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Left ventricular noncompaction, morphological, and clinical features for an integrated diagnosis

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Abstract
The presence of myocardial noncompaction (NC), regardless of the criterion used, does not identify cardiomyopathy per se. The distinction between a morphological variant and the presence of an NC cardiomyopathy is challenging. However, thanks to larger cohorts of patients and longer periods of follow-up, better clinical characterization and prognostic evaluation are becoming available. Indeed, the physician is required to integrate the evidence of NC with the clinical history of the patient, which is supplemented by necessary advanced instrumental investigations before a definite diagnosis of NC cardiomyopathy can be made. Therefore, we extensively revised the current literature in order to help the clinicians to identify clinical features which are pivotal supporting diagnostic element for the correct recognition of Left ventricular noncompaction cardiomyopathy and thus highlighting the difference between a form of cardiomyopathy and a mere intraventricular hypertrabeculation.

Keywords Left ventricular noncompaction · Cardiomyopathy · Echocardiography · Cardiac magnetic resonance · Late gadolinium enhancement · Genetics

Introduction

Left ventricular noncompaction cardiomyopathy (LVNC) is a rare heart muscle disease characterized by pronounced ventricular trabeculation, due to the arrest of the normal compaction process of the myocardial wall during fetal development [1]. Morphologically, the left ventricle (LV) is characterized by the presence of a noncompacted (NC) subendocardial layer, with trabeculae separated by deep recesses, and a thin compacted (C) epicardial layer. The inferolateral and apical regions of the LV are frequently affected [1]. However, the right ventricle (RV) may be affected as well [2–5], and RV involvement may occur with hypertrabeculation, dilatation, and dysfunction, the latter most likely due to coexistent left ventricular dysfunction [5].

The variability in the phenotypic expression and absence of gold standard diagnostic criteria make the prevalence difficult to estimate. However, current data report a prevalence of 0.1–0.3% in the adult population of this condition [6–8]. Moreover, the only presence of a phenotype characterized by pronounced NC subendocardial layer is insufficient to identify a LVNC cardiomyopathy and a correct diagnosis cannot be established using morphological criteria alone without a careful clinical characterization [9]. Indeed, there is the risk of over diagnosing the condition because several physiological circumstances characterized by volume overload, such as pregnancy [10], athleticism [11–13], African ethnicity [14], and pathological condition of volume overload [15], are often associated with a LVNC-like phenotype. On the other hand, LVNC can frequently be found in primary (dilated, hypertrophic, arrhythmogenic, and restrictive cardiomyopathy) as well as in acquired cardiomyopathies [14]. Even congenital heart diseases are often characterized by ventricular noncompaction [16–18]. A family history of LVNC, coexisting

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neuromuscular disorders, abnormal 12-lead ECG findings, presence of arrhythmia, heart failure, and previous occurrence of thromboembolism are pivotal supporting diagnostic elements [19]. We extensively reviewed the current literature in order to help clinicians in the identification of morphological and clinical features useful for the correct distinction between LVNC cardiomyopathy and forms of mere intraventricular hypertrabeculation.

Diagnostic criteria

Since the 1990s, a number of morphological criteria have been proposed (Table 1) [20–28].

Among the echocardiographic criteria, those proposed by Jenni's [21] are the most widely used. According to these criteria, an end-systolic NC/C ratio greater than 2 in the parasternal short axis view is supportive of LVNC. In 2005, Petersen et al. [24] proposed new cardiac magnetic resonance (CMR) criteria for diagnosing LVNC: an NC/C ratio greater than 2.3 in a long axis end-diastolic image, in at least two consecutive segments.

Several studies have proposed additional criteria to improve the diagnostic sensitivity and specificity (see Table 1) [25–28].

Most of these studies have been generated integrating Jenni's criteria [21] in association with one or more clinical aspects such as family history, neuromuscular disease, heart failure, arrhythmias, syncope, and previous thromboembolic events. Jacquier et al. [25] have proposed to define LVNC based on the presence of a NC to C mass ratio greater than 20% in a short axis end-diastolic cine CMR image. Grothoff et al. [26] increased the complexity of the diagnostic criteria introducing the concept of the NC mass indexed by body surface area. Captur et al. [27] studied the complexity of distribution of the NC myocardium using a mathematical model based on fractal analysis. Finally, Stacey et al. proposed using the ratio between NC to C layers at end-diastole and end-systole on cine CMR images [28].

Currently, only the Captur criteria [27] appear to be really strict and relatively precise. Indeed, Kawel et al. [29] demonstrated a lack of specificity of Petersen's criteria, with a positivity of 43% in a large cohort (N = 1000) of healthy volunteers. A subsequent study by Weir-McCall JR et al. [30] showed a 15% positivity for at least one of Petersen's [24], Jaquier's [25], Grotoff's [26], and Stacey's [28] morphological criteria in a large cohort of healthy volunteers (N = 1480).

These studies demonstrated that the use of numerical cutoff alone may be a suboptimal criterion to establish a diagnosis of LVNC. Therefore, more specific criteria are needed to improve the diagnosis of this challenging entity.

Pathogenetic considerations and morphologic evaluation

Evolutionary changes during cardiac morphogenesis suggest that LVNC reflects impaired/arrested compaction of the developing myocardium during intrauterine life [31].

The compaction process or trabecular remodeling gradually progresses from the epicardium to the endocardium, and therefore the embryonic myocardial maturation and its arrest during embryogenesis may determine the LVNC phenotype. Thus, it could be useful searching for some NC characteristics which may represent morphological traits capable of differentiating a normal variant from a pathological myocardial structure with potential clinical relevance. Especially at CMR evaluation, the association of a thinner compact myocardial wall, reflecting the expression of embryogenic arrest, with a superimposed NC layer of the myocardium could differentiate a pathological NC myocardium from intraventricular hypertrabeculation representing a normal variant which is characterized by NC within a normal myocardial thickness (Fig. 1, panels a and b).

Electrocardiogram

Twelve-lead electrocardiogram (ECG) is often abnormal in LVNC [19, 32] (see Table 2), and new alterations can emerge over time as shown by Stolberger C. et al. [38].

Zhou H. et al. [39] found that a longer corrected QT interval (QTc) was associated with more elevated native T1 values. These data suggest that patients with prolonged QTc probably have more fibrosis and QTc prolongation correlated inversely with patient outcome.

Cetin MS et al. [40] evaluated the role of fragmented QRS (fQRS) in inferior and lateral leads in 88 patients. The fQRS emerged as an independent predictor of arrhythmic events and cardiovascular mortality in patients with LVNC.

Echocardiography

Echocardiography is the first imaging technique used in daily practice in the diagnostic workup of patients with LVNC.

Potential technical pitfalls and potential confounding elements are off axis imaging, false tendons, aberrant bands, LV apical thrombi, and cardiac tumors [41].

During the general evaluation of systolic and diastolic function, an early marker of systolic impairment is a reduced global longitudinal strain (GLS) [13].

Thanks to the high spatial resolution and accuracy in volumetric quantification, three-dimensional echocardiography has been demonstrated to be a feasible tool for the identification of patients with LVNC and the assessment of the extent of NC myocardium [35].

Table 1 Morphological echocardiography and CMR criteria for LVNC definition

	Method	Number	Morphologic criteria	Cardiac phase	Recommended section
Chin et al. [20]	ECO	8	Ratio X/Y ≤ 0.5 X—Distance between the epicardial surface and through of intertrabecular recess Y—Distance between epicardial surface and peak of trabeculation	End-diastolic	Parasternal long axis Apical 4 chamber
Jenni et al. [21]	ECO	7	Ratio NC/C > 2 Color Doppler evidence of deep intertrabecular recesses filled with blood from the left ventricular cavity	End-systolic	Parasternal Short axis
Stollberger et al. [22]	ECO	14	More than three trabeculations protruding from the left ventricular wall, located apically to the papillary muscles and visible in one image plane	Not defined	Not defined
Belanger et al. [23]	ECO	60	Planimetric area of NC and NC/C ratio Mild: area ≤ 2.5 cm^2 and/or NC/C < 1 Moderate: area 2.5–5 cm^2 and/or NC/C 1–2 Severe: area ≥ 5 cm^2 and/or NC/C ≥ 2	Not defined	Apical four chamber view for quantification of planimetric area NC/C not defined
Petersen et al. [24]	CMR	7	Ratio NC/C > 2.3	End-diastolic	SSFP Long axis
Jacquier et al. [25]	CMR	16	Mass NC/C > 20%	End-diastolic	SSFP Short axis
Grothoff et al. [26]	CMR	12	Mass NC/C > 25% Mass NC index on BSA > 15 g/m^2 Ratio NC/C ≥ 3:1 in all segment excluding apex Ratio NC/C ≥ 2:1 in basal segment of inferior, inferolateral, and anterolateral wall	End-diastolic	SSFP Short axis
Captur et al. [27]	CMR	30	FD global ≥ 1.26 FD apical ≥ 1.3	End-diastolic	SSFP Short axis

Adapted from Negri F. et al. Make a point on left ventricular noncompaction. G Ital Cardiol (Rome). 2018 Jun;19 (6):371–378

N number of patients, *SSFP* steady-state free precession (or cine imaging), *FD* fractal dimension

Cardiac magnetic resonance

CMR provides both morphological evaluation and noninvasive tissue characterization and has been widely used in LVNC [33, 37] (Fig. 2).

Nucifora et al. [36] in 2011 described the CMR findings in a cohort of LVNC patients ($N = 42$). Hypertrabeculation was more frequent at the apex and at the middle segments of the anterolateral and inferolateral walls; LV systolic dysfunction was present in about half of the cases; 55% of patients showed mid-wall late gadolinium enhancement (LGE), which did not closely correlate with the NC areas. At multivariate analysis, LGE was the only independent predictor of systolic LV impairment.

Recently, in a prospective multicenter study from Andreini et al. [4], LV dilatation and systolic dysfunction and the presence of LGE were identified as independent predictors of poor outcome. Interestingly, the degree of LV trabeculation did not have a significant prognostic impact. Similarly, Ivanov et al. [42] did not attribute a prognostic value to Petersen [24], Jacquier [25], and Grothoff [26] morphological criteria. The analysis was inconclusive for Captur criteria [27] with few patients analyzed. However, both studies included only adult patients; therefore, the concept of a poor prognostic value of the presence of NC cannot be translated to infants and children with extensive area of NC. LV trabeculation, however, seems to be correlated with reduced myocardial deformation indexes, even in the presence of a normal ejection fraction. Nucifora et al. [43] demonstrated that children/adolescents with LVNC and normal ejection fraction have a significant impairment of myocardial deformation parameters compared to controls, suggesting an early onset of the ominous effects of the disease on LV function. Similar results were obtained by Cai et al. [44] in a population of apparently healthy subjects.

These observations underline the usefulness of myocardial deformation imaging as a more sensitive technique for the evaluation of LV function, compared to LVEF, and imply that a subclinical impairment of myocardial deformation properties occurs quite early in the course of the disease and raise the question of whether subtle changes of myocardial deformation parameters may predict the development of overt cardiomyopathy. Further studies, ideally with a longitudinal design and with long-term follow-up, are needed to address this issue.

Native T1 mapping has emerged as a useful tool to identify the presence of diffuse myocardial fibrosis without the use of a paramagnetic contrast agent in several cardiac diseases [45–47].

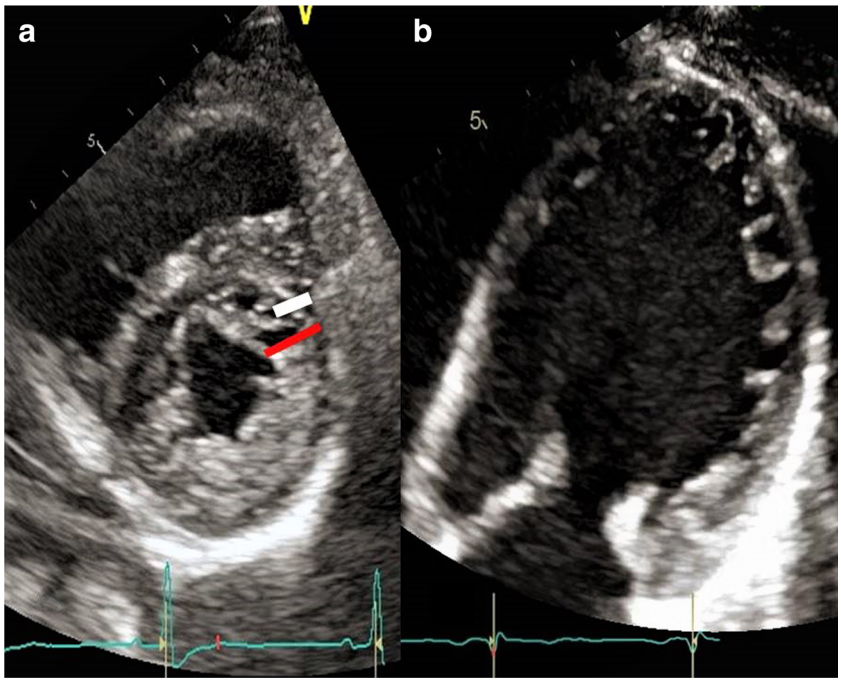

Fig. 1 Transthoracic echocardiogram. Panel **a** and **b** applications of Jenny's criteria; red dash noncompacted layer, white dash compacted layer NC/C ≥ 2

Table 2 Clinical presentation and instrumental features in LVNC

Main clinical and instrumental features in LVNC	Prevalence (%)	Reference
Family history of LVNC	10–18	[4, 33]
Neuromuscular disease	3–4	[4, 34]
Asymptomatic	50–69	[4, 33]
Heart failure	9–89	[4, 7, 33, 35, 36]
Arrhythmias		
Ventricular ectopic beats	31–49	[33, 35]
SVT/NSVT	9–41	[4, 7, 20, 33, 34, 37]
AF	10–29	[7, 33, 34]
Thromboembolic events	4–7	[4, 37]
Abnormal ECG	57–94	[7, 20, 31, 33]
Echocardiography data		
LV dilatation EDD > 60 mm	49–67	[7]
LVEF ≤ 50% and diastolic dysfunction ≥ II grade	63–100	[7, 17, 20, 21]
Segmental kinetics abnormality of LV	100	[21]
RV NC	7–22	[2, 3]
Cardiac magnetic resonance		
LV dilatation	53	[4]
LV dysfunction	40–73	[4, 33, 35, 36]
Late gadolinium enhancement (LGE)	10–55	[4, 33, 35, 36]
RV NC	9–18	[4, 5]
RV (dilatation, dysfunction, LGE)	16–26	[4, 5]

Adapted from Negri F. et al. Make a point on left ventricular noncompaction. G Ital Cardiol (Rome). 2018 Jun;19 (6):371–378

LVNC left ventricular noncompaction, *STV* sustained ventricular tachycardia, *NSVT* nonsustained ventricular tachycardia, *AF* atrial fibrillation, *EDD* end diastolic diameter (long axis view), *LVEF* left ventricular ejection fraction, *RV* right ventricular

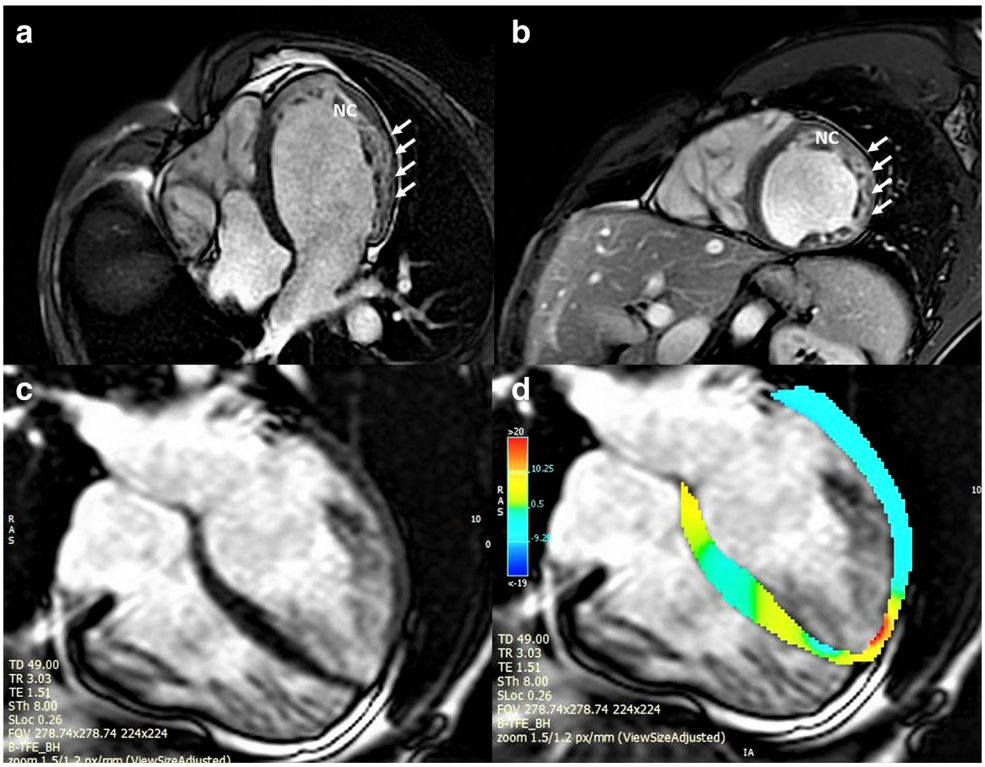

Fig. 2 Cardiac magnetic resonance. Panel **a**: four chamber oblique view; left ventricular noncompacted (NC) layer at lateral and apical wall demonstrated with cine CMR, white arrows show very thin compacted (C) layer. Panel **b**: short axis view; white arrows show the thin compacted layer. Panels **c** and **d** show reduce global longitudinal strain (GLS) in a LVNC patient, particularly at the apex, as a marker of early disease

Zhou et al. [48] have applied T1 mapping in 31 patients with LVNC and without LGE. The study demonstrated that LVNC patients have elevated native myocardial T1 values compared with normal controls, suggesting that native T1 mapping may be a more useful indicator of early-stage myocardial fibrosis than LGE imaging in LVNC patients. The results of this study were confirmed by Araujo-Filho JAB et al. [49].

Nevertheless, these findings need to be confirmed by larger studies, in order to determine the prognostic value of this technique in this population. Finally, in whom CMR is not tolerated or contraindicated [50], computed tomography (CT) has a role in the study of patients in the context of LVNC providing information of NC using Petersen criteria [51].

Genetics

Genetic characterization of LVNC is improving thanks to the next-generation sequencing (NGS) technique. However, large areas of uncertainty in the interpretation of the data [52] still persist.

Many of the genetic mutations found in LVNC are shared with other cardiomyopathies [34, 53–55], in particular dilated cardiomyopathy [55].

In their study on 95 patients, Sedaghat-Hamedani et al. [55] demonstrate that the gene most frequently involved in LVNC was Titin (TTN) with truncating variants, followed by Lamin A (LMNA).

In a recent report by Wang et al. [56] in 102 Japanese pediatric patients with LVNC, the genes most frequently involved were β-myosin heavy chain (MYH7) and Tafazzina (TAZ). This study shows that patients with pathogenic variants have a worse prognosis with an increased risk for the composite end point of death, transplantation, and defibrillator implantation. Furthermore, the same authors demonstrate that mutations in nonsarcomeric genes carry a worse prognosis compared to those in sarcomeric genes. Finally, the study [56] demonstrates that patients with several pathogenic variants have a worse prognosis compared to patients with a single pathogenic variant.

In a multicenter study carried out in four centers in the Netherlands, Waning et al. [57] investigated the prognostic role of genetic mutations in patients with LVNC. The study included 52 children and, for the first time, a large cohort of adult (275 patients) with a diagnosis of LVNC assessed by echocardiography and CMR.

Children and adults were divided into three groups: patients with a gene mutation (*genetic group*; 32%), patients with family history of LVNC without a pathogenic mutation (*probably genetic group*; 16%), and patients without family history and pathogenic mutation (*sporadic group*; 52%). Among the patients of the *genetic group*, the most common mutations involved MYH7, MYBPC3, and TTN genes. Mutations were found more frequently in children, while *sporadic* LVNC was more prevalent in adults. The presence of probable mutation or multiple mutations was associated with the occurrence of major adverse cardiac events

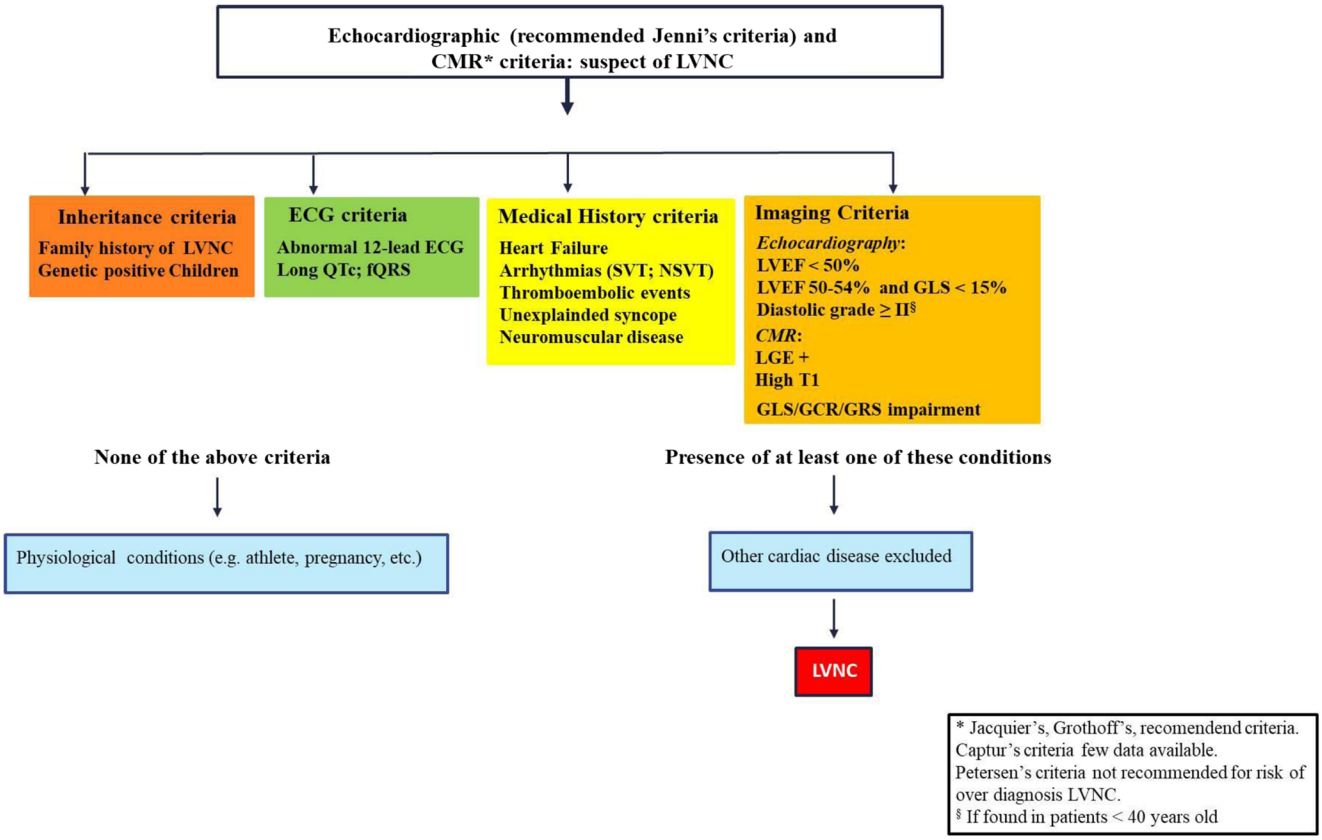

Fig. 3 Proposed diagnostic algorithm. LVNC left ventricular noncompaction, LVEF left ventricular ejection fraction, HCM hypertrophic cardiomyopathy, DCM dilated cardiomyopathy, CHD congenital heart disease, STV sustained ventricular tachycardia, NSVT nonsustained ventricular tachycardia, fQRS fragmented QRS, GLS global longitudinal strain, GCS global circumferential strain, GRS global radial strain

(MACE) during a median follow-up of 60 months in children, while no difference in risk of MACE was observed among the adults with genetic, probable genetic, and sporadic LVNC. In the context of NC, left ventricular systolic dysfunction seems to have an important prognostic role; indeed, it was associated with an increased risk of MACE while genetic patients with good LV function had a low risk of adverse cardiac events.

Clinical management

LVNC has a wide presentation range [58, 59] (see Table 2). Ventricular tachycardia (VT) is reported in 38–47% of patients with LVNC [32]. Muser et al. [60] demonstrated that the electroanatomic substrate of VT in patients with LVNC typically involves the noncompacted mid-apical LV segments. In these subjects, catheter ablation may be a safe and effective procedure to achieve a good ventricular arrhythmia control during follow-up.

Thromboembolic events are described in 4–7% of patients [4, 36, 37] and can significantly affect the prognosis and quality of life. Some authors suggest the use of oral anticoagulant therapy in patients with LVNC with left ventricular dysfunction (ejection fraction $\leq 40\%$) and sinus rhythm [31, 61]. However, it is important to mention that evidence-based recommendations for the prevention of thromboembolic events in LVNC have not been established.

Treatment of heart failure characterized by impaired LV systolic function is based on optimal medical therapy including angiotensin converting enzyme (ACE) inhibitors and beta blockers according to international guidelines [62] and ICD implantation, when indicated [62]. The majority of studies report patients in NYHA class I–II, while just a few studies report patients with advanced heart failure NYHA III–IV [7, 36, 37, 59].

Conclusions

From the early 1990s, emphasis has been placed on the morphological criteria in order to better define NC cardiomyopathy. Only recently, thanks to larger cohorts of patients and longer periods of follow-up, common clinical features and new elements (e.g. LGE; pathogenic mutation, T1 value, systolic impairment which include GLS) to define prognosis have emerged. The physician is now called to integrate the evidence of NC with the clinical history of the patient, supplemented by appropriate instrumental examinations before a definite

diagnosis of NC cardiomyopathy can be established. Finally, we propose an algorithm (Fig. 3) to help in identifying LVNC from a noncompaction condition that can be considered physiological. However, many aspects are still not fully understood: multicenter studies, registers, and observational studies are needed for a better comprehension of the pathology, adequate risk stratification, and targeted follow-up.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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References

1. Sedmera D, Pexieder T, Vuillemin M, Thompson RP, Anderson RH (2000) Developmental patterning of the myocardium. Anat Rec 258:319–337
2. Pignatelli RH, McMahon CJ, Dreyer WJ, Denfield SW, Price J, Belmont JW, Craigen WJ, Wu J, el Said H, Bezold LI, Clunie S, Fernbach S, Bowles NE, Towbin JA (2003) Clinical characterization of left ventricular noncompaction in children: a relatively common form of cardiomyopathy. Circulation 108:2672–2678
3. Ichida F, Hamamichi Y, Miyawaki T, Ono Y, Kamiya T, Akagi T, Hamada H, Hirose O, Isobe T, Yamada K, Kurotobi S, Mito H, Miyake T, Murakami Y, Nishi T, Shinohara M, Seguchi M, Tashiro S, Tomimatsu H (1999) Clinical features of isolated noncompaction of the ventricular myocardium: long-term clinical course, hemodynamic properties, and genetic background. J Am Coll Cardiol 34:233–240
4. Andreini D, Pontone G, Bogaert J, Roghi A, Barison A, Schwitter J, Mushtaq S, Vovas G, Sormani P, Aquaro GD, Monney P, Segurini C, Guglielmo M, Conte E, Fusini L, dello Russo A, Lombardi M, Gripari P, Baggiano A, Fiorentini C, Lombardi F, Bartorelli AL, Pepi M, Masci PG (2016) Long-term prognostic value of cardiac magnetic resonance in left ventricle noncompaction: a prospective multicenter study. J Am Coll Cardiol 68:2166–2181
5. Nucifora G, Aquaro GD, Masci PG, Pingitore A, Lombardi M (2014) Magnetic resonance assessment of prevalence and correlates of right ventricular abnormalities in isolated left ventricular noncompaction. Am J Cardiol 113:142–146
6. Arbustini E, Narula N, Dec GW, Reddy KS, Greenberg B, Kushwaha S, Marwick T, Pinney S, Bellazzi R, Favalli V, Kramer C, Roberts R, Zoghbi WA, Bonow R, Tavazzi L, Fuster V, Narula J (2013) The MOGE(S) classification for a phenotype-genotype nomenclature of cardiomyopathy: endorsed by the World Heart Federation. J Am Coll Cardiol 62:2046–2072
7. Aras D, Tufekcioglu O, Ergun K, Ozeke O, Yildiz A, Topaloglu S, Deveci B, Sahin O, Kisacik HL, Korkmaz S (2006) Clinical features of isolated ventricular noncompaction in adults long-term clinical course, echocardiographic properties, and predictors of left ventricular failure. J Card Fail 12:726–733
8. Stanton C, Bruce C, Connolly H, Brady P, Syed I, Hodge D, Asirvatham S, Friedman P (2009) Isolated left ventricular noncompaction syndrome. Am J Cardiol 104:1135–1138
9. Oechslin E, Jenni R (2018) Left ventricular noncompaction. J Am Coll Cardiol 71:723–726
10. Gati S, Papadakis M, Papamichael ND, Zaidi A, Sheikh N, Reed M, Sharma R, Thilaganathan B, Sharma S (2014) Reversible de novo left ventricular trabeculations in pregnant women: implications for the diagnosis of left ventricular noncompaction in low-risk populations. Circulation 130:475–483
11. Gati S, Chandra N, Bennett RL, Reed M, Kervio G, Panoulas VF, Ghani S, Sheikh N, Zaidi A, Wilson M, Papadakis M, Carré F, Sharma S (2013) Increased left ventricular trabeculation in highly trained athletes: do we need more stringent criteria for the diagnosis of left ventricular non-compaction in athletes? Heart 99:401–408
12. Minamisawa M, Koyama J, Kozuka A, Miura T, Ebisawa S, Motoki H, Okada A, Izawa A, Ikeda U (2016) Regression of left ventricular hypertrabeculation is associated with improvement in systolic function and favorable prognosis in adult patients with non-ischemic cardiomyopathy. J Cardiol 68:431–438
13. Caselli S, Attenhofer Jost CH, Jenni R, Pelliccia A (2015) Left ventricular noncompaction diagnosis and management relevant to pre-participation screening of athletes. Am J Cardiol 116:801–808
14. Arbustini E, Weidemann F, Hall JL (2014) Left ventricular noncompaction. J Am Coll Cardiol 64:1840–1850
15. Ciolli A, de Matteis G, Trambaiolo P, Castro A, Stingone A, Altamura G (2015) Is left ventricular noncompaction only a morphological feature? A case of disappearance of noncompaction after surgical correction of aorto-right ventricular fistula, interventricular septal defect and aortic stenosis. J Cardiovasc Echogr 25:26–28
16. Stähli BE et al (2013) Left ventricular non-compaction: prevalence in congenital heart disease. Int J Cardiol 167:2477–2481
17. Tian T, Yang Y, Zhou L, Luo F, Li Y, Fan P, Dong X, Liu Y, Cui J, Zhou X (2018) Left ventricular non-compaction: a cardiomyopathy with acceptable prognosis in children. Heart Lung Circ 27:28–32
18. Arunamata A, Punn R, Cuneo B, Bharati S, Silverman NH (2012) Echocardiographic diagnosis and prognosis of fetal left ventricular noncompaction. J Am Soc Echocardiogr 25:112–120
19. Hussein A, Karimianpour A, Collier P, Krasuski RA (2015) Isolated noncompaction of the left ventricle in adults. J Am Coll Cardiol 66:578–585
20. Chin TK, Perloff JK, Williams RG, Jue K, Mohrmann R (1990) Isolated noncompaction of left ventricular myocardium. A study of eight cases. Circulation 82:507–513
21. Jenni R, Oechslin E, Schneider J, Attenhofer Jost C, Kaufmann PA (2001) Echocardiographic and pathoanatomical characteristics of isolated left ventricular non-compaction: a step towards classification as a distinct cardiomyopathy. Heart 86:666–671
22. Stöllberger C, Finsterer J, Blazek G (2002) Left ventricular hypertrabeculation/noncompaction and association with additional cardiac abnormalities and neuromuscular disorders. Am J Cardiol 90:899–902
23. Belanger AR, Miller MA, Donthireddi UR, Najovits AJ, Goldman ME (2008) New classification scheme of left ventricular noncompaction and correlation with ventricular performance. Am J Cardiol 102:92–96
24. Petersen SE, Selvanayagam JB, Wiesmann F, Robson MD, Francis JM, Anderson RH, Watkins H, Neubauer S (2005) Left ventricular non-compaction. J Am Coll Cardiol 46:101–105
25. Jacquier A, Thuny F, Jop B, Giorgi R, Cohen F, Gaubert JY, Vidal V, Bartoli JM, Habib G, Moulin G (2010) Measurement of trabeculated left ventricular mass using cardiac magnetic resonance imaging in the diagnosis of left ventricular non-compaction. Eur Heart J 31:1098–1104
26. Grothoff M, Pachowsky M, Hoffmann J, Posch M, Klaassen S, Lehmkuhl L, Gutberlet M (2012) Value of cardiovascular MR in

diagnosing left ventricular non-compaction cardiomyopathy and in discriminating between other cardiomyopathies. Eur Radiol 22: 2699–2709
27. Captur G, Muthurangu V, Cook C, Flett AS, Wilson R, Barison A, Sado DM, Anderson S, McKenna WJ, Mohun TJ, Elliott PM, Moon JC (2013) Quantification of left ventricular trabeculae using fractal analysis. J Cardiovasc Magn Reson 15:36
28. Stacey RB, Andersen MM, St Clair M, Hundley WG, Thohan V (2013) Comparison of systolic and diastolic criteria for isolated LV noncompaction in CMR. JACC Cardiovasc Imaging 6:931–940
29. Kawel N, Nacif M, Arai AE, Gomes AS, Hundley WG, Johnson WC, Prince MR, Stacey RB, Lima JAC, Bluemke DA (2012) Trabeculated (noncompacted) and compact myocardium in adults: the multi-ethnic study of atherosclerosis. Circ. Cardiovasc. Imaging 5:357–366
30. Weir-McCall JR, Yeap PM, Papagiorcopulo C, Fitzgerald K, Gandy SJ, Lambert M, Belch JJF, Cavin I, Littleford R, Macfarlane JA, Matthew SZ, Nicholas RS, Struthers AD, Sullivan F, Waugh SA, White RD, Houston JG (2016) Left ventricular noncompaction. J Am Coll Cardiol 68:2157–2165
31. Oechslin E, Jenni R (2011) Left ventricular non-compaction revisited: a distinct phenotype with genetic heterogeneity? Eur Heart J 32:1446–1456
32. Towbin JA, Lorts A, Jefferies JL (2015) Left ventricular non-compaction cardiomyopathy. Lancet 386:813–825
33. Mavrogeni S, Sfendouraki E, Theodorakis G, Kolovou G (2013) Diagnosis, severity grading and prognosis of left ventricular non-compaction using cardiovascular magnetic resonance. Int J Cardiol 167:598–599
34. Luedde M, Ehlermann P, Weichenhan D, Will R, Zeller R, Rupp S, Müller A, Steen H, Ivandic BT, Ulmer HE, Kern M, Katus HA, Frey N (2010) Severe familial left ventricular non-compaction cardiomyopathy due to a novel troponin T (TNNT2) mutation. Cardiovasc Res 86:452–460
35. Caselli S, Autore C, Serdoz A, Santini D, Musumeci MB, Pelliccia A, Agati L (2012) Three-dimensional echocardiographic characterization of patients with left ventricular noncompaction. J Am Soc Echocardiogr 25:203–209
36. Nucifora G, Aquaro GD, Pingitore A, Masci PG, Lombardi M (2011) Myocardial fibrosis in isolated left ventricular non-compaction and its relation to disease severity. Eur J Heart Fail 13:170–176
37. Wan J, Zhao S, Cheng H, Lu M, Jiang S, Yin G, Gao X, Yang Y (2013) Varied distributions of late gadolinium enhancement found among patients meeting cardiovascular magnetic resonance criteria for isolated left ventricular non-compaction. J Cardiovasc Magn Reson 15:20
38. Stöllberger C, Gerger D, Jirak P, Wegner C, Finsterer J (2014) Evolution of electrocardiographic abnormalities in association with neuromuscular disorders and survival in left ventricular hypertrabeculation/noncompaction. Ann Noninvasive Electrocardiol 19:567–573
39. Zhou H, Lin X, Fang L, Zhu W, Zhao X, Ding H, Jiang M, Ge H, Fang Q, He B (2017) Prolonged QTc indicates the clinical severity and poor prognosis in patients with isolated left ventricular non-compaction. Int J Cardiovasc Imaging 33:2013–2020
40. Cetin MS, Ozcan Cetin EH, Canpolat U, Cay S, Topaloglu S, Temizhan A, Aydogdu S (2016) Usefulness of fragmented QRS complex to predict arrhythmic events and cardiovascular mortality in patients with noncompaction cardiomyopathy. Am J Cardiol 117:1516–1523
41. Stöllberger C, Finsterer J (2006) Pitfalls in the diagnosis of left ventricular hypertrabeculation/non-compaction. Postgrad Med J 82:679–683
42. Ivanov A et al (2017) Prevalence and prognostic significance of left ventricular noncompaction in patients referred for cardiac magnetic resonance imaging. Circ Cardiovasc Imaging 10:e006174
43. Nucifora G, Sree Raman K, Muser D, Shah R, Perry R, Awang Ramli KA, Selvanayagam JB (2017) Cardiac magnetic resonance evaluation of left ventricular functional, morphological, and structural features in children and adolescents vs. young adults with isolated left ventricular non-compaction. Int J Cardiol 246:68–73
44. Cai J, Bryant JA, le TT, Su B, de Marvao A, O'Regan DP, Cook SA, Chin CWL (2017) Fractal analysis of left ventricular trabeculations is associated with impaired myocardial deformation in healthy Chinese. J Cardiovasc Magn Reson 19(102):102
45. Martinez-Naharro A, Kotecha T, Norrington K, Boldrini M, Rezk T, Quarta C, Treibel TA, Whelan CJ, Knight DS, Kellman P, Ruberg FL, Gillmore JD, Moon JC, Hawkins PN, Fontana M (2018) Native T1 and extracellular volume in transthyretin amyloidosis. JACC Cardiovasc Imaging. https://doi.org/10.1016/j.jcmg.2018.02.006
46. Nakamori S, Dohi K, Ishida M, Goto Y, Imanaka-Yoshida K, Omori T, Goto I, Kumagai N, Fujimoto N, Ichikawa Y, Kitagawa K, Yamada N, Sakuma H, Ito M (2018) Native T1 mapping and extracellular volume mapping for the assessment of diffuse myocardial fibrosis in dilated cardiomyopathy. JACC Cardiovasc Imaging 11:48–59
47. Hinojar R et al (2015) T1 mapping in discrimination of hypertrophic phenotypes: hypertensive heart disease and hypertrophic cardiomyopathy: findings from the international T1 multicenter cardiovascular magnetic resonance study. Circ. Cardiovasc. Imaging 8:e003285
48. Zhou H, Lin X, Fang L, Zhao X, Ding H, Chen W, Xu R, Bai X, Wang Y, Fang Q (2016) Characterization of compacted myocardial abnormalities by cardiac magnetic resonance with native T1 mapping in left ventricular non-compaction patients—a comparison with late gadolinium enhancement. Circ J 80:1210–1216
49. Araujo-Filho JAB, Assuncao AN Jr, Tavares de Melo MD, Bière L, Lima CR, Dantas RN Jr, Nomura CH, Salemi VMC, Jerosch-Herold M, Parga JR (2018) Myocardial T1 mapping and extracellular volume quantification in patients with left ventricular non-compaction cardiomyopathy. Eur Heart J Cardiovasc Imaging 19: 888–895. https://doi.org/10.1093/ehjci/jey022
50. Grillone S, Nucifora G, Piccoli G, Gianfagna P, Hysko F, Pavoni D, Slavich G, Proclemer A, Gasparini D (2013) Biventricular non-compaction demonstrated on multi-slice computed tomography with echocardiographic correlation. J Cardiovasc Med (Hagerstown) 14:677–680
51. Sidhu MS, Uthamalingam S, Ahmed W, Engel LC, Vorasettakarnkij Y, Lee AM, Hoffmann U, Brady T, Abbara S, Ghoshhajra BB (2014) Defining left ventricular noncompaction using cardiac computed tomography. J Thorac Imaging 29:60–66
52. Richards S et al (2015) Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 17:405–424
53. Moric-Janiszewska E, Markiewicz-Łoskot G (2008) Genetic heterogeneity of left-ventricular noncompaction cardiomyopathy. Clin Cardiol 31:201–204
54. Zaragoza MV, Arbustini E, Narula J (2007) Noncompaction of the left ventricle: primary cardiomyopathy with an elusive genetic etiology. Curr Opin Pediatr 19:619–627
55. Sedaghat-Hamedani F, Haas J, Zhu F, Geier C, Kayvanpour E, Liss M, Lai A, Frese K, Pribe-Wolferts R, Amr A, Li DT, Samani OS, Carstensen A, Bordalo DM, Müller M, Fischer C, Shao J, Wang J, Nie M, Yuan L, Haßfeld S, Schwartz C, Zhou M, Zhou Z, Shu Y, Wang M, Huang K, Zeng Q, Cheng L, Fehlmann T, Ehlermann P, Keller A, Dieterich C, Streckfuß-Bömeke K, Liao Y, Gotthardt M, Katus HA, Meder B (2017) Clinical genetics and outcome of left

ventricular non-compaction cardiomyopathy. Eur Heart J 38:3449–3460
56. Wang C et al (2017) A wide and specific spectrum of genetic variants and genotype-phenotype correlations revealed by next-generation sequencing in patients with left ventricular noncompaction. J Am Heart Assoc 6:e006210
57. van Waning JI, Caliskan K, Hoedemaekers YM, van Spaendonck-Zwarts KY, Baas AF, Boekholdt SM, van Melle JP, Teske AJ, Asselbergs FW, Backx APCM, du Marchie Sarvaas GJ, Dalinghaus M, Breur JMPJ, Linschoten MPM, Verlooij LA, Kardys I, Dooijes D, Lekanne Deprez RH, IJpma AS, van den Berg MP, Hofstra RMW, van Slegtenhorst MA, Jongbloed JDH, Majoor-Krakauer D (2018) Genetics, clinical features, and long-term outcome of noncompaction cardiomyopathy. J Am Coll Cardiol 71:711–722
58. Muser D, Nucifora G, Gianfagna E, Pavoni D, Rebellato L, Facchin D, Daleffe E, Proclemer A (2014) Clinical spectrum of isolated left ventricular noncompaction. J Am Coll Cardiol 63:e39
59. Oechslin EN, Attenhofer Jost CH, Rojas JR, Kaufmann PA, Jenni R (2000) Long-term follow-up of 34 adults with isolated left ventricular noncompaction: a distinct cardiomyopathy with poor prognosis. J Am Coll Cardiol 36:493–500
60. Muser D, Liang JJ, Witschey WRT, Pathak RK, Castro S, Magnani S, Zado ES, Garcia FC, Desjardins B, Callans DJ, Frankel DS, Marchlinski FE, Santangeli P (2017) Ventricular arrhythmias associated with left ventricular noncompaction: electrophysiologic characteristics, mapping, and ablation. Hearth Rhythm 14:166–175
61. Stöllberger C, Blazek G, Dobias C, Hanafin A, Wegner C, Finsterer J (2011) Frequency of stroke and embolism in left ventricular hypertrabeculation/noncompaction. Am J Cardiol 108:1021–1023
62. Ponikowski P et al (2016) ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 891–975(2016):18