	6	36	27	4
Heart failure (%)	63	30	68	67	34	34	–	13
CV death or transplantation (%)	0	11	47	2	24	15	10	23
Sudden death (%)	13	0	18	2	5	9	10	9

LVNC, left ventricle noncompaction; CV, cardiovascular.

Table 1. LVNC clinical characteristics and outcomes.

Predictors of death and heart transplantation have been difficult to assess due to the variability of the phenotype and the variable underlying pathophysiological scenarios. However, the presence of heart failure, history of sustained ventricular tachycardia or systemic thromboembolism seem to be associated with an unfavourable prognosis among other phenotypes with distinct outcomes [21, 22]. In a recent study, mortality did not differ significantly between patients with isolated LVNC and control patients with dilated cardiomyopathy, [24] suggesting that LV dysfunction rather than the phenotype itself is the risk-increasing mechanism. However, this finding has not been confirmed by others [17].

7. Diagnosis

Cardiac imaging is essential for establishing the diagnosis of LVNC, not only to detect the characteristic features and application of the diagnostic criteria, but to assess the systolic and diastolic function, valve regurgitation, pulmonary hypertension, the presence of thrombus in the ventricular recesses. However, there is still a lack of agreement from the medical community regarding the best technique and the most reliable diagnostic criterion. **Table 2** summarises the most frequently used imaging criteria for LVNC diagnosis.

7.1. Echocardiography

Cardiac ultrasound is a first-line technique for diagnosing LVNC, since it is a bedside modality, uses no radiation and is readily available. This modality allows the detection, location,

Jenni et al. [25]	Stöllberger et al. [26]	Petersen et al. [30]	Jacquier et al. [31]
Echo	Echo	CMR	CMR
- Ratio noncompacted/compacted >2.0	- Three trabeculations protruding from the LV wall, apically to the papillary muscles, visible in one image plane	- Ratio noncompacted/compacted >2.3	- Trabecular LV mass >20% of global LV mass,
- Intratrabecular recesses filled by blood flow from the LV cavity	- Intertrabecular spaces perfused from the ventricular cavity on colour Doppler imaging	- Acquisition: long-axis end-diastolic images	- Acquisition: end-diastolic images
- Acquisition: short-axis; end-systolic images	- Trabeculations with the same echogenicity as the myocardium and synchronous with LV - Acquisition: oblique views to differentiate false chords, aberrant bands, trabeculations		

LV, left ventricle.

Table 2. The most frequently used diagnostic criteria in left ventricle noncompaction.

and confirmation of this condition. The first criterion was proposed by Chin et al. [2], who recommended the assessment of the ratio of X/Y dimensions in diastole—where X is the distance from the epicardial surface to the trough of the trabecular recesses, and Y the distance from the epicardial surface to the peak of the trabeculation. An X/Y ratio of up to 0.5 would be required for the diagnosis. The more widely used criterion, however, was proposed by Jenni et al. in which the ratio of noncompacted and compacted myocardium, measured from end systolic short-axis images. If the ratio is >2, the criterion for LVNC is considered fulfilled [25] (**Figures 1 and 2**). Additionally, observation and quantification of the apical trabeculations are available by echocardiography, although sometimes challenging, and permit the use of the LVNC criterion proposed by Stöllberger et al. [26].

The inherent limitation of echocardiography in evaluating the LV apex and, often, other LV walls poses a diagnostic issue. If the image quality is poor, LVNC can be confused with apical cardiomyopathy, thrombus or fibroelastosis. The use of contrast echocardiography, which permits the visualisation of the trabeculations and the recesses that communicate with the cavity, may help in clarifying the diagnosis [27]. Additional information with prognostic impact may be derived from the evaluation of LV systolic and diastolic function, mitral regurgitation, pulmonary hypertension. Systolic dysfunction is frequently present in LVNC. It has been hypothesised that microvascular disease with impaired coronary flow reserve and myocardial necrosis, as well as a primary myocardial disease, is responsible for the functional abnormalities [5], although in other cases a DCM may be associated, The presence of thrombus in the ventricular recesses, although rare, has been described.

More recently, speckle tracking has revealed abnormal LV rotation and twist, and these findings are promising for diagnosis even in patients with normal ejection fraction [28]. Three-dimension echocardiography has been proposed as an alternative for detecting LVNC due to

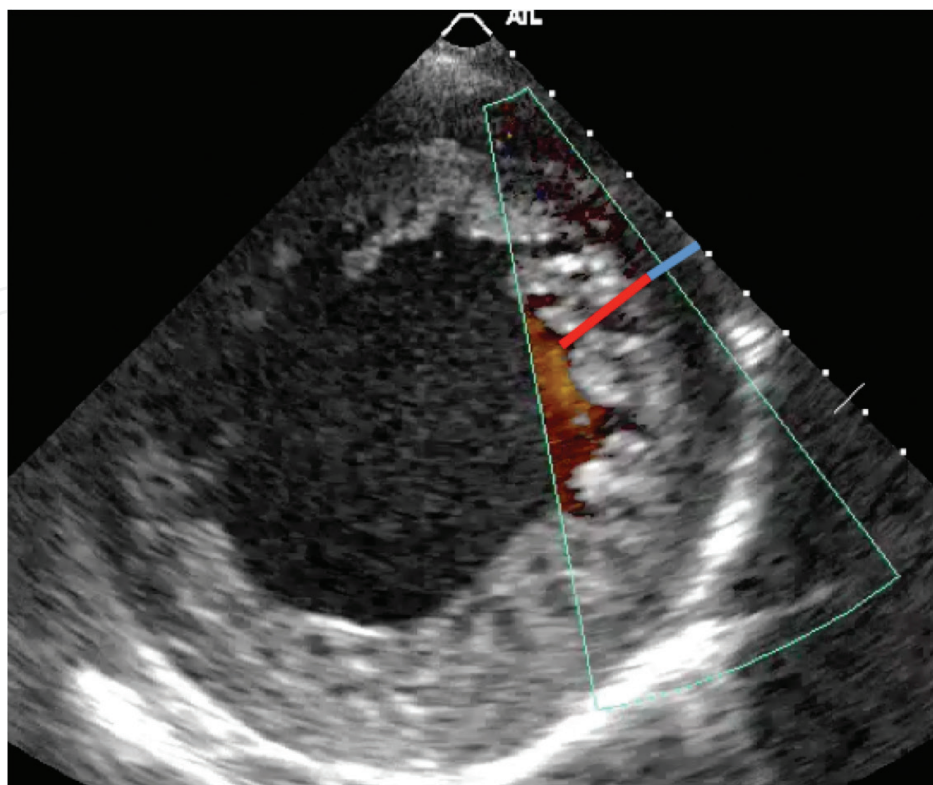


Figure 1. A systolic short-axis image from an echocardiogram of a 27-year-old patient with LVNC, showing the ratio measurement of compacted layer (blue line) to noncompact layer (red line) of >2 ; Doppler colour shows the blood flow in the recesses.

the lower dependence on the observer for image acquisition and higher reproducibility [29]. However, the image quality and resolution may be compromised in comparison with the conventional 2D, remaining uncertain its real value.

7.2. Cardiovascular magnetic resonance (CMR)

CMR is a non-ionising high-resolution technique without acoustic limitations, which reveals a wider extent of disease, particularly at the LV apex and the poorly observed segments, which are often problematic with echocardiography.

This modality confirms the presence of the anatomic features of LVNC, as well as an accurate and reproducible measurement of the noncompact and compacted myocardial layers (**Figures 3 and 4**). The diagnosis is supported if the end-diastolic thickness of the noncompact layer is ≥ 2.3 times the compacted one, as proposed by Petersen et al. [30]. This criterion yielded $>43\%$ of positive subjects in MESA study, although this population included only asymptomatic individuals, with low pretest probability of disease [4].

CMR confirmation of trabeculated LV mass $>20\%$ of global LV mass fulfils the criterion proposed by Jacquier et al. [31] although the feasibility and reproducibility of this methodology have been debated.

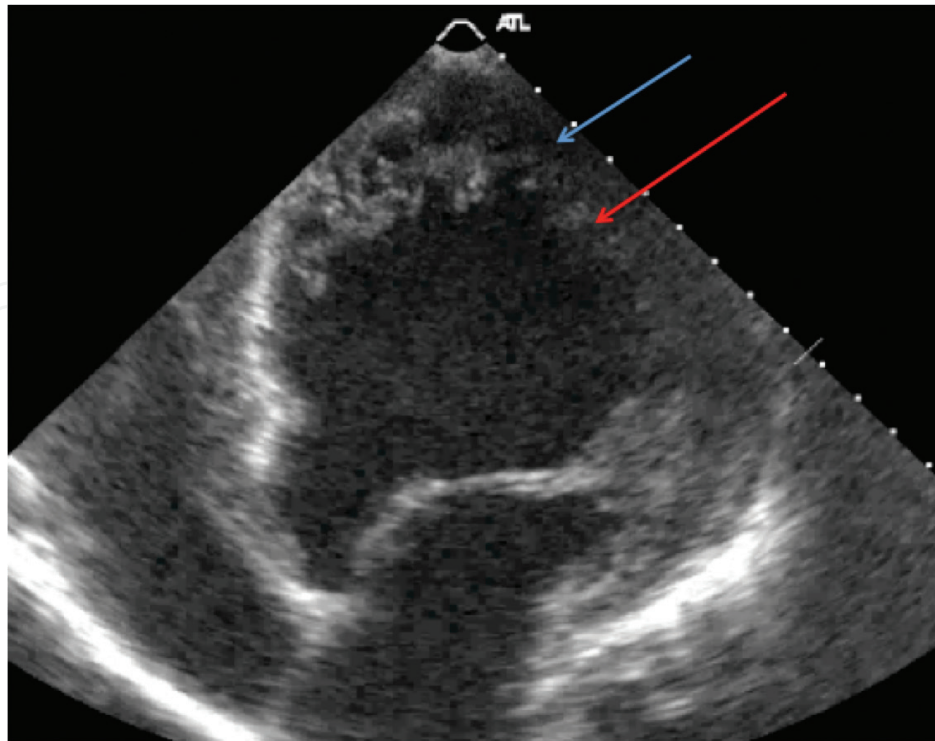


Figure 2. A diastolic four-chamber image from an echocardiogram of a patient with LVNC. Blue arrow—compacted layer; red arrow—noncompacted layer.

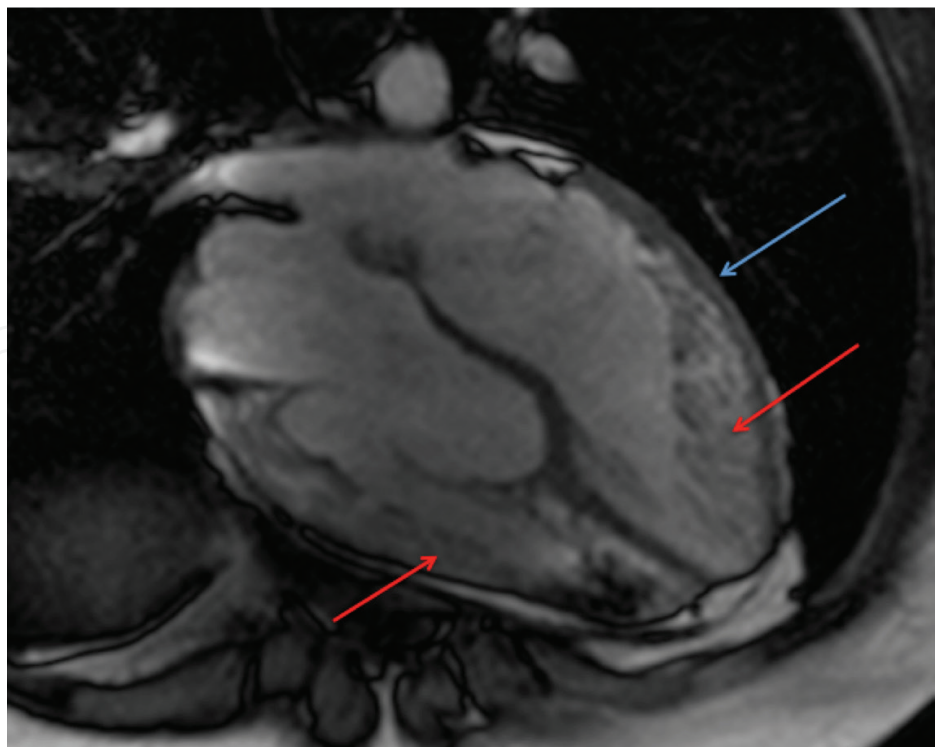


Figure 3. A diastolic four-chamber view from a magnetic resonance cine study of a 23-year-old patient with LVNC, showing biventricular noncompaction. Blue arrow—compacted layer; red arrows—noncompacted layers.

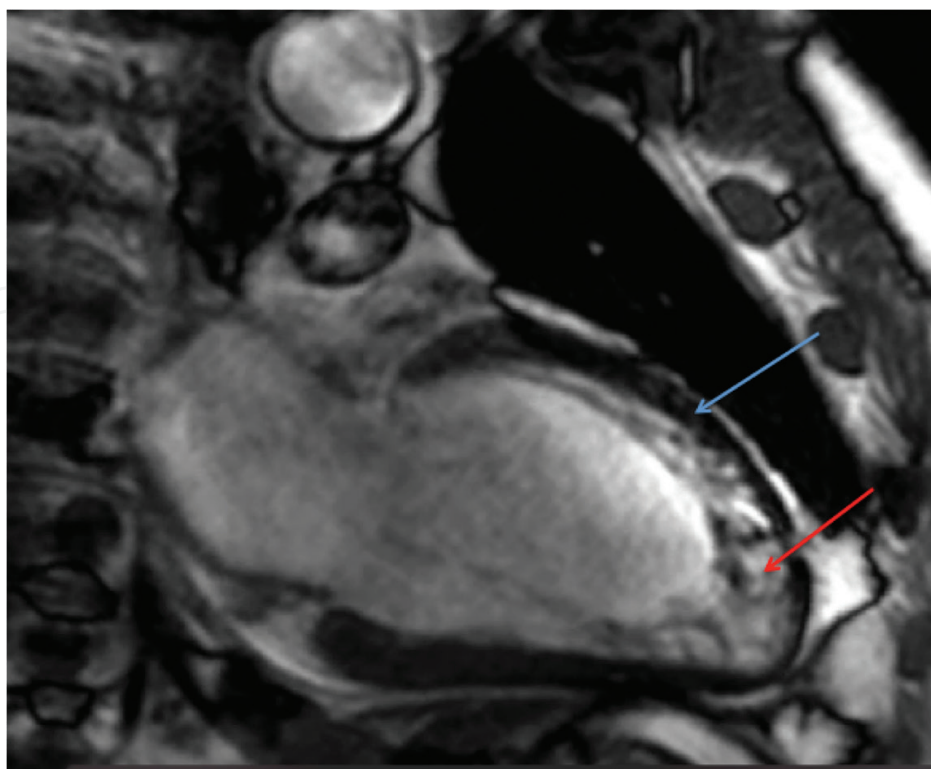


Figure 4. A diastolic two-chamber view from a magnetic resonance cine study of a patient with LVNC and arrhythmia. Blue arrow—compactated layer; red arrows—noncompactated layer.

Fractal analysis was also used to quantify LV trabeculae. In a study of 30 patients of Captur et al., the combination of end-diastolic measurements at basal, mid, and apical segments was found to be the best selector of LVNC cases from the normal population [32].

The combined use of echocardiography and CMR may contribute to lessening the risk of over diagnosing LVNC, which can occur with the isolated use of ultrasound, and overcome the limitations on reproducibility of echocardiography [33], but such an approach has not yet been validated.

Reliable evaluation of LV function is an additional advantage offered by CMR. Involvement of the right ventricle remains controversial because echocardiography presents inherent difficulties in analysing this chamber, but CMR has been increasingly detecting biventricular LVNC, although no specific criteria have been proposed so far.

Late gadolinium enhancement (LGE) CMR, as a surrogate marker of fibrosis, has been detected in patients with LVNC and confirmed by histology. A recent study suggests that the presence and amount of LGE is associated with more severe clinical [34]. Abnormal T2-weighting myocardial intensity and perfusion defects have been described as additional information obtained from CMR but its usefulness is not established so far.

7.3. Cardiac computed tomography

This modality has been proposed as an alternative to patients that have acoustic limitations to echocardiography and contra-indications for CMR, due to the high spatial resolution provided by this technique [35].

7.4. Electrocardiogram

Electrocardiogram (ECG) may be normal. ECG changes, when present, are non-specific and include LV hypertrophy and repolarisation abnormalities. Left bundle branch block is common, especially in patients with LV dysfunction. Wolff–Parkinson–White has been frequently detected in paediatric patients [36].

8. Management and prognosis

The true significance of noncompaction still remains a matter of debate, due to the genetic heterogeneity, the overlapping phenotype with other cardiomyopathies sharing the same genetic background, the high prevalence in neuromuscular diseases. These findings suggest that other factors may play a role in the development of LVNC disease [37]. Another important challenge is the clear differentiation of the LVNC phenotype from the normal heart, since this is associated with the risk of overdiagnosis.

There are no specific guidelines for management of LVNC since evidence supporting the management is limited. First of all, management includes confirmation of the diagnosis by echocardiography or CMR.

Guidelines suggest that familial LVNC should be diagnosed by echocardiographic screening of family members [38]. Echocardiographic screening is recommended for family members, given that the symptoms are variable and the risks include heart failure and sudden cardiac death.

According to current guidelines, mutation-specific genetic testing is recommended for family members and appropriate relatives, following the identification of an LVNC causative mutation in the index case. Moreover, this testing may be useful for patients where the cardiologist has established a clinical diagnosis of LV noncompaction based on examination of the patient's clinical manifestations (namely with increased pre-test probability or left ventricular dysfunction [39]) and family history, electrocardiographic and echocardiographic phenotype or when associated with another cardiomyopathy or congenital heart disease. Following genetic and imaging assessment, the possibility of an early diagnosis of LVNC increases, ensuring appropriate monitoring and prophylactic measures.

According to recent American Heart Association/American College of Cardiology Scientific Statement on Eligibility and Disqualification Recommendations for Competitive Athletes With Cardiovascular Abnormalities, "until more clinical information is available, participation in competitive sports may be considered for asymptomatic patients with a diagnosis of LVNC and normal systolic function, without important ventricular tachyarrhythmias on ambulatory monitoring or exercise testing, and specifically with no prior history of unexplained syncope (Class IIb; Level of Evidence C)" [40].

The main therapeutic objectives are the prevention and treatment of complications, using conventional measures. Thromboembolism, heart failure, and arrhythmias constitute the typical clinical features of LVNC to be addressed.

Anticoagulation for prevention of thromboembolism is probably only indicated in cases of LV dilatation and dysfunction, or when a previous history of embolic events is present, although

to date no data are available to support these options. For symptomatic ventricular arrhythmias, particularly the ones associated with LV and for heart failure, the treatment should follow current guidelines. In patients with severe LV dysfunction, ICD implantation and CRT therapy are measures to improve heart failure and prevent sudden death. In some cases, heart transplantation may be the option for patients with refractory heart failure [41].

9. Conclusion

The pathogenesis and diagnosis of LVNC remains a challenge. The disease may be secondary to genetic mutations that induce the myocardial pathology. However, phenotypes are heterogeneous, are frequently shared with other cardiomyopathy, suggesting the influence of additional modifiers or a common aetiology.

The detection of new genetic mutations and the evaluation of its relationship with phenotypes may shed light on the pathogenesis of this condition, which may have an impact on follow-up and management.

The current awareness of the disease and the availability of high-resolution imaging, namely CMR, have increased the number of diagnosed patients. There is, however, a risk of overdiagnoses. The genotype and phenotype heterogeneity suggests the need for multicentre studies involving large populations, allowing more

robust conclusions regarding all the important areas of LVNC including the clinical ground, genetics, pathogenesis, diagnosis, and management.

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Author details

Ana G. Almeida

Address all correspondence to: anagalmeida@gmail.com; amalmeida@medicina.ulisboa.pt

Faculty of Medicine of Lisbon University, University Hospital Santa Maria/CHLN/Academic Centre of Lisbon University, Cardiovascular Centre of Lisbon University (FCT), Lisbon, Portugal.

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