REVIEW

Left ventricular noncompaction cardiomyopathy: Recent advances

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ABSTRACT

From its initial description to the present day, left ventricular noncompaction cardiomyopathy has been the subject of numerous studies and publications. In question as a real cardiomyopathy, left ventricular noncompaction can appear in isolation or in association with other cardiac malformations, genetic syndromes, and neuromuscular disorders. As a genetically heterogeneous disorder, it can be sporadic or familial, with an autosomal dominant pattern with variable penetrance most frequently observed. Different diagnostic criteria have been described through the years, first by using echocardiogram and later on by cardiac magnetic resonance. The lack of universally accepted diagnostic criteria has led to the condition being over-diagnosed in the general population. Differential diagnosis between real cardiomyopathy, epiphenomenon (phenocopy in the setting of loading conditions or even other cardiomyopathies), and physiological hypertrabeculation, like in the athlete's heart must be considered. Clinically it can present as heart failure, ventricular arrhythmias, and even sudden death, but it can also be asymptomatic during familial screening. The main prognosis factors are left ventricular dilatation, dysfunction, and fibrosis. There is no specific treatment. Familial screening is recommended and special recommendations in the case of athletes must be taken into account. In the present article, we review the myth and reality concerning main and more recent aspects of left ventricular noncompaction.

Key words: cardiac magnetic resonance, cardiomyopathy, left ventricular noncompaction

INTRODUCTION

Left ventricular noncompaction (LVNC) is a heterogeneous and complex entity morphologically characterized by a thin compacted epicardial layer and an extremely thick endocardial layer with prominent trabeculation and deep recesses that communicate with the left ventricular cavity but not with coronary circulation [1].

Since its first description in 1926 by Grant, it has been the subject of numerous studies and publications, but even today there are still some doubts to be resolved. While the American Heart Association classified it among genetic cardiomyopathies, the European Society of Cardiology considers it unclassified cardiomyopathy [3–5].

Classically, it is considered the result of an interruption of normal myocardial development during weeks 5 to 8 of embryogenesis and has been linked to several genetic mutations with a familiar presentation [6, 7].

Nevertheless, it can present sporadically isolated or in association with other congenital defects, neuromuscular syndromes, and heart diseases [8]. In addition, hypertrabeculation may appear as a physiological adaptation, making diagnosis even more difficult. For all of these reasons, sometimes it remains unclear whether it represents a distinct clinical entity or just an epiphenomenon [9].

The heterogeneity is also reflected in its clinical manifestations, ranging from no symptoms to heart failure, malignant arrhythmias, and cardiac death [10].

Diagnosis is based on noninvasive imaging, with echocardiography and cardiac magnetic resonance (CMR) most widely used, but currently there is no gold standard, nor universally accepted diagnostic criteria [11].

This review aims to summarize the current knowledge and the most recent findings of LVNC.

A BRIEF HISTORICAL REVIEW

The first description of the spongy appearance of the myocardium was made by Grant in 1926 in a variety of congenital heart defects [3]. Other authors, however, think that it was made by Bellet and Gouley in 1932 [12]. At that time, the autopsy was the only method available, in the absence of current imaging modalities. Feldt et al. [13] in 1969 and Westwood et al. [14] in 1975 reported the first cases of biventricular noncompaction. Also in 1975, Dusek et al. [15] speculated that there was postnatal persistence of the spongy myocardium, and focused on the clinic, describing a severe condition characterized by the classic triad of heart failure, thromboembolism, and arrhythmia. In 1984, Engberding [16] described using echocardiography a case of persistence of myocardial sinusoids in absence of any other structural heart disease. But, the term "isolated LVNC" was not proposed until 1990 by Chin et al. [17] based on a study of eight patients, in which the authors also recognized the hypothesis of a rest of the normal compaction process during embryogenesis. Since then, the number of studies of this complex entity has increased, and the condition has received different names, such as spongious myocardium, non-compacted cardiomyopathy, myocardial dysgenesis or persistence of myocardial sinusoids, hypertrabeculation syndrome, and others [18, 19]. The first description of LVNC using CMR was published by Hany et al. in 1997 [20].

Finally, in 1996 LVNC was included in the World Health Organization/International Society and Federation of Cardiology classification of cardiomyopathies grouped as unclassified cardiomyopathy [21]. In contrast, the American Heart Association recognized in 2006 the rapid evolution of genetics and classified it as primary genetic cardiomyopathy [4]. However, the European Society of Cardiology still considered LVNC as "unclassified" cardiomyopathy [5] because it is not clear whether it is separate cardiomyopathy or an epiphenomenon shared by many cardiomyopathies and other disorders, and even by some physiological adaptations.

EPIDEMIOLOGY

The true prevalence and incidence of LVNC are not known. In children, based on studies that used echocardiography, the prevalence varies between 0.014% and 1.3% [22]. In a retrospective cohort study on Australian children, the LVNC was the third most frequent cardiomyopathy, present in 9.2% of patients diagnosed by echocardiography [23]. Very similar to the study of the Texas Children's Hospital which found 36 cases of LVNC (9.5%) from a total of 344 cases of cardiomyopathy [24].

In adults, the variability in the reported prevalence is much greater. A recent systematic review and meta-analysis tried to assess the prevalence of LVNC in adults. While using echocardiography, the prevalence was 1.28% (95% CI, 0.95––1.64), and the prevalence with CMR imaging was 14.79% (95% CI, 8.85–21.85); both with a high level of heterogeneity in prevalence estimates across cohorts. Furthermore, the prevalence is strongly influenced by the specific diagnostic criteria applied and the characteristics of the cohort being studied. There was a much higher prevalence in primigravida pregnant and athletic cohorts in comparison with healthy and cardiac cohorts, which supports the presence of trabeculations in the heart as a physiological adaptation and highlighted the importance of not using imaging results for the diagnosis of LVNC in isolation [11, 25]. Otherwise, the higher prevalence can be the result of both the introduction of new imaging techniques (specially CMR) and the heterogeneity of the diagnostic criteria, raising the risk of overdiagnosis, overtreatment, and unnecessary follow-up.

DIAGNOSTIC CRITERIA FOR LEFT VENTRICULAR NONCOMPACTION: REVIEW AND EVOLUTION

Since its first description, publications have been trying to describe diagnostic criteria for LVNC. From the first publication, where the diagnosis was based on echocardiography to the most recent one using cardiac computed tomography (CT), we review the history and evolution of LVNC diagnosis.

Echocardiography: The first diagnostic technique

The first diagnosis of LVNC was made by echocardiography, which was for years the main and only diagnostic tool until the development of CMR. Thus, in 1990, Chin et al. [17] published 8 cases of isolated LVNC. The diagnosis was made based on the presence of numerous, excessively prominent trabeculations associated with deep interventricular recesses. They established a diagnostic echocardiography pattern quantified by the X:Y ratio $\leq$0.5.

Some years later, Jenni et al. [26], published a clear-cut morphological echocardiographic diagnostic criteria in agreement with necropsy findings. In the absence of coexisting anomalies, the main echocardiographic diagnostic criteria were the maximal end-systolic ratio of the non-compacted (NC) endocardial layer to the compacted (C) myocardium >2. In 2002, Stollberger et al. [27] published the largest series to date on patients with left ventricular hypertrabeculation criteria diagnosed with LVNC suggesting also the association of this entity with neuromuscular disorders. Classic known criteria proposed by the authors are summarized in Table 1.

In 2007 Kohli et al. [28] published a critical article revealing the risk of over-diagnosing LVNC with the three existing

Table 1. Main echocardiographic criteria for left ventricular noncompaction diagnosis

Authors	Criteria	Views
Chin et al. [17]	X:Y ≤0.5[a]	Short axis and apical views
Jenni et al. [26]	N:C >2[b]	End systole at the parasternal short-axis views
Stöllberger et al. [27]	More than 3 trabeculations Excluding papillary muscles	Apically to the papillary muscles, visible in a single image plane

[a]X is the distance from the epicardial surface to the trough of the trabecular recess; Y is the distance from the epicardial surface to the peak of trabeculation [17]; [b]N is the non-compacted layer of the myocardium and C is the compacted layer of the myocardium [26]

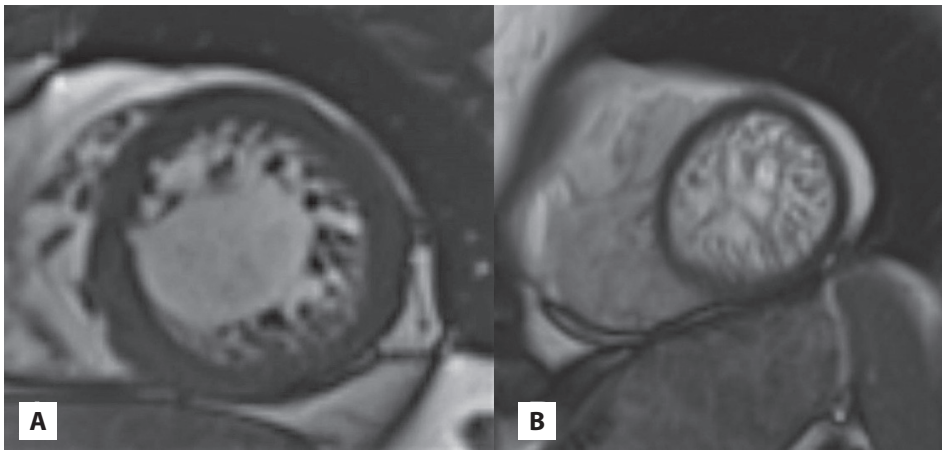

Figure 1. Cardiac magnetic resonance imaging. Short axis view. T1-weighted image cine sequence two cases of left ventricular noncompaction. **A.** Hypertrabeculation in the lateral and inferior segments. **B.** Hypertrabeculation in the apical segments

criteria, suggesting their high sensitivity. Besides, they also found a poor correlation between the three echocardiographic definitions. So, this publication became the turning point that, together with the progressive development of CMR, led to the search for new diagnostic criteria.

The advent of advanced echocardiography

Given the limitations of echocardiography (operator variability, dependence on acoustic windows, difficulties in apex visualization), novel techniques have been tried to help establish the diagnosis of LVNC, like using contrast echocardiogram or strain. Tarando et al. [29] compared longitudinal deformation (strain) between patients with LVNC and Dilated Cardiomyopathy (DCM) and found that longitudinal deformation (strain) was greater in LVNC than in DCM patients. Longitudinal shortening was greater in the non-compacted segments than in the compacted ones and in a multivariable model, the base-apex mid-wall gradient in an apical 4-chamber view was the only independent echocardiographic criterion allowing for the distinction between LVNC and DCM.

Similarly, the role of speckle myocardial imaging in patients who fulfilled the morphologic criteria for LVNC compared with healthy controls has been evaluated by Cortés et al. [30], who found that, global longitudinal strain (GLS) was lower than controls. He concluded that speckle imaging could be useful in the differential diagnosis of LVNC.

Cardiac MRI: Quantification of the mass and late gadolinium enhancement

Considering the inherent limitations of echocardiography mentioned earlier, especially in apical segments, Petersen et al. [31] tested the accuracy of CMR diagnosis in distinguishing pathological LVNC in a small sample of patients with a previous diagnosis of noncompaction. Their study was the pioneer in using CMR and the first to define the ratio NC:C >2.3 in diastole as the diagnostic criteria for LVNC, which are an adapted version of those already existing in echocardiography. In this way and due to the progressive and growing evolution of CMR, with higher spatial resolution than echocardiography, Jacquier et al. [32] described a different and reproducible method for quantification noncompaction mass in 16 patients being the established criteria for diagnosis of the relationship of a noncompaction mass greater than 20% of the global mass of the left ventricle. The authors already pointed out that the presence of fibrosis would be a risk marker in these patients (Figure 1).

A few years later, Grothoff et al. [33] published new criteria for LVNC also based on CMR diagnosis. Their four basic criteria are summarized in Table 2. These criteria show some discrepancies regarding masses and volumes in comparison with Jacquier's criteria, mainly due to a different methodology with the exclusion of blood pool. They also include a novel parameter, which is the total non-compacted mass, allowing the diagnosis of no compaction independently of the compacted mass.

Table 2. Main magnetic resonance imaging criteria for left ventricular noncompaction diagnosis

Authors	Criteria	Measure
Petersen et al. [31]	NC:C >2.3[a]	In diastole, 7 patients included
Jacquier et al. [32]	NC mass >20% global mass	Blood pool included in the trabeculated region, 16 patients included
Grothoff et al. [33]	NC mass >25%, NC mass >15g/m^2 NC:C ≥3:1 (1–3.7–16) Segments 4–6 ≥2:1	Exclusion of blood pool, 12 patients included

[a]NC is non compacted layer and C is compacted layer

Both methods, Jacquier's and Grothoff's, have good interobserver reproducibility although the last one requires post-processing software not available for everyone [34].

To add more controversy to the diagnostic criteria, Stacey et al. [35] published a comparison between systolic and diastolic criteria for isolated LVNC in CMR. In conclusion, they found that end-systolic measures of LVNC have stronger associations with events, heart failure, and systolic dysfunction than other measures.

Another critical analysis compared two methods of measuring the non-compacted mass and its percentage in the left ventricle mass: the Jacquier´s criteria [32] and Hautvast's computed algorithm [36], evaluating their possible impact on both end diastolic volume (EDV) and ejection fraction (EF). As reflected by the authors, Hautvast´s algorithm has shown excellent reproducibility, given its semi-automatic and might be a solution to increase reproducibility and repeatability. The manuscript opens the debate about the correct quantification of the trabeculated mass and the diagnosis of LVNC [32, 36, 37].

An aspect of special interest derived from CMR studies is the possibility of performing tissue characterization using late gadolinium enhancement (LGE) sequences. The presence of LGE indicates myocardial fibrosis that acts as an arrhythmogenic substrate and therefore as a risk marker in different cardiomyopathies [38].

In LVNC, delayed contrast enhancement has been described both in areas of noncompaction and compaction myocardium related to regional fibrosis (Figure 2).

It may be difficult to distinguish between delayed gadolinium enhancement and deep intertrabecular recesses. The pathophysiological mechanism of delayed enhancement in LVNC may be the result of different mechanisms such as genetic predisposition, abnormal modulation of the immune system, abnormal microvasculature, and microvascular ischemia in the setting of increased myocardial mass [39–41]. Different studies, like the one by Nucifora et al. [42], have evaluated the prevalence and extent of myocardial fibrosis in patients with LVNC. In their study, the LGE pattern was mainly intramyocardial (mid-myocardial or at right ventricular insertion areas); subendocardial and transmural LGE was less frequently observed. Otherwise, they also found a significant association between the presence and extent of LGE and the number of abnormal clinical features. Additionally, an inverse relationship between the presence and extent of LGE and left ventricular EF was found, with LGE as an independent determinant of LV systolic function and a marker of adverse prognosis. This finding was corroborated by Andreini et al. [43] in a multicenter study in which the presence of fibrosis, left ventricular systolic dysfunction and dilatation were independent predictors of poor prognosis.

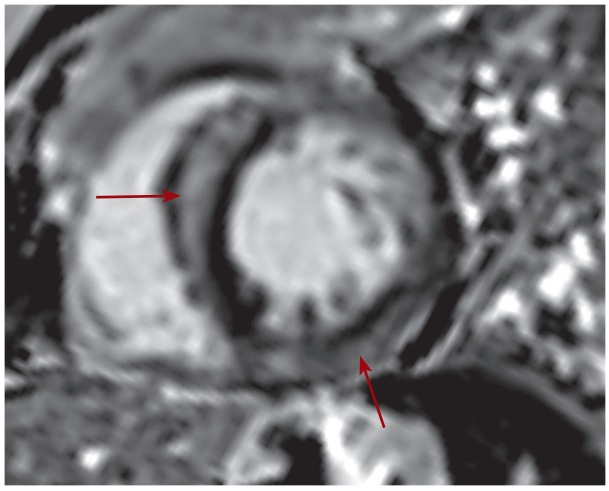

Figure 2. Cardiac magnetic resonance imaging: inversion recovery image shows intramyocardial late gadolinium enhancement (the arrows) in the septum and subepicardial in the inferior and subepicardia in the inferior and inferior-lateral wall in a patient with the mixed phenotype (hypertrophic and noncompaction cardiomyopathy)

Therefore, as it has been shown in many studies, CMR plays a fundamental role in the diagnosis of cardiomyopathies and is especially useful in the case of noncompaction, both for its definitive diagnosis and prognostic stratification [44].

Cardiac computed tomography: The most recent diagnostic tool

Finally, in the last years, and with the the crescent used of cardiac CT, different articles have also been published on CT usefulness in the study of cardiomyopathies and, specifically, in noncompaction cardiomyopathy. Sidhu et al. [45] reported eight cases previously diagnosed by echocardiogram and CMR in which cardiac CT accurately characterized LVNC with an NC:C ratio >2.3 as the cutoff value. A similar study, with 10 patients was published later by Melendez-Ramirez et al. [46] proposing an NC:C ratio of 2.2 at end-diastole involving ≥2 segments as diagnostic criteria. Its advantage is the possibility of evaluating coronary arteries in the same study; however, the use of cardiac CT in the diagnoses of LVNC has not yet been established.

Controversies and future directions

Although CMR is the main diagnostic tool for LVNC, there is no consensus about the best diagnostic criteria and there are limited data regarding their prognostic value [47].

To add more controversy, Kawel et al. [48] analyzed the CMR findings of 1000 participants of the Multiethnic Study of Atherosclerosis. They found that 43% of the patients without cardiac disease or hypertension had at least one of 8 regions evaluated with trabeculated-to-compacted myocardial ratio >2.3, raising concern about potential false positive results and overdiagnosis.

Besides hypertrabeculation can be present also in physiological conditions as a result of increased myocardial stress with reversible remodeling, or, otherwise, it can be considered as an epiphenomenon of other heart diseases with pathological remodeling, behaving this case as a phenocopy of cardiomyopathy [49–51].

Taking all these aspects into account, it seems necessary to clearly define and homogenize diagnostic imaging criteria and then establish a diagnostic algorithm that could be similar to that of arrhythmogenic cardiomyopathy, including both clinical, imaging, and genetic criteria. We advocate for the creation of national and international registries that allow the universalization of diagnostic criteria, knowledge of the genetic bases, and the natural history of this fascinating entity.

CLINICAL PRESENTATION AND OUTCOME

Clinical presentation of LVNC is highly variable and heterogeneous and patients may be asymptomatic or diagnosed incidentally or during a familial screening or they can present with a severe heart failure and sudden cardiac death. Classic symptoms also include supraventricular and ventricular arrhythmias, sudden death, and thromboembolic events. Patients with preserved ejection fraction are usually asymptomatic and heart failure symptoms are related to myocardial dysfunction and the worst prognosis. LVNC can occur in isolation or in association with other pathologies of the heart, like congenital heart defects or Ebstein anomaly with or without associated gene mutations [22]. Besides, in families with other types of cardiomyopathy, a noncompaction phenotype may be found, which raises the question if LVNC is distinct cardiomyopathy or a subtrait [52, 53] (Figure 3).

LVNC has also been described as associated with other genetic syndromes like Barth syndrome, an X-linked disorder with cyclic neutropenia, skeletal myopathy, cardiomyopathy, mitochondrial functional impairment, 3-methylglutaconic aciduria, lactic acidosis, growth deficiency, and cardiolipin deficiency. It has also been associated with the 1p36 gene deletion syndrome which causes developmental delay and mental retardation. Other syndromes like Holt Oram, Sengers, or Kearns-Sayre may also present with an LVNC phenotype [52, 53].

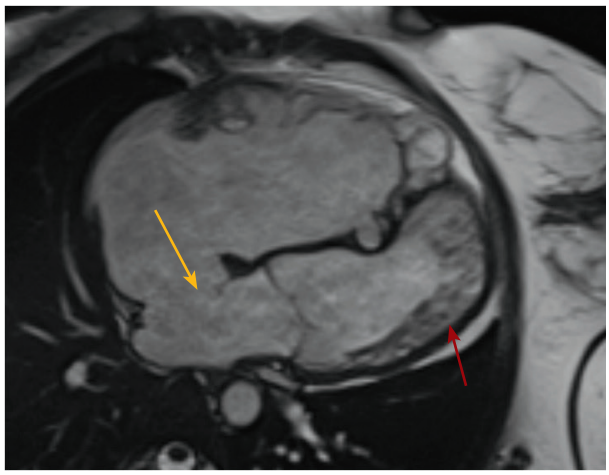

Figure 3. Cardiac magnetic resonance imaging: Ebstein disease, atrial septal defect (the yellow arrow), and left ventricular noncompaction (the red arrow). T1-weighted image cine sequence

A review published by Oechslin and Jenni [22] collected the existing publications up to that moment with the clinical presentation and evolution of patients diagnosed with LVNC. The prognostic factors do not differ from dilated cardiomyopathy with ventricular dysfunction; however, the authors reflect that there could have been selection bias regarding the inclusion of patients in the different published series since they included mainly symptomatic patients referred to reference centers.

Later, Brescia et al. [55] identified four phenotypes of isolated LVNC in children: dilated, hypertrophic, mixed, and normal dimensions with different prognoses among all of the groups. Lower mortality was found in those with normal cardiac dimensions; however, the children with myocardial dysfunction or ventricular arrhythmias had a worse prognosis than those with isolated hypertrabeculation. In conclusion, phenotypic variability and clinical presentation could depend on specific genetic mutations that could predispose individuals to both heart failure and malignant arrhythmias. In their series, they had a high mortality rate in children presenting in the first year of life and the reason for this phenomenon could underscore a more malignant genotype or more global, systemic disease. They found electrocardiogram (ECG) abnormalities in 87% of patients both symptomatic and asymptomatic. Characteristic ECG abnormalities included ventricular hypertrophy and repolarization abnormalities such as T-wave inversion and ST-segment changes which were independently associated with cardiac death, whereas normal ECGs were associated with decreased mortality. In general, nonspecific ECG changes have been described in LVNC.

Regarding prognosis, Van Waning et al. [56] investigated in a large cohort of LVNC (both children and adults) the correlation between genetics, clinical presentation, and long-term outcome. As a result, they found that children with a mutation were more frequently diagnosed

before they were 1 year old; they had cardiac symptoms, left ventricular systolic dysfunction, and a high risk for major adverse cardiac events (MACE).On the contrary, children with sporadic LVNC were diagnosed incidentally, had a normal cardiac function, and a low risk of MACE. In adults with a mutation, a high risk of MACE was strongly correlated with left ventricular systolic dysfunction. So, in conclusion, adverse cardiac events were more frequent in mutation carriers associated with left ventricular dysfunction. Otherwise, the clinical phenotype within families and among unrelated individuals with the same mutation can be highly variable, suggesting that there must be other factors, such as modified genes, that influence the clinical expression of the disease.

Also, Van Waning et al. [57], have also tried to assess which specific clinical and morphologic characteristics of the myocardium may predict a likely pathogenic genetic variant and which of the cardiovascular magnetic resonance diagnostic criteria for LVNC can be best used for that purpose. The authors conclude that in a holistic view of this pathology and for a more accurate diagnosis, there should be a model in which imaging criteria are combined with clinical characteristics, genetics, and functional features.

Finally, the study published by Andreini et al. [43], about the relevance of CMR findings concluded that the degree of LV trabeculation has no prognostic impact over and above left ventricular dilation, left ventricular systolic dysfunction, and presence of LGE (a surrogated of myocardial fibrosis).

In our opinion, the integrative approach proposed by Van Waning et al. is the most comprehensive and appropriate approach to establish a correct diagnosis not based on a single imaging criterion but the sum of them. Moreover, it is necessary to establish criteria that allow a correct prognostic stratification, similar to the existing algorithms for hypertrophic cardiomyopathy, to identify those patients at risk of sudden death or worse clinical evolution.

DIFFERENTIAL DIAGNOSIS OF LVNC: CARDIOMYOPATHY, PHENOCOPY, OR PHYSIOLOGICAL HYPERTRABECULATION?

Cardiomyopathies are divided into distinct morphological phenotypes, with hypertrophic and dilated cardiomyopathy being two of the most prevalent. They both can share morphologic criteria that can overlap with LVNC [58].

Otherwise, in a first echocardiography approach, there are several conditions affecting apical left ventricular regions that can be confused with LVNC; these conditions are apical hypertrophic cardiomyopathy, thrombi, cardiac metastases, and endocardial fibroelastosis [27]. A further approach using CMR will help to better define the apical region, especially in those cases with bad acoustic windows. Once CMR has been performed, a diagnostic algorithm must be followed that includes clinical aspects, imaging, family history, and genetic study if it is available. The possible differential diagnoses to consider at this time will be true noncompaction cardiomyopathy, phenocopy in the context of load conditions (dilated cardiomyopathy of another origin with hypertrabeculation), or physiological hypertrabeculation present in other situations such as athlete's heart. The presence of ventricular dysfunction and the absence of other concomitant pathologies causing dilated cardiomyopathy, together with genetics, would guide a diagnosis of LVNC, rather than a phenocopy or an epiphenomenon [59].

In a promising study, Izquierdo et al. [58] have recently published the results of a machine learning-based radiomics model which has shown excellent performance for differentiating between hypertrophic cardiomyopathy, dilated cardiomyopathy, left ventricular noncompaction, as well as identifying healthy subjects. Further analysis is needed to know the future and applicability of the use of radiomics and confirm its value for quantifying relevant tissue patterns in cardiomyopathy differential diagnosis.

In Figure 4 we summarize the diagnostic possibilities of hypertrabeculation with noncompaction criteria. Thus, the first question to ask once hypertrabeculation has been confirmed, will be: is it physiological, as in an athlete; is it another heart disease, and is it a phenocopy; or is this really noncompaction cardiomyopathy?

GENETICS IN NONCOMPACTION CARDIOMYOPATHY

LVNC is a genetically heterogeneous condition having sporadic and familial forms. Autosomal dominant inheritance with variable penetrance seems to be more common than X-linked inheritance, recessive, or mitochondrial inheritance, which has also been observed [22]. Depending on the series and number of genes screened, 17% to 50% of patients have a family member with cardiomyopathy. Genes associated with LVNC have also been related to hypertrophic and dilated cardiomyopathy. It can be linked to mutations in mitochondrial, cytoskeletal, Z-line, and sarcomeric proteins [60, 61].

The most frequently involved genes are those that code for sarcomeric proteins and patients with isolated LVNC, hypertrophic, and dilated cardiomyopathy share common mutations in sarcomere protein genes, with the variants in MYH7 being the most frequently related [59]. Other genes like the sarcomeric elastic-fiber gene TTN and MYBPC3 have also been described as associated with LVNC [62]. Sedaghat-Hamedani et al. [53] found that the truncating TTN variants were mainly located in the A-band, which is a region that harbors most pathogenic titin variations. These authors also found an exonic rare variant (RBM20: p.R634L, c.G1901T) validated by Sanger sequencing. This novel variant is located in exon 9, and the amino acid change affects the arginine/serine-rich (RS) domain of RBM20, which is highly conserved across species.

In a recent meta-analysis, Mazzarotto et al. [63] have discussed a large genetic overlap between LVNC and dilated hypertrophic and arrhythmogenic cardiomyopathy. LVNC can be both a morphological variant of other cardiomyop-

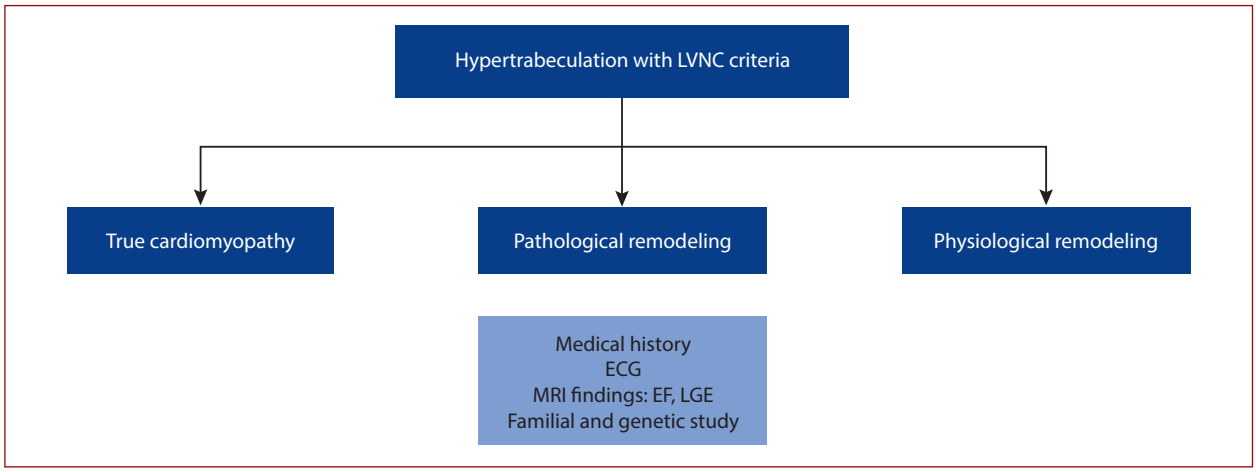

Figure 4. A comprehensive approach to left ventricular hypertrabeculation

Abbreviations: ECG, electrocardiogram; EF, ejection fraction; MRI, magnetic resonance imaging; LGE, late gadolinium enhancement; LVNC, left ventricular noncompaction; other — see Figures 1 and 2

athies with which it shares a genetic substrate or an entity of its own with an independently demonstrated genetic substrate. They found in LVNC patients truncating in MYH7, ACTN2, and PRDM16, which appears to be associated solely with an LVNC phenotype, which confirms also the association of RYR2 and HCN4 with complex noncompaction/arrhythmia phenotypes.

According to the recent study published by Ross et al. [64], genetic testing applied broadly to adult index patients with LVNC is likely to have a low diagnostic yield. Their analysis suggests that genetic testing is likely to be most beneficial in LVNC associated with other cardiac features, such as LV dysfunction, other cardiac and noncardiac syndromic features. It is least useful in adults with only isolated LVNC in the absence of cardiac dysfunction and syndromic features.

Besides, identification of genetic LVNC is more predictive of adverse cardiac events in the pediatric population than in adults, and the presence of LV dysfunction further predicted a high risk for MACE in carriers of a mutation as opposed to non-genetic cases.

The genetic study must be a basic pillar in the diagnosis and prognosis of this entity, in a similar way as it is for the confirmation of left dominant arrhythmogenic cardiomyopathy. Hence, and as we have previously mentioned, the creation of national and international registries should be considered.

SPECIAL SETTINGS: ATHLETES AND CHILDHOOD

Athletes: the left ventricular noncompaction dilemma

Regarding physical activity and LVNC, it is often very difficult to differentiate an athlete's heart from a real LVNC cardiomyopathy. Athletes usually show LV hypertrabeculation, in fact, a high proportion of athletes fulfill conventional criteria for LVNC without other phenotypical features of the disorder. According to Gati et al. [65], up to 8% of them meet echocardiographic criteria for the diagnosis of LVNC. The mere presence of increased trabeculation or even isolated LVNC diagnostic criteria are likely to be of no clinical significance and can be explained in the context of the "athlete's heart". One of the hypotheses is that an increase in preload, typical of high-intensity athletes, causes trabeculae to appear [49]. Caselli et al. [66] conducted a study with 2501 athletes who underwent an evaluation that included a physical examination, an ECG, stress test, and echocardiography. In addition, additional studies such as CMR and genetic testing were carried out selectively only in those athletes with abnormal ECGs, ventricular arrhythmias, borderline LV dysfunction, or a positive family history. In this study, they observed a marked trabeculation pattern in 1.4% of the patients. However, only a small proportion of these athletes (0.1%) also showed other results that could lead to suspicion of the diagnosis of LVNC, such as family history, compatible symptoms, or other morphological data. As observed in other studies, in most athletes, the increase in trabeculations was not associated with ventricular dysfunction or with a positive family history, which probably represents a morphological variant of LV, without clinical importance [66].

Therefore, the suspicion of LVNC in athletes should only be considered if the echocardiographic criteria for LVNC are met, and they also show left ventricular dysfunction (ejection fraction <50%), symptoms suggestive of heart disease, or there is a family history [67].

Additional echocardiographic criteria that could support the diagnosis of LVNC in these patients include a very thin compacted epicardial layer (on CMR of 5 mm in end-diastole or <8 mm in systole) and impaired myocardial relaxation (E' <9 cm/s in Doppler tissue) [68, 69].

Caselli et al. [70] proposed an algorithm to aid in the management and diagnosis of athletes with a morpho-

logical pattern suggestive of LVNC. They propose to do it through a clinical approach based on the precept that the diagnosis of LVNC resting on purely morphological criteria seems to be insufficient since they have a low predictive value when correlated with the clinical ones. Therefore, to solve this problem, they recommend an algorithm based on EF (more or less than 50%), familiar history, and CMR testing, taking into account whether LGE was present or absent. In those cases with EF <50%, CMR with LGE positive and /or positive genetic testing, diagnoses of LVNC are likely and restriction in sports participation must be advised. In the same way, in those with EF >50% but with a positive family history, ECG abnormalities, and /or ventricular tachyarrhythmias, CMR and genetic testing must be performed before allowing sports participation [70].

The clinical outcomes of LVNC are determined by the presence of symptoms, the severity of LV dysfunction, and the nature of the ventricular arrhythmias. No adverse cardiac events have been reported in the absence of LV dysfunction regardless of the severity of LV trabeculation [66]. Regular follow-up is recommended for patients with LVNC. The appearance of new symptoms should force discontinuation of exercise and a reassessment [71].

In this case, given the relevance of the diagnosis, the European guidelines on sports practice have considered this entity, proposing stratification criteria and specific recommendations for athletes.

Children: Again a heterogeneous entity

Regarding children, new diagnoses have been on the rise in recent years, which may be due to an increase in the knowledge of this entity and better diagnostic imaging techniques, rather than an increased incidence [70]. An incidence of 0.11 per 100 000 children between the ages of 0 and 10 years and up to 7 times higher incidence in infants has been described. In children with a diagnosis of cardiomyopathy, a prevalence of 9.2% was found in children under 10 years of age [23]. An association has been seen with other types of cardiomyopathies such as hypertrophic cardiomyopathy and dilated cardiomyopathy. The mean age at diagnosis was significantly higher in the cases of isolated LVNC, which was 9.8 years, compared to patients with mixed phenotypes, 0.4 to 0.6 years [72].

The clinical presentation, as in adult patients, can be very varied, from an accidental finding to thromboembolic events, arrhythmias, or heart failure [19]. This reflects the great phenotypic diversity of this entity. When associated with other cardiomyopathies, they can also contribute to the clinical picture. In the largest cohort of pediatric patients with LVNC, in whom 40% were infants, 37% began as a chance finding, 17% with arrhythmias, 25% with heart failure, and 19% with heart murmurs [55]. Twenty-three percent of them had a family history of some cardiomyopathies. However, only 25% had a family history of LVNC.

The prognosis in pediatric patients is highly variable and depends to a large extent on the underlying pathophysiology [73]. Brescia et al. [55] conducted a review of the risk of overall mortality and sudden death in a large cohort of pediatric patients. They found important differences depending on the phenotype, with the 5-year transplant-free survival being very good in cases of a normal-sized left ventricle, intermediate in cases like hypertrophic cardiomyopathy, and poor in patients with a phenotype expanded. The strongest predictors for death or transplantation were the presence of systolic dysfunction or arrhythmias. The incidence of sudden death was 6.2% in a 19-year follow-up, and the presence of ventricular dysfunction was 95%, while that of documented arrhythmias was 60% in these patients whose outcome was fatal. Another independent risk factor was early presentation during the first year of life [55]. Jefferies et al. [72] found similar findings – the patients with the worst prognosis were those with a dilated phenotype and who debuted earlier.

Otherwise, patients with an isolated LVNC phenotype have been described to have a favorable prognosis. However, progression to another type of cardiomyopathy is not uncommon, so close monitoring is recommended [71, 74].

TREATMENT

There are no specific guidelines for the management of LVNC, and therefore no specific treatment for this entity has been described to date. The recommendation is management based on the predominant phenotype [22, 75]. Patients should be managed according to their clinical needs and the corresponding clinical practice guidelines [76, 77].

Although it has not been demonstrated in prospective clinical trials aimed particularly at this disease, in patients with ventricular dysfunction, standard treatment, according to the current practice guidelines, is recommended. The prevention of embolic complications is one of the main factors to consider. Certain groups are in favor of a more aggressive strategy regardless of the degree of ventricular dysfunction. However, it seems clear that patients without ventricular dysfunction and in sinus rhythm do not benefit from the initiation of anticoagulation [75, 76]. Since very deep trabeculae can increase blood stasis, anticoagulation is recommended in patients with these findings and ventricular dysfunction (left ventricular ejection fraction <40%). However, the absence of robust evidence in this regard must be considered. Of course, this therapy must be individualized in each patient and weigh both the bleeding risk and the thrombotic risk.

On the other hand, when it comes to therapy using pacing, including implantable cardioverter-defibrillator (ICD) and biventricular pacing, the guidelines should be applied [76]. There is no robust evidence to issue other types of recommendations.

In some groups, the need to perform an electrophysiological study is postulated for all patients with LVNC and symptomatic arrhythmias. ICD implantation would be indicated in patients with LVNC presenting with syncope,

symptomatic ventricular arrhythmias, or severe ventricular dysfunction (left ventricular ejection fraction <35%) [78].

CONCLUSIONS

LVNC is a complex entity and is surrounded by controversies in terms of its diagnosis, presentation, and prognosis. Whether LVNC is isolated or associated with other heart diseases, its diagnostic imaging criteria are not yet well defined and the borderline between true cardiomyopathy, physiological manifestation, or epiphenomenon is not entirely clear. An adequate diagnostic strategy requires integration of different parameters such as family history, genetics, and imaging studies. Concerning the latter, multicenter studies and registries are necessary to establish uniform and definitive diagnostic criteria that could help with its recognition as true cardiomyopathy.

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