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Non-compaction Cardiomyopathy: Prevalence, Prognosis, Pathoetiology, Genetics, and Risk of Cardioembolism

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Abstract Left ventricular non-compaction (LVNC) is thought to arise from arrest of the normal process of trabecular remodeling or "compaction" that takes place during embryonic life and is characterized by the presence of a two-layered ventricular wall, with a compact epicardial layer and a non-compacted endocardial layer. It is an uncommon condition that can occur isolated or in association with other disorders, including congenital heart anomalies and mitochondrial or musculoskeletal disorders. Both familial and sporadic forms are recognized, and several responsible genes have been identified, although only a minority of patients can be successfully genotyped. The diagnosis is usually made by echocardiography, but cardiac magnetic resonance imaging has been used increasingly. Management is mainly empirical and directed at the major clinical manifestations: heart failure, arrhythmias, and systemic embolic events. This article will review the major features of LVNC and present new trends in the diagnosis and management of this intriguing condition.

Keywords Left ventricular non-compaction · Pathogenesis · Epidemiology · Genetics · Clinical presentation · Diagnosis · Management · Natural history · Prognosis

Abbreviations

ICD	Implantable cardioverter-defibrillator
LGE	Late gadolinium enhancement
LV	Left ventricle
LVNC	Left ventricular non-compaction
CMR	Cardiac magnetic resonance imaging

Introduction

Left ventricular non-compaction (LVNC) is a condition that has received increasing attention during the past three decades. The typical spongy appearance of the myocardium was first reported in association with congenital heart defects in 1926 [1] and may occur in association with several congenital anomalies, such as Ebstein anomaly, obstruction of the right or left ventricular outflow tracts, bicuspid aortic valve, cyanotic congenital heart disease, and coronary artery anomalies [2–4]. Some cases of LVNC in association with channellopathies have also been reported [5]. The first description of the persistence of myocardial sinusoids in the absence of any other heart disease was published in 1984 [6], and the term "non-compaction of left ventricular myocardium" was introduced in 1990 [7]. The distinctive feature of LVNC is a two-layered ventricular wall, comprising a thinner compact epicardial layer and an inner non-compacted layer, with prominent trabeculations associated with deep, intrabecular recesses that communicate with the ventricular cavity, but not with the coronary circulation, unlike what occurs with myocardial sinusoids, seen in association with pulmonary atresia with intact ventricular septum and other congenital heart diseases [2, 7, 8]. LVNC is also commonly found in association with neuromuscular or mitochondrial disorders [2, 9–12].

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LVNC is categorized as an unclassified cardiomyopathy by the World Health Organization/International Society and Federation of Cardiology and as a primary genetic cardiomyopathy by the American Heart Association [13, 14]. The more recent classification of cardiomyopathies proposed by the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases grouped LVNC as a familial unclassified cardiomyopathy and recognized that it is unclear whether this condition is a separate cardiomyopathy or merely a morphological feature shared by many phenotypically distinct cardiomyopathies [15].

Pathogenesis

LVNC is thought to arise from the arrest of the normal process of endocardial and myocardial morphogenesis during embryonic life, leading to the distinct morphological features of the condition [16]. At the end of the fourth week of gestation in the human embryo, myocardial trabeculations start developing, and at the eighth week of gestation, trabecular remodeling begins due to the increase in ventricular volumes and compression of the trabeculations [16]. This "compaction" process, which is more pronounced in the left than in the right ventricle, is also possibly stimulated by hypoxia in the outermost subepicardial layer of the myocardium as it coincides with the development of the epicardial coronary arteries and progresses from the epicardium to the endocardium, from the base to the apex, and from the septum to the lateral wall of the LV [16]. Thus, the time of arrest of the embryonic myocardial maturation determines the extent of non-compaction; this also explains why the LV apex is always involved [1]. Right ventricular involvement is described in less than one half of patients [17–19], but several authors dispute its existence, due to difficulties in distinguishing the normal highly trabeculated right ventricle from the pathological non-compacted ventricle [8]. A recent study showed that LVNC is associated with a greater right ventricle (RV) apical trabecular thickness, but not with an increase of the ratio between the thickness of the non-compact and compact myocardial layers in the RV, and that low RV ejection fraction may be associated with a worse prognosis in this population [20•]. Impairment of RV systolic function can also occur in patients with LVNC without RV hypertrabeculation [19].

There is no proof of an arrest in endomyocardial morphogenesis as the mechanism of LVNC, and it is not clear whether it can be acquired [12]. Echocardiographic studies suggest that non-compaction may become evident during serial examinations [1, 21], and genetic studies revealed that LVNC shares common mutations in sarcomere protein genes with dilated cardiomyopathy and hypertrophic cardiomyopathy, which typically develop during postnatal life [1]. These data raise the hypothesis that LVNC may also develop later in life, but its recognition in adult life does not permit to conclude whether LVNC represents a long-standing condition or a delayed morphological manifestation.

Epidemiology

The prevalence of LVNC varies considerably between series and is still not clear [22]. The reported prevalence in patients referred to echocardiography laboratories ranges between 0.14 and 1.26 % [23], but these numbers are most likely overestimations of the true prevalence due to selection bias. In a retrospective study in children, LVNC accounted for 9.5 % of all cardiomyopathies [24]. In the initial series of isolated LVNC, the median age at diagnosis was 7 years (ranging from 11 months to 22 years) [7], but this condition has been increasingly diagnosed in adults. In a recent series of eight patients, the median age at diagnosis was 58 years (ranging from 28 to 80 years) [25]. Men appear to be affected more often than women in most but not in all series [7, 17, 23, 25–27].

Genetics

LVNC is a genetically heterogeneous disorder, with both familial and sporadic forms [1]. Sporadic forms are identified in the majority of cases, and the familial forms may present as autosomal dominant, autosomal recessive, X-linked, or maternally inherited (matrilineal) mitochondrial inheritance, although autosomal dominant inheritance seems to be the most common [24, 28, 29]. Several genes responsible for familiar forms have been identified, including mitochondrial, cytoskeletal, sarcomeric, and ion channel genes [5, 28].

Mutations in the *G4.5* or taffazin (TAZ) gene, located at Xq28, which encodes an acyltransferase, were the first to be associated with a familial form of LVNC in children [21, 30]. Other mutations in this chromosome region are also associated with other myopathies with myocardial involvement and X-linked inheritance in the pediatric population, such as Barth syndrome, Emery-Dreifuss muscular dystrophy, and myotubular myopathy [18, 19, 20•, 21]. However, mutations in this gene are rare in the adult population, suggesting that non-compaction presenting in adulthood may be genetically distinct from pediatric cases [1].

A mutation in the α-dystrobrevin gene, a cytoskeletal protein that links the extracellular matrix to the dystrophin cytoskeleton of the muscle fiber, was identified in patients with LVNC associated with congenital heart diseases [9], while mutations in the Z-line protein Cypher/ZASP, also called LIM domain binding protein 3 (LBD3), a protein found in the cytoplasm of cardiac and skeletal muscle, have been identified in association with LVNC and dilated cardiomyopathy [31].

LVNC has also been reported in association with mutations in the lamin A/C protein, which is known to cause dilated cardiomyopathy, conduction system disorders, and muscular dystrophy [22]. Mutations in sarcomere protein genes, usually linked to hypertrophic cardiomyopathy, have been associated with the development of LVNC as well [32–34]. Klaassen et al. [35] found mutations in the genes encoding the sarcomere proteins beta-myosin heavy chain (MYH7), alpha-cardiac actin (ACTC), and cardiac troponin T (TNNT2) in 11 of 63 unrelated adult patients with LVNC without other associated congenital heart anomalies, showing that there may be a shared molecular etiology of different cardiomyopathies. MYH7 mutations appear to be implicated in cases of LVNC associated with Ebstein anomaly [4].

Recently, mutations in the NOTCH pathway regulator MIB1 have also been shown to cause LVNC in autosomal dominant pedigrees [36•].

In spite of these advances, only a minority of patients with LVNC can be successfully genotyped, although the use of larger panels of genes can increase the yield of genetic testing [28]. In a recent study, Hoedemaekers et al. [29] were able to identify mutations in 35 % of adults and 75 % of children with isolated LVNC using a 17-gene panel. Given this low rate of positive genetic test, the utility of genetic testing for the definitive diagnosis of the index patient is probably of limited use and is given a class IIa recommendation in a recent Heart Rhythm Society/European Heart Rhythm Association consensus document [28]. However, mutation-specific genetic testing for family members and relatives following the identification of a causative mutation in the index case is given a class I recommendation [28], in order to reach an early diagnosis and ensure appropriate monitoring and prophylactic measures.

Clinical Features

Three major clinical manifestations of LVNC have been described: heart failure, arrhythmias, and systemic embolic events [7, 17]. However, the initial presentation varies considerably, and many patients are asymptomatic when diagnosed. Heart failure manifestations occur in more than half of patients, and left ventricular systolic dysfunction has been reported in up to 84 % of patients [1, 2, 23, 37]. Left ventricular diastolic function compromise has also been described and may be related to both abnormal relaxation and restrictive filling due to the prominent trabeculae, myocardial ischemia, and fibrosis, which represent underlying pathophysiologic mechanisms [23, 38].

Arrhythmias are also common in patients with LVNC. Atrial fibrillation has been reported in about 25 % of adults [17, 23, 25], and ventricular tachyarrhythmias in up to 47 % [17]. In several series, sudden death accounted for about one half of all fatalities in patients with this condition [7, 17, 23]. The occurrence of embolic events varies widely, ranging from 0 to 38 % [7, 24, 26, 39]. Stroke, transient ischemic attack, pulmonary embolism, and mesenteric infarction have been reported and may be related to the development of thrombi in the trabeculated ventricles, to depressed LV systolic function, or to atrial fibrillation [17, 38]. The incidence of both arrhythmic and embolic complication seems to be decreasing in more recent reports [39–42], which probably reflects an overestimation of adverse outcomes in earlier reports due to a negative selection bias with inclusion of symptomatic patients referred to tertiary centers.

Less often, patients may present with anginal chest pain and suspected acute coronary syndrome [43], probably due to decreased coronary flow reserve and impaired microvascular function [44].

Electrocardiographic abnormalities are present in around 90 % of patients but are nonspecific [7, 12, 23, 26]. Patients with a normal electrocardiogram are usually younger, asymptomatic, and have less structural abnormalities [45]. The most common findings are intraventricular conduction delay (usually left bundle branch block), LV hypertrophy, and repolarization abnormalities [45]. Findings of Wolff-Parkinson-White syndrome have been described in around 15 % of pediatric patients, but not in adult patients [7, 23, 26]. Some electrocardiographic abnormalities were found to be associated with mortality and other major clinical events in a population of mostly symptomatic patients, but future studies are required to assess their role in the risk stratification of these patients [46].

Diagnosis

Echocardiography

Echocardiography is the first line imaging modality for the diagnosis of LVNC. Usually, this diagnosis is considered when a two-layered myocardium with a thin compact epicardial layer and a thick endocardial layer with prominent trabeculations and deep recesses is present (Fig. 1). Color flow Doppler imaging demonstrates blood flow in these recesses in continuity with the LV cavity (Fig. 2) [38]. However, LV trabeculae are normally found and prominent trabeculations can be present in healthy subjects [47]. So, differentiation of LVNC form normal patterns may be difficult and diagnostic criteria vary according to different authors (Table 1).

The first diagnostic criteria were proposed by Chin et al. [7]. They quantified the distance between the epicardial surface and the through of the intertrabecular recesses (X) and the distance between the epicardial surface and the peak of the trabeculations (Y) at end diastole and calculated the ratio between the two distances (X to Y). These criteria were validated against a control group of subjects with normal echocardiographic studies.

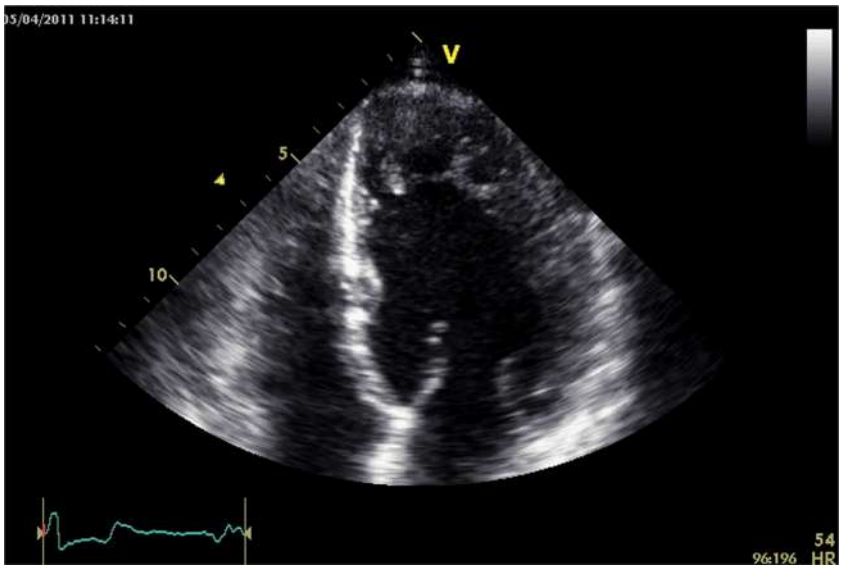

Fig. 1 Transthoracic echocardiogram showing the typical two-layered myocardium, with prominent trabeculations and deep recesses

The criteria proposed by Jenni et al. [8] require the measurement of the thickness of the compact epicardial layer (*C*) and of the non-compact endocardial layer (*N*). Unlike the previous criteria, measurements are made at end systole. LVNC is diagnosed when the *N*/*C* ratio is greater than 2.0. In addition, to diagnose isolated LVNC, perfusion of the deep trabecular recesses should occur from the LV cavity and no other cardiac abnormality should be present. These criteria were validated with histological heart preparations.

Finally, the criteria proposed by Stollberger and Finsterer [48] are based on the finding of more than three trabeculations protruding from the LV wall, located apically to the papillary muscles, with the same echogenicity as the myocardium and synchronous movement with ventricular contractions. Furthermore, perfusion of the intrabecular spaces must occur from the LV cavity and the ratio of the thickness of non-compact to compact segments should be greater than 2.0. Distinct from the other criteria, where measurements are made at the parasternal short-axis view, these criteria require measurements at the apical four chamber view, with angulation of the transducer to differentiate trabeculations from false chords or aberrant bands.

The echocardiographic diagnosis of LVNC has several important limitations. The reproducibility of the measurements required for the diagnosis is poor [49•], and a comparison of the three criteria showed that there is a poor correlation between them, which is expected taking into consideration the differences in the acquisition and measurements of each method [50]. Furthermore, the criteria may be too sensitive, especially in black individuals [50], which could result in

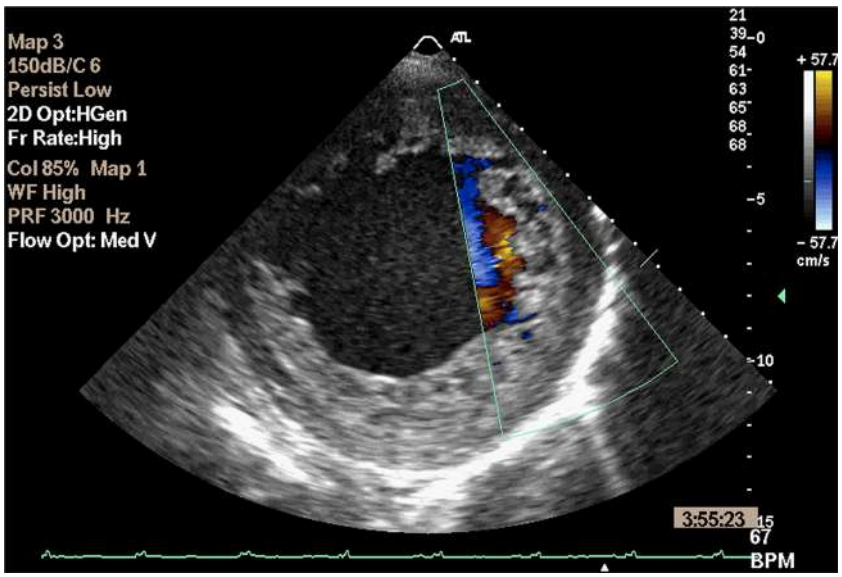

Fig. 2 Color Doppler imaging revealing blood flow in the recesses coming from the left ventricle cavity

Table 1 Diagnostic criteria for left ventricular non-compaction

Echocardiography
Chin et al. [7]
Two-layered structure of the myocardium (epicardial compacted, endocardial non-compacted layer) with *X*-to-*Y* ratio ≤0.5
X—the distance between the epicardial surface and through of intertrabecular recess
Y—the distance between the epicardial surface and peak of trabeculation
Acquisition in parasternal short axis view, measurement at end diastole
Jenni et al. [8]
Thickened myocardium with two-layered structure consisting of a thin compacted epicardial layer (*C*) and a thick non-compacted endocardial layer (*N*)
N/*C* ratio >2.0
Acquisition in parasternal short axis view, measurement at end systole
Perfusion of the deep trabecular recesses from the LV cavity as visualized with color Doppler imaging
Absence of coexisting cardiac abnormalities (in isolated LVNC)
Stollberger and Finsterer [48]
>3 trabeculations protruding from the LV wall, located apically to the papillary muscles and visible in one image plane
Same echogenicity as the myocardium and synchronous movement with ventricular contractions
Perfusion of the intertrabecular spaces from the LV cavity as visualized with color Doppler imaging
Ratio of non-compacted to compacted segment >2.0 at end diastole
Acquisition in apical four chamber view with angulation and atypical views to differentiate between false chords/aberrant bands and trabeculations
Magnetic resonance imaging
Petersen et al. [58]
Ratio between non-compacted and compacted layer >2.3
Measurement at end diastole
Jacquier et al. [59]
Trabeculated LV mass >20 % of the global LV mass
Measurement at end-diastole

Adapted from [1], by the permission of the Oxford University Press and the European Society of Cardiology

LV left ventricular, *LVNC* left ventricular non-compaction

overdiagnosis. There are also some limitations related to the body constitution of some patients and often in evaluating the LV apex. To avoid these limitations, it is critical to obtain images that are not foreshortened and are perpendicular to the ventricular long axis. The use of contrast may also be helpful (Fig. 3) [51].

Novel echocardiographic modalities, like tissue Doppler, and speckle tracking are also receiving increasing attention, as they allow the identification and characterization of regional myocardial function and may aid in the distinction between normally trabeculated myocardium and LVNC [52–54]. A parameter that seems particularly attractive is LV twist,

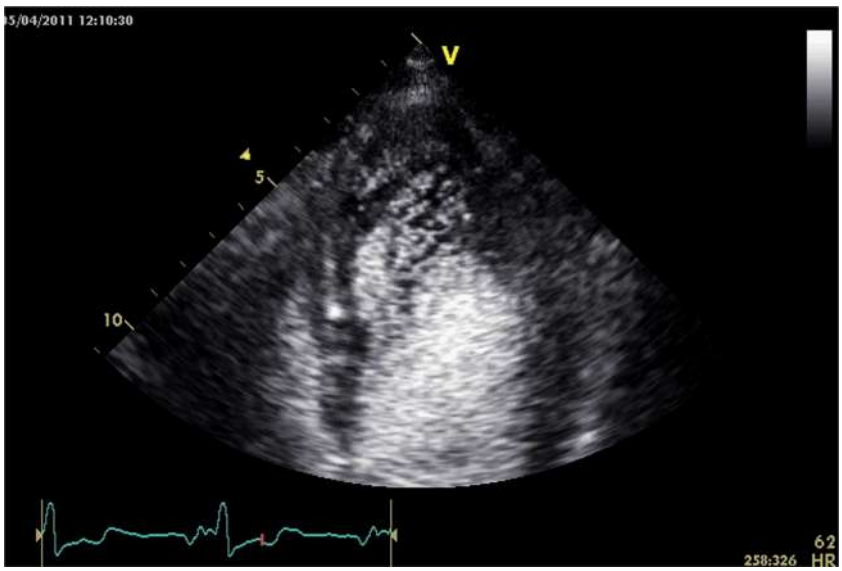

Fig. 3 Contrast echocardiogram demonstrating blood flow in the recesses

determined by speckle tracking. In normal hearts, rotation is clockwise at the base and counterclockwise at the apex, and this pattern is usually preserved in several pathological conditions, such as dilated cardiomyopathy [55]. However, in LVNC, basal rotation, apical rotation, and LV twist are significantly diminished and most patients present with rigid body rotation, defined as rotation of the base and apex in the same direction, which is associated with worse functional clinical status [55, 56•]. Three-dimensional echocardiography may also become an attracting modality for the assessment of LVNC [57•].

Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging (CMR) has been increasingly used in the diagnosis and assessment of LVNC, since it may overcome some of the limitations of echocardiography, and is also extremely useful for the evaluation of LV volumes and function and for the assessment of right ventricle involvement (Fig. 4) [22, 43].

Petersen et al. [58] compared CMR findings in patients with LVNC with those in normal hearts, athletes, patients with hypertrophic and dilated cardiomyopathy, hypertensive heart disease, and aortic stenosis and found that a ratio of non-compacted to compacted myocardium in diastole greater than 2.3 distinguished pathological non-compaction with excellent specificity and negative predictive value and good sensitivity and positive predictive value.

On a different approach, Jacquier et al. [59] quantified a global and trabeculated LV mass in patients with LVNC, dilated and hypertrophic cardiomyopathy, and control subjects. In this study, the percentage of trabeculated LV mass to the global LV mass was similar in control subjects and in patients with hypertrophic or dilated cardiomyopathy, but was almost three times higher in patients with LVNC. Moreover, a value greater than 20 % was found to be highly sensitive and specific for the diagnosis of LVNC.

A comparison of CMR systolic and diastolic criteria for the diagnosis of LVNC revealed that systolic criteria have stronger associations with clinical events, heart failure, and systolic dysfunction [60].

Recently, fractal analysis of trabeculations obtained by CMR showed a higher reproducibility and accuracy for LVNC diagnosis than the current CMR methods and is a promising new methodology [61•].

CMR may also reveal the presence of late gadolinium enhancement (LGE), a surrogate marker of myocardial fibrosis. A recent study showed that LGE is present is more than half of isolated LVNC patients, and both its presence and extent are related to clinical disease severity and LV systolic dysfunction [62•]. Microcirculation disturbances have been described in patients with LVNC, and the presence of perfusion abnormalities [44] as a substrate for ischemia and fibrosis may be assessed by CMR.

Differential Diagnosis

Similarity with other defects and nonspecific clinical features, make the diagnosis of LVNC particularly challenging [26]. Combination of multiple imaging modalities, specially echocardiography and CMR, but also contrast ventriculography [6, 63] and computed tomography [63–66], may be necessary, and could diminish the risk of overdiagnosis. Serum biomarkers may also be useful in some cases [67]. The differential diagnosis of LVNC is broad and includes prominent trabeculations (virtually always less than three in normal variants) [68], apical hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, hypertensive heart disease, endocardial fibroelastosis, abnormal chords, thrombus, or tumors [1, 2, 12, 26, 38, 43, 69]. Particular care is required in patients with dilated LV since dilated cardiomyopathy and LVNC can coexist in the same patient.

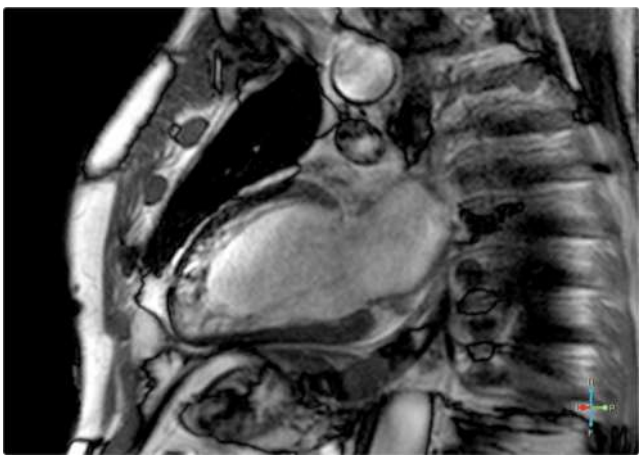

Fig. 4 Cardiac magnetic resonance imaging showing non-compaction of the mid and apical segments of the left ventricle myocardium

Management

Since there is no specific therapy for LVNC, the management is focused on the three major clinical manifestations: heart failure, arrhythmias, and systemic embolic events.

Standard heart failure therapy according to current guidelines is commonly used in these patients [70]. Even though there is no scientific evidence of the benefit of beta-blockers, renin-angiotensin-aldosterone system blockers, biventricular pacing, or any other heart failure therapy in patients with isolated LVNC, recent studies show that midterm mortality in this population is similar to that seen in patients with dilated

cardiomyopathy and that death occurred only in patients with decreased LV ejection fraction [39]. These findings suggest that the risk in this population is related to LV dysfunction rather than LVNC itself, so the institution of heart failure therapy may prevent the occurrence of complications. A report of a single 4-month-old infant with isolated LVNC treated with carvedilol revealed beneficial effects on LV hypertrophy and function and metabolic and adrenergic abnormalities after 14 months of treatment [71], but these effects have not been tested in large-scale studies. Penela et al. [72] found that patients with LVNC have a high prevalence of mechanical dyssynchrony, as assessed with echocardiography, regardless of QRS width, which could justify an extended indication of biventricular pacing in this population. Finally, in patients refractory to medical therapy, cardiac transplantation is an option but has been rarely used in this condition [73].

Given the frequency of atrial and ventricular arrhythmias and the poorly defined risk of sudden cardiac death and systemic embolism, periodic ambulatory ECG monitoring is usually performed in all patients [2] and some authors recommend electrophysiological study for patients with symptomatic arrhythmias or syncope [1]. Since the data on risk factors for ventricular arrhythmias and sudden death is scarce, the decision regarding implantation of an implantable cardioverter-defibrillator (ICD) is based on current guidelines [70, 74] and is usually reserved for patients with syncope, symptomatic ventricular arrhythmias, or severely impaired LV systolic function (LV ejection fraction <35 %) [1]. Interestingly, in a retrospective study of 12 adults with isolated LVNC who underwent ICD implantation and were followed for a median of 36 months, appropriate ICD therapy was found in four of the eight patients (50 %) in whom the ICD was implanted as a secondary prevention, but only in one of the four patients (25 %) for whom the ICD was implanted for primary prevention [75]. In addition, two thirds of the patients had supraventricular tachyarrhythmias documented, which have implications regarding the selection and programming of the devices.

Prevention of embolic events in this population also remains a matter of debate, with no clear data to support any management strategy. In the past, some authors recommended long-term prophylactic anticoagulation for all patients with LVNC, regardless of the presence of thrombus [17, 23], but since thromboembolic complications are very rare in patients in sinus rhythm with normal systolic function, the use of anticoagulation is more limited nowadays [76]. In the absence of any other formal indication, Oechslin and Jenni [1] suggest anticoagulation (target INR 2.0–3.0) only in patients with impaired systolic function (LV ejection fraction <40 %), as the presence of a slow flow may aggravate the risk of thrombus formation in the deep intertrabecular recesses. The $CHADS_2$ and the CHA_2DS_2-VASc risk scores may also be useful for this decision [77].

Finally, because of the familial association of LVNC, screening of first degree relatives with echocardiography is recommended [78] and some authors also recommend neurological and musculoskeletal evaluations for all patients, given the high percentage of associated neuromuscular disorders [2].

Prognosis

The prognosis of adult patients with isolated LVNC varies considerably but seems to be improving in more recent series. In one of the largest early series, after a mean follow-up of 44 months, 35.3 % of patients had died, half of which due to sudden death, and 11.8 % had undergone heart transplantation [23]. In a recent series, after a mean follow-up of 46 months, only 10.8 % had died, 42.9 % of which due to sudden death, and 13.8 % had undergone cardiac transplantation [41]. Importantly, there were no major cardiovascular events in patients who were symptom-free when diagnosed.

Considering five different series with different durations of follow-up, mortality ranges between 1.8 and 35.3 % and heart transplantation is required in 0 to 13.8 % of patients [23, 39–42].

Several studies have also identified predictors of outcome in adult patients with isolated LVNC (Table 2) [23, 41, 42, 79•]. For instance, Lofiego et al. [41] found that the New York Heart Association functional class III/IV, sustained ventricular arrhythmias, and left atrial size were independent predictors of cardiovascular death or heart transplantation in their population. Patients with these risk characteristics might benefit from a more aggressive management strategy, like standard heart failure therapy and ICD implantation, similarly to dilated cardiomyopathy, but so far, this has not been tested in clinical trials. Besides, studies reported include small and heterogeneous populations and their results are difficult to compare, which complicates the identification of actual predictors of outcome in this condition.

Table 2 Predictors of outcome in adult patients with isolated LVNC

Clinical predictors
Functional capacity, NYHA functional class III/IV [23, 41, 42, 79•]
Chronic atrial fibrillation [23]
Bundle branch block [23, 79•]
Sustained ventricular arrhythmias [41]
Blood pressure [79•]
Echocardiographic predictors
Left ventricular end diastolic diameter [23, 79•]
Left ventricular ejection fraction [42, 79•]
Left atrial size [41]
Pulmonary hypertension [79•]

LVNC left ventricular non-compaction

A recent report also suggested that cardiac sympathetic nervous dysfunction, as assessed by 123iodine-metaiodobenzylguanidine myocardial scintigraphy, may be associated with the risk of ventricular arrhythmias [80].

Conclusions

Perhaps the most important challenge regarding LVNC is the clear differentiation of this condition from anatomical and structural variants that are present in the normal heart. Care must be taken to avoid overdiagnosis [81], by the existing echocardiographic and CMR criteria. In this regard, the use of CMR will likely have an increasing role in diagnosing this condition, especially as the availability and experience with this technique increases and the structural and functional features of LVNC are better defined. A small CMR study demonstrated that non-compaction is present in 91 % of the LV apical segments, 78 % of mid-cavity segments of healthy subjects, and also in athletes and patients with hypertrophic and dilated cardiomyopathies, hypertensive heart disease, and aortic stenosis, but the relative thickness of the non-compacted layer was significantly smaller than in patients with LVNC [58]. These findings suggest that LVNC may represent an extreme of a continuous spectrum of the physiological compaction process during embryogenesis. These data need to be confirmed in larger populations, including different age groups and ethnicities in order to establish more sensitive and specific diagnostic criteria.

Another area of intense ongoing research is the genetics of LVNC. So far, several genes have been implicated in the pathogenesis of this disorder, but each gene is involved in only a small number of cases, and many questions remain regarding genotype-phenotype correlation. In addition, most cases appear to be sporadic and could represent de novo mutations. Also unclear is the relation between LVNC and other conditions, like metabolic diseases, genetic syndromes, congenital heart diseases, and cardiomyopathies like hypertrophic and dilated cardiomyopathy. In fact, several genes that have been implicated in LVNC are also known to be involved in the pathogenesis of other conditions. In addition, a recent study showed that mice expressing a mutation in the cardiac troponin T gene, described in a family with LVNC, displayed impaired LV function and induction of marker genes of heart failure, but not LVNC, suggesting that a non-compaction phenotype is not required for the development of cardiomyopathy, at least with this particular mutation [82]. Taking these data together, it is hypothesized that LVNC may be a morphological expression of several diseases, rather than a distinct cardiomyopathy. Multimodality imaging, family screening, and genetic testing are required to further characterize the morphological expression of genetic mutations and to better understand the genotype-phenotype correlation [1].

Finally, several other characteristics of LVNC need to be better clarified, namely, the diagnosis, natural history, prognosis, and management. Taking into consideration the rarity of this condition, improving our understanding of LVNC will only be possible through the development of multicenter studies, involving larger populations.

Compliance with Ethics Guidelines

Conflict of Interest Pedro Carrilho-Ferreira, Ana G. Almeida, and Fausto J. Pinto declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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