Left Ventricular Noncompaction
– A Diagnostically Challenging Cardiomyopathy –
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Diagnosing left ventricular noncompaction (LVNC) cardiomyopathy is a challenge for the medical community because the condition shares morphologic features of hypertrophic and dilated cardiomyopathies. The uncertainty surrounding the diagnosis of LVNC is related to the lack of a “perfect diagnostic tool,” such as a reproducible genetic marker. The diagnosis requires expertise in the broad spectrum of overlapping cardiomyopathies. The demarcation between LVNC and normal phenotypic variations is often indistinct. Echocardiography, used in routine clinical practice to identify the typical morphologic features of LVNC, can be overly sensitive and lack specificity with the presently defined measurements and ratios used to diagnose LVNC. The available diagnostic criteria show a propensity toward overdiagnosing LVNC. The complex clinical sequelae of atrial and ventricular arrhythmias, heart failure, thromboembolic events and sudden death associated with LVNC make a valid and reproducible diagnosis critical. The trend to using a morphologic/pathophysiologic, instead of a solely morphologic, approach holds promise in the quest for an accurate, reliable diagnosis of LVNC. We must understand the distinction between morphological findings and morphological findings with pathophysiology. Our future understanding of LVNC depends on an integration of cardiac morphology, physiology, pathophysiology and evolving genetics. (Circ J 2012; 76: 1556–1562)

Key Words: Cardiomyopathy; Left ventricular noncompaction; Myocardial fibrosis

Left ventricular noncompaction (LVNC) results from an arrest of myocardial maturation during embryogenesis and is defined by distinct morphologic features. Characteristic LVNC morphologic features identified with echocardiography include: (1) thick, bilayered myocardium composed of noncompacted and compacted layers; (2) prominent trabecular outpouchings; and (3) deep endomyocardial recesses (Figures 1–4, Movies S1,S2). Morphologic variations of the endomyocardial recesses and trabecular outpouchings have the medical community probing for definitive tools to diagnose LVNC. Diagnosis is complicated by the fact that LVNC shares morphologic features with hypertrophic and dilated cardiomyopathies. These overlapping cardiomyopathies present the medical community with a diagnostic puzzle.

Individuals with LVNC have variable phenotypic expressions of the cardiomyopathy, and clinical features can range from asymptomatic to symptomatic, with heart failure (HF), atrial and ventricular arrhythmias, thromboembolic events and sudden cardiac death. Identification of LVNC occurs in every age group from the fetus to the octogenarian. LVNC associated with complex congenital heart disease was described 80 years ago. Inconsistency in the nomenclature used to describe this unique cardiomyopathy has limited our understanding of LVNC. In 1990, Chin et al reported a series of patients with a persistence of trabecular meshwork and deep intertrabecular recesses communicating with the LV cavity, suggested a unifying terminology of LVNC and proposed echocardiographic criteria for the diagnosis of this entity.

Today, LVNC is included among the primary cardiomyopathies by the World Health Organization, but the European Society of Cardiology Working Group on Myocardial and Pericardial Disease has placed LVNC among the “unclassified” cardiomyopathies and states: “It is not clear whether LVNC is a separate cardiomyopathy, or merely a congenital or acquired morphologic trait shared by many phenotypically distinct cardiomyopathies.” LVNC was classified as a genetic cardiomyopathy by the America Heart Association in 2006. There is general agreement that a distinct “left ventricular noncompaction” phenotype can occur with congenital heart and neuromuscular diseases and in isolation.

This review will detail the physiology, pathophysiology, diagnostic criteria and clinical spectrum of LVNC. We also will describe the challenges facing the medical community and the future directions of diagnosing LVNC.

Pathophysiology
LVNC is hypothesized to result from early cessation of the tra-
LV Noncompaction

Trabecular meshwork compaction during embryogenesis.\textsuperscript{1,2,18} Trabecular compaction in humans occurs between 12 and 18 weeks of gestation, starts at the base of the heart and progresses toward the apex.\textsuperscript{1,2,18} From the fourth month of gestation in humans, the compacted layer forms the bulk of the ventricular myocardium.\textsuperscript{2} Cessation of compaction results in a bilayered myocardium consisting of a compacted epicardial layer and a noncompacted layer composed of a loose, interwoven meshwork of prominent trabecular outpouchings and deep endomyocardial recesses that communicate with the LV cavity. The temporal variability of myocardial maturation arrest can result in a broad spectrum of both phenotypic and clinical expression of LVNC.

LVNC can occur as a random genetic mutation or it can be familial with an autosomal dominant mode of transmission.\textsuperscript{19} Currently, a genetic mutation that consistently results in the LVNC phenotype has not been identified. The most common mutations occur in cardiac sarcomere proteins, such as beta-myosin heavy chain.\textsuperscript{20–22} LVNC sarcomeric mutations have a broad range of expressivity.\textsuperscript{23} Individuals carrying identical sarcomeric mutations display phenotypes ranging from early-onset lethal disease to no evidence of cardiomyopathy. This variable expression of cardiomyopathic disease phenotypes likely reflects an interaction of genotype, genotype modifiers and environmental factors.\textsuperscript{16,17} This genotype-to-phenotype heterogeneity reifies why the diagnosis of LVNC can be elusive and challenging.

Diagnostic Criteria

Echocardiography is the most frequently used imaging modality to diagnose LVNC. Two-dimensional (2D) echocardiography is used to establish the diagnosis, and has increased the awareness of LVNC and its variable phenotypic expression.

There are several definitions that attempt to describe the morphology of LVNC. These definitions are variable, and it is difficult to know which criteria are “best” for making a valid diagnosis of LVNC.\textsuperscript{24–26} Chin et al defined LVNC using a ratio of compacted (C) and noncompacted (NC) myocardium: $C/NC+C \leq 0.5$ at end-diastole. Stöllberger et al defined LVNC as 4 or more trabeculations protruding from the LV wall located apical to the papillary muscles and visible in 1 imaging plane.\textsuperscript{27} The diagnostic criteria of Jenni et al include a ratio of bilayered myocardium (NC/C >2) at end-systole.\textsuperscript{4} We use the ratio NC/C >2 at end-diastole as supporting data in the diagnosis of LVNC.\textsuperscript{28} This modification is based on two reasons. First, the observation that delineation, hence measurements, of the compacted and noncompacted layers of the myocardium are more precise at end-diastole than at end-systole. This approach is consistent with the American Society of Echocardiography’s convention of chamber and wall thickness measurements, which are performed at end-diastole. Second, a ratio based on measurement of wall thickness at end systole by definition incorporates the influence of the contrac-
tile state of the compacted myocardium. Since noncompacted myocardium shows little systolic thickening, the ratio of NC/C can change significantly depending on the extent of systolic thickening of compacted myocardium. The diagnostic criteria for LVNC are summarized in Table 4.12,27–30 The available diagnostic methods have limitations; namely, they are measurement- and ratio-dependent. The criteria of Jenni et al4 and Chin et al12 have been validated against autopsy and other structural heart disease.4,12,31 However, autopsy was used as the gold standard for diagnosis of LVNC and not for the validation of the proposed echocardiographic ratio. A recent study32 emphasized the limitations of the current echocardiographic diagnostic criteria. That study used the echocardiographic criteria of Chin et al,12 Jenni et al4 and Stöllberger et al27 for identification of LVNC in HF and control groups.

There was meager correlation among the 3 sets of echocardiographic criteria, with only 30% of patients satisfying all of them.32 Additionally, 8% of controls met at least 1 of the diagnostic criteria for LVNC. This information raises the concern that the current echocardiographic criteria are too sensitive, particularly in individuals of African heritage, resulting in overdiagnosis of LVNC (false positive).

This potential false-positive diagnosis of LVNC has prompted some investigators to question the rationale for using ratios to identify this cardiomyopathy.30 Clinicians dream of perfect diagnostic tools38 and are looking for a process that will solve the puzzle of diagnosing LVNC.24 A refinement of the echocardiographic criteria is needed for accurate diagnosis of LVNC.33 Why is it so difficult to validate the diagnosis of LVNC with certainty? There are several reasons. First, accurate diagnosis requires awareness and meticulous imaging technique by experts who understand the imaging tips and tricks and caveats to clearly and reliably identify compacted from noncompacted myocardium.23 The second important reason is that the threshold of prominent physiologic trabeculations to disease is often blurred. The complex meshwork of muscle bundles of the apical-third of the LV and muscle bundles aligning the border of the myocardium are normal structures. These normal trabecular patterns can mimic LVNC. The current echocardiographic diagnostic criteria often fail to distinguish the boundary of normal morphologic features and disease.

Lastly, the difficulty in diagnosing LVNC is due to the lack of clarity between morphologic findings of “left ventricular noncompaction” and the disease entity LVNC cardiomyopathy. The disease should not be defined by the rigid criteria of measurements, such as ratios of the bilayered myocardium. Clearly, we cannot identify a NC/C ratio equal to 2 at end-diastole or end-systole as disease and a ratio of 1.9 as no disease. There must be recognition that any NC/C ratio with normal LV systolic and diastolic function and normal myocardial mechanics should not be defined as a disease. This set of circumstances must be characterized as morphologic findings that need close follow-up over time to determine if and when there is a transition to disease phenotype (ie, LVNC cardiomyopathy).

Figure 2. Apical short-axis view in a 42-year-old man with marked left ventricular noncompaction. Note the abnormal systolic, diastolic and myocardial mechanics. No thrombus seen. (Same patient is shown in Movie S1.)

Figure 3. A 20-year-old male rugby player with apical left ventricular noncompaction (LVNC) cardiomyopathy and abnormal systolic, diastolic and myocardial mechanics: (A) Paterick et al (Milwaukee) criteria: apical short-axis view (end-diastolic frame) reveals LVNC with a noncompacted (NC; white arrow) and compacted (C; blue arrow) myocardium; the end-diastolic NC/C myocardium ratio is 4, consistent with severe LVNC. (B) Jenni et al (Zurich) criteria: apical short-axis view (end-systolic frame) reveals LVNC with an NC/C myocardium ratio of 3.4. Apical obliteration in LVNC can mimic apical hypertrophic cardiomyopathy. (Reproduced from Paterick et al38 with permission from Elsevier.)
This predicament has resulted in a search for more objective, quantitative and functional criteria for the diagnosis of LVNC. The hope is that measurement of morphologic features and echocardiographic parameters, such as strain, strain rate, rotation/torsion and deformation analysis, would enable diagnosis as reliably as a genetic marker. Although speckle tracking echocardiography appears to hold promise in helping to solidify the diagnosis of LVNC, its results are neither reliable nor reproducible at this time (Figure 4).

Cardiac magnetic resonance imaging (CMR) is another diagnostic tool being used in attempts to validate the diagnosis of LVNC. Definitions for the diagnosis of LVNC using CMR have been proposed and used in published studies.\textsuperscript{29,30,34} CMR has been used to distinguish myocardial trabeculations from global LV mass.\textsuperscript{34} A trabeculated mass >20% of the global LV mass is regarded as a sensitive and specific marker for the diagnosis of LVNC.\textsuperscript{34} CMR with gadolinium enhancement (DGE) identifies myocardial fibrosis and may have prognostic implications.

\textbf{Differential Diagnoses Challenge}

The diagnosis of LVNC is imperative given the potential for complex, life-threatening sequelae. The challenge is daunting because there is no diagnostic “gold standard” and LVNC shares many features with hypertrophic and dilated cardiomyopathies. The distinction of these overlapping cardiomyopathies can be ambiguous, despite the use of all our diagnostic tools. Additionally, further differential diagnoses in each case must include apical thrombus, false tendons, aberrant chords, cardiac fibromas, eosinophilic heart disease, endomyocardial fibrosis and cardiac metastasis. All LVNC imitators must be considered when making a diagnosis.

\textbf{Clinical Spectrum of LVNC}

The distinction between asymptomatic and symptomatic LVNC is notable. Incidental and familial discoveries of LVNC have a stable course over several years, whereas symptomatic patients frequently follow a deteriorating clinical course with a dismal prognosis.\textsuperscript{35} Survival rates of patients with isolated LVNC or dilated nonischemic cardiomyopathy are similar. Asymptomatic patients with LVNC have a 2% incidence of HF compared to 61% of symptomatic LVNC patients.\textsuperscript{36} Device therapy should be considered in progressive HF that is unresponsive to optimal medical therapy.\textsuperscript{37} Patients with symptomatic HF, New York Heart Association (NYHA) class III or ambulatory class IV, LV ejection fraction <35% and QRS duration >120 ms who are receiving optimal medical therapy...
should receive cardiac resynchronization therapy (CRT) with an implantable cardioverter-defibrillator (ICD) as a Class I recommendation.\(^3\) CRT therapy has been reported to improve functional capacity and LV ejection fraction.\(^38,39\) Heart transplantation should be considered when HF is refractory to optimum medical and device therapies.\(^40\)

Ventricular arrhythmias and sudden cardiac death are serious concerns in patients with LVNC. A recent study of 15 patients with a diagnosis of LVNC who underwent Holter monitoring revealed ventricular tachycardia (sustained or nonsustained) in 4 of them (27%).\(^41\) The incidence of ventricular arrhythmias in patients with LVNC ranges from 2% to 62%.\(^42,43\)

Patients with LVNC and sustained ventricular tachycardia or ventricular fibrillation need ICD implantation. LVNC patients with impaired LV systolic function (LV ejection fraction <35%) are treated similarly to patients with dilated cardiomyopathy and impaired LV systolic function in regard to ICD implantation. Prophylactic ICD implantation in the absence of documented hemodynamically significant ventricular tachycardia is not a current recommendation. Presently, there is a lack of evidence-based data and a knowledge gap in the management of LVNC patients with ventricular arrhythmias and normal LV systolic function or mild to moderate LV systolic dysfunction. There are no available risk-stratification guidelines for these patients at risk for serious ventricular arrhythmias and adverse clinical consequences, as demonstrated by anecdotal cases.

Systemic thromboembolic events are associated with LVNC. Thromboembolic risk is increased with atrial fibrillation and LV systolic dysfunction.\(^44\) The incidence of thromboembolic events varies from 5% to 38% in patients with LVNC.\(^45,46\) The use of warfarin and/or antiplatelet therapy in patients with LVNC and normal ejection fraction is still a point of clinical debate and must be individualized based on risk/benefit analysis. The challenge for the medical community is to develop uniform diagnostic approaches to distinguishing normal variations from structural heart disease that are valid and reproducible. An additional challenge will be collaboration among centers with expertise in cardiomyopathies so that registries can be developed to study the entire spectrum of LVNC from diagnosis to autopsy.

### Future Directions

It is essential to understand that there should be a distinction between the morphologic findings of LVNC and the disease entity known as LVNC cardiomyopathy. This clarification will advance our understanding of how to manage individuals with morphologic findings only vs. those with morphology and pathophysiology associated with LVNC cardiomyopathy. Presently, our measurements and ratios do not allow us to diagnose LVNC with acceptable sensitivity and specificity. A ratio of NC/C >2 at end-diastole in a patient with normal systolic and diastolic functions and normal myocardial mechanics does not

### Table. Diagnostic Criteria Used to Define LVNC

<table>
<thead>
<tr>
<th>Criteria</th>
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<tr>
<td><strong>Echocardiography criteria</strong></td>
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<tr>
<td>• LVNC is defined as a ratio of X/Y ≤0.5</td>
<td>Chin et al(^2) (California criteria)</td>
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<td>• These criteria evaluate trabeculae at the LV apex using the parasternal short-axis and apical views, and on the LV free wall thickness at end-diastole</td>
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<tr>
<td><strong>Jenni et al(^1) (Zurich criteria)</strong></td>
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<tr>
<td>• Bilayered myocardium consisting of a thin C layer and a much thicker NC layer with deep endomyocardial recesses: NC/C &gt;2</td>
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<td>• Predominant location of the pathology is mid-lateral, mid-inferior, and apex</td>
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<td>• Evidence of intertrabecular recesses filled with blood from the LV cavity</td>
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<td>• Acquisition of image views: short-axis with measurement of NC/C ratio performed at end-systole</td>
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<td><strong>Stöllberger et al(^7) (Vienna criteria)</strong></td>
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<td>• 4 or more trabeculations protruding from the LV wall, located apical to the papillary muscles and visible in 1 imaging plane</td>
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<td>• Trabeculations with the same echogenicity as the myocardium and synchronous movement with ventricular contractions</td>
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<td>• Perfusion of the intertrabecular recesses from the LV cavity</td>
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<tr>
<td>• Acquisition of images in the apical 4-chamber view, atypical views to obtain the best quality image to differentiate between false chords, aberrant bands and trabeculations</td>
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<tr>
<td><strong>Paterick et al(^8) (Milwaukee criteria)</strong></td>
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<tr>
<td>• An evaluation of the trabeculations’ sizes (NC myocardium) in relation to C wall thicknesses in multiple imaging windows and at different ventricular levels throughout the cardiac cycle</td>
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<tr>
<td>• Identification of the bilayered myocardium (C and NC), in the short-axis views at the mid- and apical levels, and in the apical 2- and 4-chamber and apical long-axis views</td>
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<tr>
<td>• Thicknesses of the C and NC sections of the myocardium are best measured in the short-axis views at end-diastole, with NC/C ratio &gt;2 being diagnostic of LVNC</td>
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<tr>
<td>• Abnormal ventricular function and abnormal myocardial mechanics along with the above noted features to diagnose LVNC cardiomyopathy</td>
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<tr>
<td><strong>MRI criteria</strong></td>
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<tr>
<td>• Ratio between NC and C layers &gt;2.3 at end-diastole</td>
<td>Petersen et al(^9)</td>
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<tr>
<td>• Trabeculated LV mass &gt;20% of global LV mass (measurements made at end-diastole)</td>
<td>Jacquier et al(^10)</td>
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LVNC, left ventricular noncompaction; X, distance from the epicardial surface to the trough of the trabecular recess; Y, distance from the epicardial surface to the peak of the trabeculation; LV, left ventricular; NC, noncompacted; C, compacted; MRI, magnetic resonance imaging. (Adapted from Paterick et al\(^8\) with permission from Elsevier.)
identify a specific disease entity. This is akin to the lessons learned from the past in relation to hypertrophic cardiomyopathy. In those earlier days, asymmetric septal hypertrophy (ASH) with a septal- to posterior-wall thickness ratio >1.3 was considered pathognomonic of the disease state known as hypertrophic cardiomyopathy. Subsequent investigations and experience revealed that ASH was a nonspecific finding and seen in disparate cardiovascular conditions including systemic hypertension, pulmonary hypertension, aortic stenosis, coarctation of the aorta and several congenital heart defects.45,48 Hence, the fallacy of relying on a ratio being pathognomonic of a disease entity. This scenario identifies the reason why measurements and ratios must be integrated with clinical, pathophysiologic and evolving genetic variables to make an accurate diagnosis of cardiomyopathy and prevent overdiagnosis.

The ratio of compacted and noncompacted myocardium and the extent of LVNC are not able to allow a distinction between disease and normal phenotypic variations. Aras et al49 and Belanger et al40 found that the extent of noncompacted LV myocardium was related to the severity of LV systolic dysfunction. In contrast, Habib et al51 and Fazio et al52 reported exactly opposite findings, identifying no relationship between the extent of noncompacted myocardium and LV systolic function. These discrepant findings reify the vulnerability of using measurements and ratios in isolation.

We must move forward with the concept of integrating morphologic measurements and cardiac physiology and pathophysiology. The morphology of LVNC is often well defined by echocardiography. CMR reinforces identification of LVNC morphologic features and allows assessment of cardiac pathophysiologic findings, with DGE identifying myocardial fibrosis. Nuñifora et al45 found myocardial fibrosis with DGE in 45% (n=42) of patients with isolated LVNC, and both the presence and extent of myocardial fibrosis with DGE were related to the number of abnormal clinical features and the extent of LV systolic dysfunction. They also identified small areas of myocardial fibrosis with DGE in LVNC patients with preserved systolic function. This may represent a surrogate prognostic marker for a future decline in systolic function. Additionally, they found myocardial fibrosis in both compacted and noncompacted myocardium, supporting the theory that noncompacted myocardium is a phenotypic marker of an underlying diffuse cardiomyopathic process. Nuñifora et al also identified that the presence and extent of myocardial fibrosis is related to adverse clinical events.53 There appears to be a causal relationship between myocardial fibrosis and LV systolic dysfunction. Thus, measurements and ratios in patients with a potential diagnosis of LVNC can lead to over- and underdiagnosis. An accurate diagnosis requires integration of clinical variables, morphologic measurements and pathophysiologic parameters, such as DGE. This integration will enable an improved understanding of LVNC cardiomyopathy and study of its natural history.

**Conclusion**

LVNC is a diagnostically challenging entity. First, the distinction between morphologic findings consistent with the presence of noncompacted and compacted myocardium and the morphologic findings and pathophysiology consistent with a myopathic state called LVNC cardiomyopathy must be clarified. As reliable diagnostic processes identify patients with “left ventricular noncompaction” and LVNC cardiomyopathy, there should be registries created to systematically study these subsets of patients and their first-degree relatives. Screening of all first-degree relatives should include echocardiography and genetic testing, when feasible, to better understand the genotype and phenotype correlations. We must search for genetic and imaging biomarkers that identify those patients who will progress to cardiomyopathy with all its attendant risks. Moreover, an understanding of these subsets of patients based on systolic and diastolic functions and myocardial mechanics and fibrosis will help define cardiac performance and prognosis. These data are needed to provide optimal medical care and allow evidence-based guidelines for exercise prescription/restriction, optimal medical therapy and anticoagulation and ICD implantation.

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**Disclosures**

Conflict of Interest: None.

**References**


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**Supplementary Files**

**Supplementary File 1**

**Movie S1.** Parasternal short-axis view of a 42-year-old man (same patient as in Figure 2) with symptomatic heart failure. Echocardiography reveals a dilated left ventricle and marked apical left ventricular noncompaction. Abnormal systolic, diastolic function and apical twist mechanics can be seen.

**Supplementary File 2**

**Movie S2.** Parasternal short-axis 3-dimensional (3D) image of the left ventricle looking toward the left ventricular outflow tract and the mitral valve in a 17-year-old male high-school basketball player with known left ventricular noncompaction (same patient as in Figure 1). 3D imaging vividly demonstrates the noncompacted myocardium.