

Adult Left Ventricular Noncompaction

Reappraisal of Current Diagnostic Imaging Modalities



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ABSTRACT

Left ventricular noncompaction (LVNC) cardiomyopathy is morphologically characterized by prominent myocardial trabeculations and deep recesses. The precise stage of development and the natural history of the disorder are not fully understood. Studies in heart failure patients demonstrate a high prevalence of myocardial trabeculations, raising the potential diagnosis of LVNC. Given the high prevalence compared with other primary cardiomyopathies, it is unclear whether the myocardial morphology is representative of LVNC or merely epiphenomena associated with increased cardiac pre-load. Imaging modalities including echocardiography and cardiac magnetic resonance imaging facilitate identification and assessment for LVNC; however, current diagnostic criteria are based on small cohorts and are liable to result in an overdiagnosis of LVNC. This review re-evaluates current diagnostic criteria and their potential impact on overdiagnosis of LVNC in low-risk populations. (J Am Coll Cardiol Img 2014;7:1266-75) © 2014 by the American College of Cardiology Foundation.

Left ventricular noncompaction (LVNC) cardiomyopathy is a new and as yet unclassified cardiomyopathy with an estimated prevalence of 0.014% to 0.17% (1,2). The disorder is morphologically characterized by increased left ventricular (LV) trabeculation and intertrabecular recesses communicating with the LV cavity. However, increased LV trabeculation may be found in up to 30% of patients with LV systolic dysfunction from any cause (3). It is therefore unclear whether LVNC is more common than usually supposed or whether increased trabeculation may be an epiphenomenon of LV dilation. If so, then can it also occur with physiological LV dilation associated with increased cardiac pre-load? This review re-evaluates current diagnostic criteria and their potential impact on overdiagnosis of LVNC in low-risk populations.

CLASSIFICATION OF LVNC

Arbustini et al. (4) have recently proposed a novel classification system for cardiomyopathies termed MOGE(S). The aim of this is primarily to provide a pragmatic method of correlating the cause of disease with clinical phenotype by means of a single notation. Using this system, cardiomyopathies may be classified based on their morphofunctional

characteristics (M), organ involvement (O), genetic or familial inheritance pattern (G), etiology (E), and functional status (S). Although it is appealing to have a generic classification that is applicable to all cardiomyopathies, LVNC provides a number of specific challenges that potentially limits the use of MOGE(S) for this condition. First, as well as exhibiting considerable genetic and clinical heterogeneity, LVNC may represent the morphological spectrum of many phenotypically distinct cardiomyopathies rather than a single, separate entity. The yield of genetic testing in affected patients for LVNC is 40% to 50%. LVNC has been linked to several mutations in the sarcomeric, cytoskeletal, Z-line, and mitochondrial proteins; however, the final common pathway leading to the LVNC phenotype remains to be elucidated (5,6). Secondly, there is considerable heterogeneity in terms of functional capacity and morphological change. Whereas some individuals present with overt heart failure, fatal arrhythmias, and thromboembolic events, others remain asymptomatic (7). Finally, there remains a degree of uncertainty as to the precise etiological factors responsible for the development of LVNC. These factors make a diagnosis of LVNC difficult to establish and classification with the MOGE(S) system imperfect.

PATHOGENESIS OF LVNC

There is controversy whether isolated LVNC is a congenital abnormality as a result of the arrest of the normal compaction process in utero or whether it is acquired during life.

During the early embryological developmental process, the myocardium is a loose meshwork of trabeculations and recesses that communicate with the LV cavity (8). The myocardium becomes compacted between the fifth and eighth week, proceeding from the basal segments to the apex and from epicardium to endocardium (Figure 1). The congenital theory proposes that the process of myocardial compaction is disrupted through unknown mechanisms. The severity of myocardial noncompaction is dependent on the stage at which the arrest of the normal embryonic myocardial maturation takes place.

The ability to acquire LVNC is supported by case reports and studies demonstrating increased LV trabeculation developing on serial echocardiographic assessment (9–11). Bleyl et al. (12) reported an absence of LVNC features in 3 infants with fetal echocardiography who were later diagnosed with LVNC. If LVNC can be acquired, what are the triggers for this? Microcirculatory dysfunction or a metabolic disorder may cause myocardial ischemia or microinfarcts, stimulating an increased trabecular response and features consistent with LVNC (13). Autopsies have identified subendocardial fibrosis, suggesting that myocarditis may be responsible in some cases. Furthermore, it is also recognized that patients with disease processes associated with chronically increased LV pre-load and afterload, such as chronic renal failure, heart valve disease (10), and sickle cell disease (14), have a high prevalence of trabeculations and may also fulfill criteria for LVNC. An increased cardiac pre-load may be associated with an exaggeration in myocardial trabeculations as part of an epiphenomenon rather than a primary cardiomyopathy. In a recent study (15) of more than 1,000 asymptomatic athletes, 18% had increased LV trabeculation. However, 76 (8%) fulfilled echocardiographic criteria for LVNC, of whom 10 (0.9%) had T-wave inversion and reduced resting indices of systolic function that may be considered diagnostic of LVNC. These findings may represent an incomplete expression of the LVNC phenotype in predisposed athletes unmasked through intensive exercise (Figure 2) or an extreme form of cardiac adaptation to exercise.

Gati et al. (16) studied pregnancy as a natural model of increased pre-load. All 102 women had completely normal echocardiograms at their booking

visit, but 26 (25%) developed de novo trabeculations as pregnancy progressed. By a mean 24 months after delivery, 19 (73%) had complete resolution of trabeculations, and 6 had a marked reduction in the trabeculated layer. One became pregnant again and was excluded from follow-up. These data support the theory that a cardiomyopathy is unlikely even if there are criteria for LVNC when symptoms of heart failure or a family history of cardiomyopathy are absent.

It is likely that increased trabeculation is the final common pathway for interactions between a number of genetic and acquired factors. For example, the predisposition to increased LV trabeculation in response to increased afterload may be genetically determined. It has also been suggested that non-compaction may compensate for abnormal myocardial contractility from a genetic defect (6).

DIAGNOSIS OF LVNC

Two-dimensional echocardiography is the most frequently used imaging modality, and 3 main sets of criteria have been proposed to define LVNC (7). The predominant feature common to all 3 is the presence of a double-layered (compacted and noncompacted)

ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance imaging

CTA = computed tomographic angiography

LV = left ventricular

LVNC = left ventricular noncompaction

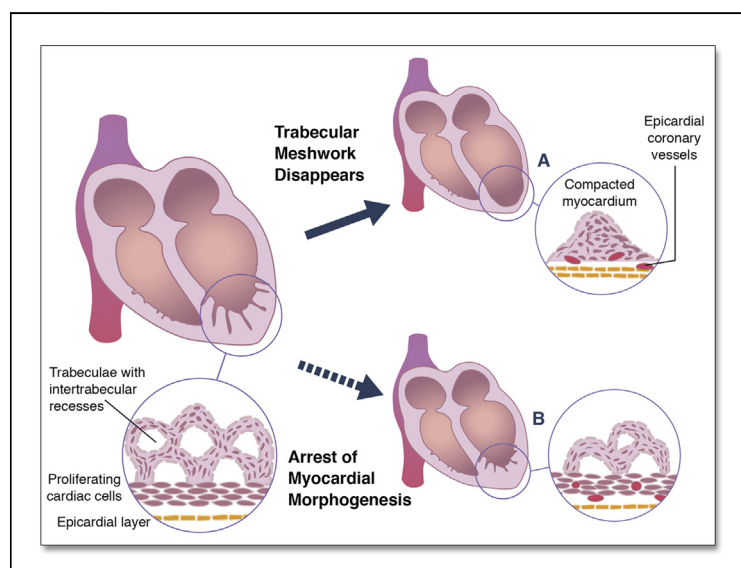
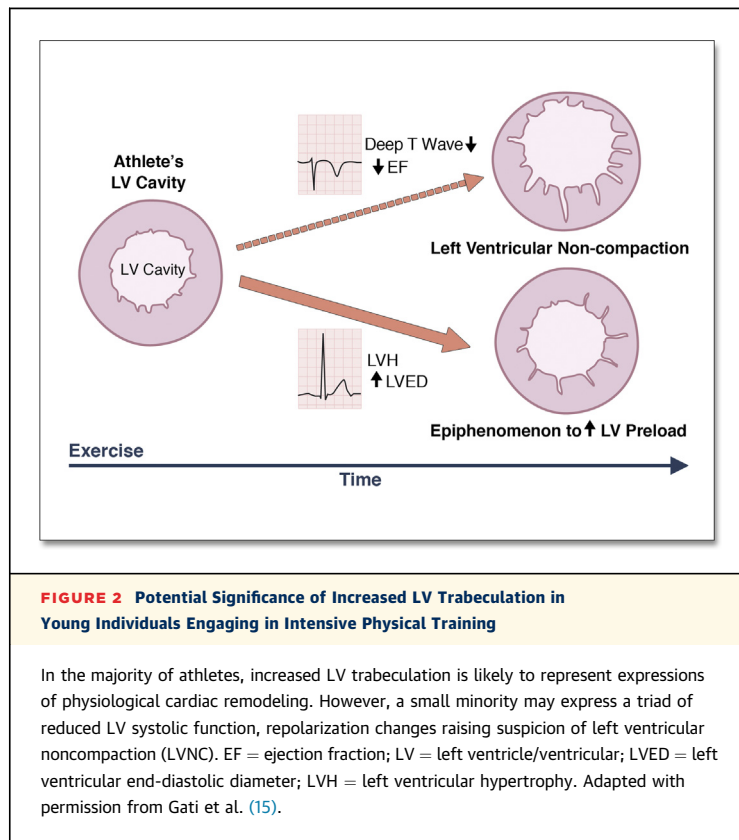


FIGURE 1 Embryonic Development of LVNC

The myocardium starts off as a meshwork of fibers that regress at weeks 5 to 8 to form compacted outer and inner smooth muscle layers (A). In left ventricular noncompaction (LVNC), there is retarded myocardial morphogenesis and persistence of the trabecular meshwork (B).



myocardial architecture. However, their individual definitions for diagnosis of LVNC vary considerably, making it difficult to establish a firm diagnosis in many clinical situations. Chin et al. (17) were the first to propose echocardiographic criteria based on 8 cases (mostly pediatric) validated by autopsy and a control group of 8 normal subjects (Table 1). They calculated the ratio of the distance from the epicardial surface to the trough of the trabeculae (X) to the distance from the epicardial surface to the peak of the trabeculae (Y) measured at end-diastole (17). A progressive decrease in the X/Y ratio was seen from the base to apex in LVNC patients, but not in the 8 controls (17). Recent studies suggest that a ratio of ≤ 0.5 based on measurements acquired in the parasternal short-axis views are best for establishing a diagnosis of LVNC (7). The criteria by Chin et al. (17) do not specify a minimum number of trabeculations required, the location of the noncompacted segments, or the need to perfuse intertrabecular recesses.

The Jenni et al. (18) criteria are the most commonly used in clinical practice (Table 1): a noncompaction-to-compaction ratio >2.0 at end-systole on short-axis views; the absence of other cardiac abnormalities; and color Doppler

demonstrating perfusion of the intertrabecular recesses. Jenni et al. (18) showed that noncompacted segments were frequently in the mid-lateral and inferior walls and apex. In their 34 individuals with LVNC, the definition was validated in 7 patho-anatomic specimens and against 9 patients with hypertensive heart disease and 10 with dilated cardiomyopathy. There was no comparison with normal controls. Interestingly, the original work of Jenni et al. described regional hypokinesia in the non-compacted segments, and this was included in the initial diagnostic criteria. However, on a subsequent study (19) of 139 patients with cardiovascular disease, regional hypokinesia showed low specificity and has since been removed (7).

Stöllberger et al. (20) defined LVNC as more than 3 individual trabeculations protruding from the LV wall apical to the papillary muscle in 1 imaging plane (Table 1). The Stöllberger et al. (20) definition was based on a post-mortem analysis of 474 normal hearts performed by Boyd et al. (21). The Stöllberger et al. (20) criteria were further refined to include a 2-layered myocardium with a ratio of noncompacted-to-compacted myocardium >2.0 at end-diastole (22).

A fourth set of criteria (23) used a slightly different methodology, measuring the LV trabeculations by planimetry in 4-chamber views. Belanger et al. (23) measured the LV trabeculations on echocardiography by planimetry in 4-chamber views to diagnose LVNC. They described the trabeculated areas of LVNC being mild (<2.5 cm²), moderate (2.5 to 4.9 cm²), and severe (≥ 5.0 cm²). Based on their assessment of 380 patients, 15.8% exhibited LVNC. However, their criteria did not correlate with the modified Jenni et al. (18) criteria and have not been validated.

LIMITATIONS OF ECHOCARDIOGRAPHIC ANALYSIS.

The current echocardiographic criteria for LVNC have several limitations. The criteria were derived from a small number of patients and have not been validated prospectively in larger cohorts of patients from different ethnic origins. This was highlighted by Kohli et al. (3), who showed that 24% of patients in a general cardiology outpatient clinic with heart failure fulfilled 1 or more criteria (Chin et al. [17], Jenni et al. [18], and Stöllberger et al. [22]) for LVNC. In addition, 8% of healthy black controls fulfilled 1 or more diagnostic criteria (3). This observation raised the question whether the current echocardiographic criteria derived from Caucasian patients are oversensitive in individuals of African/Afro-Caribbean ethnicity. Uniformly accepted, anatomically controlled, echocardiographic diagnostic criteria, possibly modified for ethnicities, are needed. These criteria should be easily applicable and

generally reproducible with low interobserver and intraobserver variability.

The 2 most common pitfalls in establishing a diagnosis of LVNC during echocardiographic assessment are: 1) the identification of abnormal trabeculations; and 2) their accurate assessment. Abnormal trabeculations can be mistaken for normal myocardial trabeculations, false tendons, aberrant bands, cardiac tumors, and LV apical thrombi (24). Incorrect interpretation can be limited by recognizing relevant distinguishing features. Normal individuals usually have <3 myocardial trabeculations that are located in the LV apex (21). False tendons and aberrant bands generally cross the LV cavity (25). LV apical thrombi can be differentiated from LVNC by their different echogenicity compared with the surrounding myocardium (26). An awareness of LVNC and its phenotypic presentations is likely to limit misdiagnosis. Should LVNC be suspected, it is important to measure the trabeculations in the correct phase of the cardiac cycle and the correct imaging plane, and also to identify the compacted and noncompacted ratios correctly in order that a correct ratio can be calculated in accordance with the diagnostic criteria being used.

EMERGING ECHOCARDIOGRAPHIC TECHNIQUES FOR LVNC. New echocardiographic techniques, including tissue Doppler imaging, strain rate imaging, and speckle tracking, are available to provide a more objective and quantitative assessment of LVNC. Myocardial strain values have been shown to be abnormal in patients with LVNC even in the presence of normal LV systolic/diastolic function. In a recent study of 20 patients with LVNC and 20 age- and sex-matched controls, Bellavia et al. (27) were able to demonstrate a reduction in systolic strain, strain rate, displacement, and rotation/torsion in patients with LVNC that was independent of ejection fraction. Additional studies have been both concordant (28,29) and discordant (30) with these findings, thereby casting doubt as to the discriminatory value of LV twist and torsion mechanics in the setting of LVNC.

Additional morphological evaluation can be performed with 3-dimensional echocardiographic analysis and contrast echocardiography (31,32). Both techniques allow detailed, accurate assessment of the number of trabeculations, compacted segments, intertrabecular recesses, and trabecular volumes. However, both techniques retain an element of user dependency and experience to perform and interpret the imaging findings.

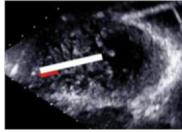
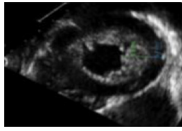
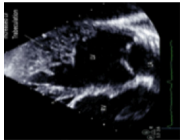
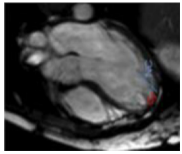
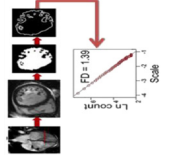
CARDIAC MAGNETIC RESONANCE AND COMPUTED TOMOGRAPHIC IMAGING. Cardiac magnetic resonance imaging (CMR) is increasingly used to confirm the diagnosis of LVNC (Table 1). It is particularly

valuable when echocardiographic image quality is poor. Two sets of CMR criteria are in use, the first proposed by Petersen et al. (33) in 2005 and the other by Jacquier et al. (34) in 2010. Petersen et al. (33) tested the precision of CMR in the diagnosis of LVNC in 177 individuals with and without cardiac disease. Using cine CMR images, the authors were able to identify a distinct 2-layered appearance of trabeculated and compacted myocardium on the horizontal and vertical long-axis and LV outflow tract views at end-diastole in 7 patients with a clinical diagnosis of LVNC. Interestingly, the authors also identified a spectrum of noncompaction in patients with normal or athletic hearts and in patients with known cardiac disease (aortic stenosis, hypertension, hypertrophic cardiomyopathy). The noncompaction was frequently at the apex and lateral wall rather than the basal and septal LV segments as seen in LVNC. On the basis of these findings, Petersen et al. (33) proposed a non-compaction/compaction ratio >2.3 in diastole as a cut point for LVNC (Table 1). This gave a sensitivity of 86% and a specificity of 99% based on statistical analysis of receiver-operating characteristics to generate cutoff values to distinguish LVNC from all other groups of subjects. However, the MESA (Multi-Ethnic Study of Atherosclerosis) investigators found that 43% of 329 patients with no cardiac disease or hypertension achieved this cut point in 1 segment, and 6% in at least 2 segments of the left ventricle (35). This suggests that the Petersen criteria have low specificity in patients at low risk of LVNC.

Jacquier et al. (34) calculated the LV trabecular mass using steady-state free precession short-axis views (Table 1). Based on the assessment of 16 patients (12 known and 4 suspected) with LVNC, and in comparison with patients with dilated cardiomyopathy, hypertrophic cardiomyopathy, and healthy controls, a LV trabecular mass >20% of the total LV mass was predictive of LVNC. The sensitivity and specificity of the Jacquier criteria (34) was 93.7% based on the Jenni et al. (18) criteria as the gold standard for LVNC. Although the reproducibility of trabecular mass percentage was not reported in this study, subsequent evaluation of the Jacquier criteria in other published literature has demonstrated a poor interobserver variability (36).

A further question arises as to whether measurements should be taken in end-diastole or end-systole for the diagnosis of LVNC. Stacey et al. (37) studied a retrospective cohort of 122 individuals with reported trabeculations or LVNC on CMR. The authors found that an end-systolic ratio >2 was a strong predictor of existing heart failure (adjusted odds ratio: 29.4; 95% confidence interval: 6.6 to 125)

TABLE 1 Summary of LVNC Criteria and Their Advantages and Disadvantages

	Chin et al. (17)	Jenni et al. (1,18)	Stöllberger et al. (20)	Petersen et al. (33)	Jacquier et al. (34)	Captur et al. (38)
Patients (n)	8	34	62	7	16	30
Selection criteria	Patients referred for echocardiography	Patients referred for echocardiography fulfilling LVNC criteria presented below	Patients referred for echocardiography demonstrating >3 trabeculations distal to papillary muscle on 4CV	Clinical diagnosis of LVNC based on echo or CMR appearance of a 2-layered trabeculated and compacted myocardium Plus 1 of the following: a) 1st degree relative with similar appearance b) associated neuromuscular disorder c) thromboembolism or RWMA	Diagnosis of LVNC was established on Jenni et al. echocardiographic criteria were enrolled	Fulfillment of Jenni et al. echocardiographic criteria for LVNC and the additional presence of at least 1 of the following: positive family history, associated neuromuscular disorder, RWMA, LVNC-related complications (arrhythmia, heart failure, or thromboembolism)
Age range	11 months to 22.5 yrs	16 to 75 yrs	18 to 75 yrs	14 to 46 yrs	48 ± 17 yrs	41 ± 13 yrs
M:F ratio	5:3	25:9	49:13	5:2	10:6	16:14
Asymptomatic patients (n)	2	—	7	4	Not reported	—
Available pathological correlation (n)	3	7	Not reported	Not reported	Not reported	Technique validated in 24 embryonic murine hearts
Interobserver variability	Not reported	Not reported	Not reported	Not reported	ICC = 0.95 (95% CI: 0.89-0.97), k = 0.87; p < 0.001	ICC = 0.97
Intraobserver variability	Not reported	Not reported	Not reported	Not reported	Not reported	ICC = 0.96
Description of criteria	2-layered structure with an epicardial compacted and endocardial noncompacted layer (Later revised to include a ratio)	2-layered structure with a compacted epicardial and noncompacted endocardial layer Color Doppler evidence of intertrabecular recesses supplied by intraventricular blood Absence of coexisting cardiac structural abnormalities	>3 trabeculations protruding from LV wall apically to papillary muscle in 1 imaging plane (Later revised to include ratio and a 2-layered myocardium)	2-layered structure with a compacted epicardial and noncompacted endocardial layer Images from horizontal and long-axis views at points of prominent trabeculations	Calculated total LV trabeculated mass from SSFP short axis; papillary muscles excluded from trabeculated mass Myocardial mass	Global LV trabecular complexity as a continuous variable termed fractal dimension 2D space is divided into a grid of boxes and skeletonized data within are calculated for 4 different-sized grids The exponent of line of best fit across the points on log-log plot of box counts represents fractal dimension
Cardiac phase	End-diastole	End-systole	End-diastole	End-diastole	End-diastole	—
Ratio*	X/Y ≤ 0.5	NC/C ≥ 2	NC/C ≥ 2	NC/C >2.3	LV trabecular mass >20%	FD ≥1.30
						

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TABLE 1 Continued						
	Chin et al. (17)	Jenni et al. (1,18)	Stöllberger et al. (20)	Petersen et al. (33)	Jacquier et al. (34)	Captur et al. (38)
Advantages	Echocardiography widely available Portable investigation Cost-effective test			Superior contrast-to-noise ratio and signal-to-noise ratio Unlimited imaging planes Ability to use tissue characterization in the diagnosis High sensitivity and specificity Interobserver reproducibility of trabecular mass measurement in Jacquier criteria reported to be high Interobserver and intraobserver variability of Captur criteria high		
Disadvantages	Based on small cohorts for Chin and Jenni criteria Not prospectively derived Not validated properly Measurements in different phases of the cardiac cycle Image quality dependent on body habitus Oversensitive in certain populations Nonspecific in low-risk populations			Based on small cohorts Not prospectively derived Petersen criteria require high pre-test probability Reproducibility of the trabecular mass percentage not reported in Jacquier criteria Not widely available Expensive Requires expertise in the field Captur criteria not available for replication and assessment yet		
<p>*C = compacted; FD = fractal dimension; N = noncompacted. 2D = 2-dimensional; 4CV = 4-chamber view; CI = confidence interval; CMR = cardiac magnetic resonance; ICC = intraclass correlation coefficient; LV = left ventricle/ventricular; LVNC = left ventricular noncompaction; RWMA = regional wall motion abnormality; SSFP = steady-state free precession.</p>						

but also combined clinical events (death, heart failure readmission, embolic events, or ventricular arrhythmias), (adjusted odds ratio: 8.6; 95% confidence interval: 2.5 to 33). However, this study was limited by the retrospective analysis, small sample size, wide confidence intervals, and insufficient information on the natural history of patients with normal and impaired systolic function. Therefore, it remains unclear whether end-systolic measurements are superior to end-diastolic criteria for the diagnosis of LVNC and associated clinical events.

Captur et al. (38) recently described a new CMR technique, fractal analysis, which does not rely on the conventional compacted-to-noncompacted ratio. It summarizes global LV trabecular complexity as a continuous variable termed fractal dimension (38). Fractal analysis involves dividing 2-dimensional space into a grid of boxes and counting the number of boxes that contain part of the skeletonized data. This is repeated for 4 different box sizes on the short-axis cine stack (38). The exponent of the line-of-best fit across the points on the log-log plots of box count represents the fractal dimension. Captur et al. (38) validated their new methodology using 3-dimensional images of 24 embryonic murine hearts selected between days 14.5 and 18.5 of cardiomorphogenesis with high-resolution episcopic microscopy. As the heart compacted, there was a fall in fractal dimension. When this technique was applied to 135 human subjects on CMR, 35 of whom had LVNC, a fractal dimension ≥ 1.3 gave the optimal prediction for patients with LVNC with an area under the curve of 1.0. This fractal approach was reproducible compared with the techniques proposed by Petersen and Jacquier, and more accurate in diagnosing LVNC based on fractal dimension (intraclass correlation coefficient 0.97 and 0.96 for intraobserver and interobserver readings, respectively) (38). Although this technique can be performed on any cardiac-enabled magnetic resonance imaging scanner (1.5-T or 3.0-T), the sensitivity of the methodology using different scanners, different manufacturers, and varying scan parameters has not been tested, and specific software is required. The presence of contrast, noise artifact, and arrhythmogenic load on fractal analysis also requires further assessment. Further large-scale trials are indicated in alternative patient populations.

CMR also offers direct characterization of myocardial fibrosis, which is an independent prognostic marker in different types of cardiomyopathies (39-41). Nucifora et al. (42) identified 42 patients with LVNC using strict CMR criteria (2-layered myocardium with excessive trabeculation and intertrabecular recesses, and ratio of noncompacted-to-compacted layers

>2.3). Late gadolinium enhancement, a surrogate of myocardial fibrosis, was observed in 23 (55%) patients. Although, there was a strong association between the presence and extent of delayed enhancement and symptoms and LV ejection fraction, the prognostic value of this technique has not been demonstrated in LVNC patients with ventricular arrhythmias or correlated to mortality. Late gadolinium enhancement occurred in mid-myocardial segments or where the right ventricle inserted into the left ventricle, and was equally distributed in compacted and non-compacted myocardium (42). Histological studies show good agreement in LVNC between the pattern of late gadolinium enhancement and scarring on myocardial tissue obtained at the time of cardiac transplantation or autopsy (43,44). In addition, histological fibrosis has also been identified in noncompacted myocardium within the prominent trabeculae (17,18) and within the thickened endocardium (18). It is likely that increased wall stress, myocyte necrosis, and progressive LV wall stress account for the delayed enhancement seen within the mid-myocardial segments, along with diminished coronary flow reserve within both the noncompacted and compacted myocardium (45), as well as impaired microvascular function.

Multidetector computed tomographic angiography (CTA) may also be used to assess features of LVNC (46). It provides excellent spatial and contrast resolution for the evaluation of myocardial morphology with the added advantage of providing information relating to the coronary arteries and intrathoracic vasculature. Although not usually recommended as a first-line investigation, it may be useful where magnetic resonance imaging is contraindicated or insufficient image quality has been obtained echocardiographically (47). It is important to note that there are currently no computed tomographic-specific diagnostic criteria for LVNC. Because conventional criteria recommend myocardial assessment at end-systole or end diastole, a coronary CTA would be required at 40% of the R-R interval for end-systole and 0% or 90% of the R-R interval for end-diastole. These phases may not be routinely available on a low-dose, prospective, electrocardiographic-gated coronary CTA. Furthermore, CTA is associated with the disadvantage of radiation exposure, which may be of particular relevance should serial studies be required.

RIGHT VENTRICULAR NONCOMPACTION

Although there are no established diagnostic criteria for noncompaction of the right ventricle, this

phenomenon has been reported in a number of cases. Right ventricular noncompaction has been reported in newborns with congenital heart defects and also in adult patients presenting with neurological symptoms (48). Isolated right ventricular noncompaction is an extremely rare occurrence in adults and usually coexists with LVNC (49,50). The diagnosis has usually been made using 3-dimensional echocardiography from the presence of prominent right ventricular trabeculations and a dilated hypokinetic right ventricle (51). It is likely with the increasing availability of CMR that this condition will be better identified and characterized in the future.

DIAGNOSTIC AND CLINICAL EVALUATION OF LVNC

A multimodal diagnostic approach is the current recommendation for the diagnosis of LVNC. Although echocardiography may be limited by its dependence on ultrasound windows and the skill of the operator, it remains the front-line imaging modality of choice. A thickened myocardium with a noncompacted-to-compacted ratio >2 measured in a systolic short-axis frame is the most commonly used diagnostic threshold. Other echocardiographic functional parameters, including speckle tracking and strain, may be helpful in borderline cases. Other findings suggestive of cardiomyopathy are an E' velocity <9 cm/s and reduced LV contractile reserve on exercise (15). In situations where image quality is poor on transthoracic echocardiography, CMR may help suggest a myopathic process by showing fibrosis on late gadolinium enhancement. However, current diagnostic criteria are limited. The Petersen et al. (33) criteria may result in overdiagnosis in low pre-test probability populations, and the Jacquier et al. (34) criteria have low reproducibility for trabecular mass percentage measurements (52). It is therefore generally recommended that analysis by echocardiography and CMR must be concordant to prevent overdiagnosis of LVNC.

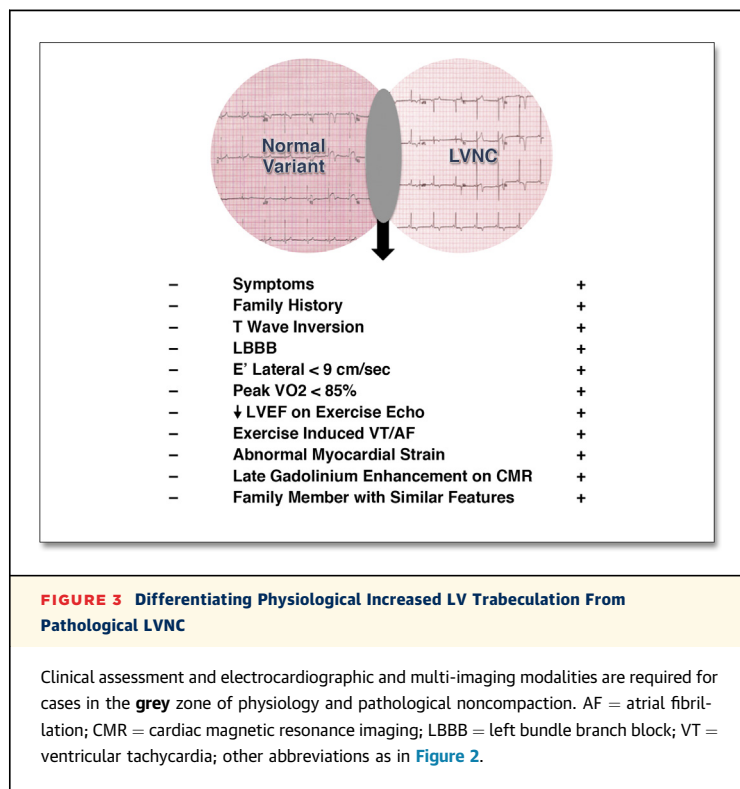
We propose an algorithm to guide the assessment of individuals presenting with increased LV trabeculations suggestive of LVNC, impaired resting LV function, and abnormal electrocardiographic findings (Figure 3). This algorithm was derived from our observations of both athletes with increased LV trabeculations and patients with LVNC (15). In the study by Gati et al. (15) athletes were asymptomatic, whereas 75% of patients with LVNC had symptoms from LV impairment. A minority of athletes with increased LV trabeculation and reduced LV systolic function (ejection fraction range of 45% to 50%) showed

normal indices of longitudinal LV function and diastolic function. In comparison, patients with LVNC often (66%) showed a LV diastolic diameter >64 mm, an ejection fraction <45%, suppressed longitudinal LV function (systolic velocity <9 cm/s), and impaired LV filling. On the 12-lead electrocardiogram, the pattern of T-wave inversion was different between the 2 groups; the majority of athletes showed T-wave inversion in V₁ to V₃, whereas patients with noncompaction show T-wave inversion in the inferolateral leads. Following further comprehensive evaluation, a cardiopulmonary exercise stress test followed by a peak exercise echo showed that athletes had a high peak Vo₂ (>120% predicted for age and size) and dynamic LV contraction, whereas patients with LVNC had low peak Vo₂ and persistently reduced LV function. The findings of nonsustained ventricular tachycardia during exercise in athletes with criteria for LVNC would suggest pathology. The presence of late gadolinium enhancement on CMR would also suggest a cardiomyopathic process. We recommend screening of first-degree relatives for features of LVNC; the detection of another relative with a comparable phenotype would support LVNC.

On the basis of the investigation proposed in the algorithm, Gati et al. (15) did not feel there was sufficient evidence of a cardiomyopathy in the small minority of athletes fulfilling criteria for LVNC with repolarization changes and depressed basal systolic function to warrant disqualification from competitive sport. During a subsequent follow-up period of over 4 years, none of these athletes experienced adverse events. This algorithm was designed to aid the clinician in a pragmatic approach to low-risk individuals fulfilling criteria for LVNC.

CONCLUSIONS

The etiology and natural history and even the diagnosis of LVNC remain unclear and controversial. The identification of a high prevalence of LVNC in low-risk populations such as athletes suggests that increased LV trabeculation and recesses maybe epiphenomena in response to a chronic increase in pre-load. Current diagnostic criteria using echocardiography and CMR are based on small cohorts and tend to overdiagnose LVNC. In order to minimize this problem, we propose



guidance that integrates clinical, electrocardiographic, and imaging characteristics.

FUTURE DIRECTIONS. There are still many unanswered questions in LVNC. Despite significant improvements in echocardiography and tissue harmonics, there still remains a discrepancy and limitations among the available published criteria for diagnosis of LVNC. Future directions for accurate diagnosis may incorporate a multimodality imaging approach, possibly modified for ethnicities, with particular focus on the functional diagnostic assessment of LVNC. Multicenter collaboration is required to build up a large international registry of patients with LVNC for an improved understanding of this complex cardiomyopathy to allow incorporation of genetics and functional imaging to better define LVNC.

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