Left Ventricular Noncompaction Cardiomyopathy: What Do We Know?

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Noncompaction is a rare and primary genetic cardiomyopathy affecting the left ventricle. The diagnosis is usually established by echocardiography, or, less frequently, by left ventriculography. Cardiac magnetic resonance and electrocardiography-gated multidetector computed tomography are evolving noninvasive modalities to image cardiac structures, and have the utility to detect noncompacted myocardium. Estimates of the frequency and incidence of left ventricular noncompaction (LVNC) are limited because of the controversy over whether LVNC is a discrete disease entity. There is considerable overlap with dilated cardiomyopathy, apical hypertrophy, and hypertrophic cardiomyopathy. Symptoms, diagnosis, and prognosis are variable because of the heterogeneous nature of these diseases, making treatment often empirical and mimicking the treatment of other cardiomyopathies. However, there are management issues that should be addressed in each patient with LVNC, including genetic testing and family screening, the need for implantable cardioverter defibrillator placement, the role of anticoagulation in prevention of thromboembolic complications, and prescriptions/restrictions for implementation of physical activity.

[Rev Cardiovasc Med. *2010;11(2):92-99 doi: 10.3909/ricm0531*]

Key words: Noncompaction • Cardiomyopathy • Hypertrabeculation • Automatic implantable cardioverter defibrillator • Thromboembolism

A 48-year-old woman was referred to the Cardiology Clinic at Mayo Clinic Florida (Jacksonville, FL) for chest pain occurring at rest. She is active and jogs several miles per day without chest pain. Results of the cardiovascular examination were normal.

An electrocardiogram revealed sinus bradycardia at 45 beats/min and nonspecific T-wave abnormalities. The QT corrected was 475 milliseconds, the QRS was 60 milliseconds, and the PR interval was 200 milliseconds.

The results of her stress echocardiogram were negative for ischemic changes or chest pain. She achieved 19.5 METS and 102% of her predicted maximum heart rate.

The echocardiogram also revealed excessive apical thickening and noncompaction of the left ventricle (LV). The LV chamber size and systolic function were normal. Magnetic resonance imaging (MRI) confirmed normal cardiac chamber sizes, normal LV function, and the presence of prominent trabeculations of the LV myocardium, particularly at the apex.

Background

Left ventricular noncompaction (LVNC) was given its name in 1990,[1] and is labeled by the World Health Organization (WHO) as an *unclassified cardiomyopathy*. It is identified as persistence of isolated myocardial sinusoids.[2] It was classified by the American Heart Association in 2006 as a genetic cardiomyopathy.[3] Etiology of LVNC is hypothesized to be due to early cessation of muscle fiber compaction during embryogenesis, resulting in persistent embryonic myocardium. At 5 to 8 weeks of normal embryonic development, intertrabecular recesses or "sinusoids" form. The recesses are in direct communication with the LV endocardium. As normal development progresses and myocardial compaction occurs, the intertrabecular recesses transform into capillary beds.[4] LVNC results from defective morphogenesis of this endomyocardium. An architecturally aberrant ventricular wall is left, consisting of a compacted epicardial layer and a loose interwoven meshwork with prominent trabeculae and deep intertrabecular recesses that communicate with the LV cavity.[5-8]

Etiology of LVNC is hypothesized to be due to early cessation of muscle fiber compaction during embryogenesis, resulting in persistent embryonic myocardium.

Incidence

The frequency and incidence of LVNC is thought to be rare, representing a classic example of the complexity of defining cardiomyopathies.[3] Currently, the incidence is documented highest among children and is estimated to occur in 1 in 123,000 infants annually.[9,10] In adults, the estimates of frequency and incidence of LVNC are limited as there is considerable overlap with dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM),[11,12] confounding its acceptance as a discrete disease entity. Epidemiologic surveys have not separated LVNC from unclassified cardiomyopathies; thus, valid statistics regarding the frequency and incidence of LVNC are not available. The overlap among LVNC, DCM, and HCM often limits a precise diagnosis. LVNC is considered a "phenocopy" of HCM and there is often ambiguity in the diagnosis. The incidence of HCM is 1:500 versus 1:120,000 in LVNC, and the true incidence of DCM is confounded by its plural causal nature and the fact that it is frequently a diagnosis of exclusion (Table 1).[13] Echocardiographers' heightened awareness of LVNC, as well as the advancement of diagnostic imaging modalities, should increase the frequency and the incidence of the diagnosis.[14]

There are no universally accepted criteria to precisely define LVNC at the present time, making it difficult to determine the incidence of this entity.[1,2,6,15] The incidence of LVNC is variable in the literature and is dependent upon the criteria used to make the diagnosis; several criteria have been published for the diagnosis of LVNC (Table 2). In truth, the current state of medical literature addressing LVNC largely consists of observational and retrospective case studies. This limits the strength of conclusions available regarding LVNC. There is no doubt that LVNC exists, but to better understand incidence and prevalence, universal criteria will need to be defined and accepted.

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Prognosis

Early reports suggested LVNC was associated with an ominous prognosis; however, recent case reports document variability in initial presentation and clinical outcomes. Prognosis is thought to be primarily related to the degree of systolic dysfunction and the magnitude of heart failure. Complications such as arrhythmias and thromboembolic events negatively impact the prognosis.[16-18] In one study it was reported that 75% of 65 adult patients followed with LVNC were free of cardiovascular mortality at 5 years.[19] The remaining 25% ranged from clinically well to experiencing heart failure, rhythm disturbances, and syncope. It is also documented that there was a 58% survival from cardiovascular death or heart transplant at 5 years.[20] Both studies identify LV dysfunction as a marker for increased risk of mortality.

Diagnosis

Traditionally, transthoracic echocardiography (TTE) has been the initial

Table 1
HCM, DCM, and LVNC: Overlapping Cardiomyopathies

	Hypertrophic Cardiomyopathy	Dilated Cardiomyopathy	Left Ventricular Noncompaction
Presentation	Variable with genotype, birth to > 75 y, common presentation is dyspnea, chest pain, syncope	Most develop symptoms between 20-60 y, classic heart failure symptoms	Variable, asymptomatic to classic heart failure symptoms, syncope, embolic events
Incidence	1/500	Unknown	Adult: unknown Children: 1/123,000
Imaging modalities	2D echocardiography/MRI	2D echocardiography	2D echocardiography for initial detection, diagnosis confirmation with CT or cardiac MRI
Genetic markers	MHY7, MYL2, MYL3, MYBPC3, TNNT2, TPM1, TNN13, TNNC1, ACTC	TPM1, ACTC, VCL, DES, TTN, SGCD, MYH7, TNNT2	MYH7, TAZ
Therapy	β-blockers, disopyramide, AICD for primary and secondary prevention, SCD, septal ablation or myomectomy, avoidance of afterload-reducing agents	β-blockers, ACE inhibitor/ ARB, diuretics, digoxin, cardiac resynchronization therapy, AICD for primary prevention, SCD if EF < 35%, heart transplant	Empirical use of β–blockers, ACE inhibitor/ARB, diuretics if EF > 55%, AICD for symptomatic VT, primary prevention SCD if EF < 55%, heart transplant
Outcomes	2% SCD in < 35 y, 1% annual death rate all ages	Skewed by overlapping data	Unknown

2D, two-dimensional; ACE, angiotensin-converting enzyme; AICD, automatic implantable cardioverter defibrillator; ARB, angiotensin receptor blocker; CT, computed tomography; DCM, dilated cardiomyopathy; EF, ejection fraction; HCM, hypertrophic cardiomyopathy; LVNC, left ventricular noncompaction; MRI, magnetic resonance imaging; SCD, sudden cardiac death; VT, ventricular tachycardia.

Table 2
Variable Diagnostic Criteria for the Diagnosis of LVNC

- Absence of coexisting cardiac abnormalities
- Segmental thickening of the LV wall composed of 2 layers
- Pathologic findings located in the midlateral, apical, and midinferior region of the LV
- Perfused intertrabecular recesses
- More than 3 trabeculations protruding from the LV wall, apically to the papillary muscle, visible in a single plane in combination with intertrabecular spaces perfused from the LV cavity

LV, left ventricle; LVNC, left ventricular noncompaction.

imaging modality in the diagnosis of LVNC. Echocardiographic criteria for the diagnosis of LVNC have been ill defined, but include the following: (1) absence of coexisting cardiac abnormalities; (2) segmental thickening of the LV wall (this is composed of 1 thin compacted epicardial layer and 1 thick noncompacted layer with the classic prominent trabeculations and deep endomyocardial spaces); (3) pathologic findings primarily located in the midlateral, apical, or midinferior regions of the LV; (4) perfused intertrabecular recesses visible via color Doppler; and (5) an end-diastolic ratio of noncompacted to compacted myocardium of > 2.[6,15] It has been suggested that the WHO classification of cardiomyopathies be reconsidered to include LVNC as a distinct cardiomyopathy.[6] The echocardiographic diagnosis of LVNC may be facilitated by contrast echocardiography, transesophageal echocardiography, and 3-dimensional echocardiography in specific cases (Figure 1).

Other imaging modalities, such as cardiac MRI, cardiac computed tomography (CT), and contrast ventriculography, are used particularly when the quality of TTE images precludes a definitive diagnosis. Echocardiography is recognized as the diagnostic imaging modality of choice for LVNC, but cardiac MRI shows great promise, particularly in patients for whom adequate echocardiographic windows are not available (Figure 2). In addition to defining the trabecular recesses in great

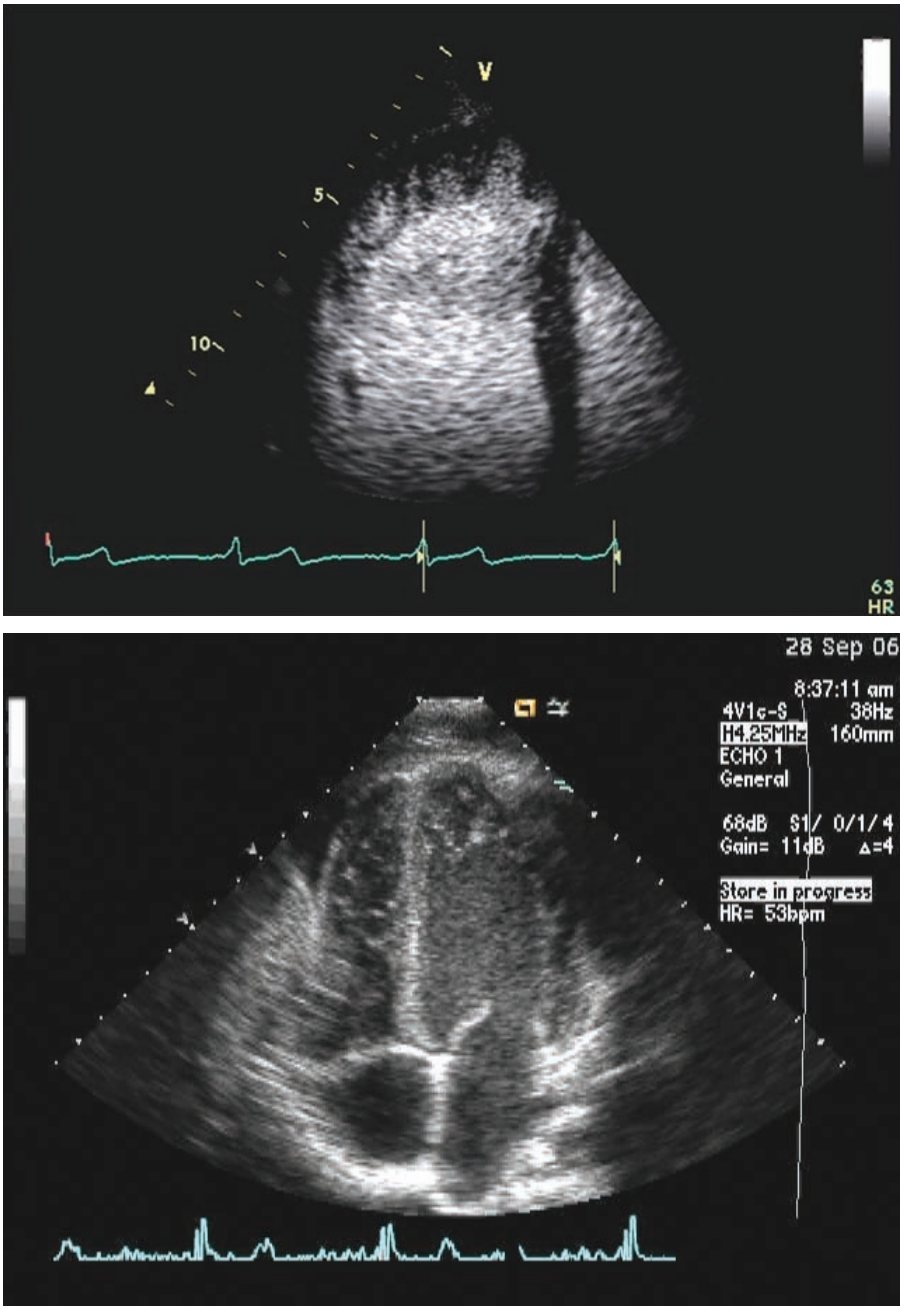

Figure 1. *Contrast echocardiography demonstrating trabeculation of left ventricular noncompaction.*

morphologic detail, MRI may provide useful information regarding abnormal microvascular perfusion or thrombi within the trabeculations.[20-22] A recent prospective study on the diagnosis of LVNC has suggested that measurement of LV trabecular mass by cardiac MRI is sensitive and specific in the differentiation of LVNC, HCM, and DCM. A trabecular mass > 20% provided an accurate criterion that was highly supportive of LVNC.[23] Perfusion abnormalities within the noncompacted myocardium documented by cardiac MRI and positron emission tomography are thought to be primarily responsible for compromised LV function and ventricular arrhythmias that can define the presentation and prognosis of patients with LVNC.[4,20,24]

Differential diagnoses for LVNC by imaging criteria include false tendons, HCM (in particular apical HCM), DCM, endocardial fibroelastosis, endomyocardial fibrosis, apical thrombosis or tumor, the neuromuscular cardiomyopathies, and other myocardial or pericardial diseases.[20-22,24-26]

Symptoms

Patients with LVNC who have preserved LV function are often asymptomatic, although there are reports of patients presenting with a cerebrovascular accident from thromboembolism, syncope, or sudden death due to ventricular arrhythmias despite normal LV function.

Heart failure is the most common symptomatic presentation, followed by arrhythmia and thromboembolic events.[19,20] In one cohort of patients with LVNC it was reported that 62% had symptomatic heart failure, 35% of whom had New York Heart Association class III or IV symptoms.[20] Electrocardiogram abnormalities such as left bundle branch block were present in 13% of patients.[20] LV hypertrophy, axis shifts, ST- and T-wave abnormalities, atrial fibrillation, and atrioventricular block have also been described.[25]

Treatment

The medical treatment of LVNC is empirical and mimics that of other cardiomyopathies in which the use of angiotensin-converting enzyme (ACE) inhibitors, β-blockers, and spironolactone are the cornerstones of therapy. Cardiac transplantation

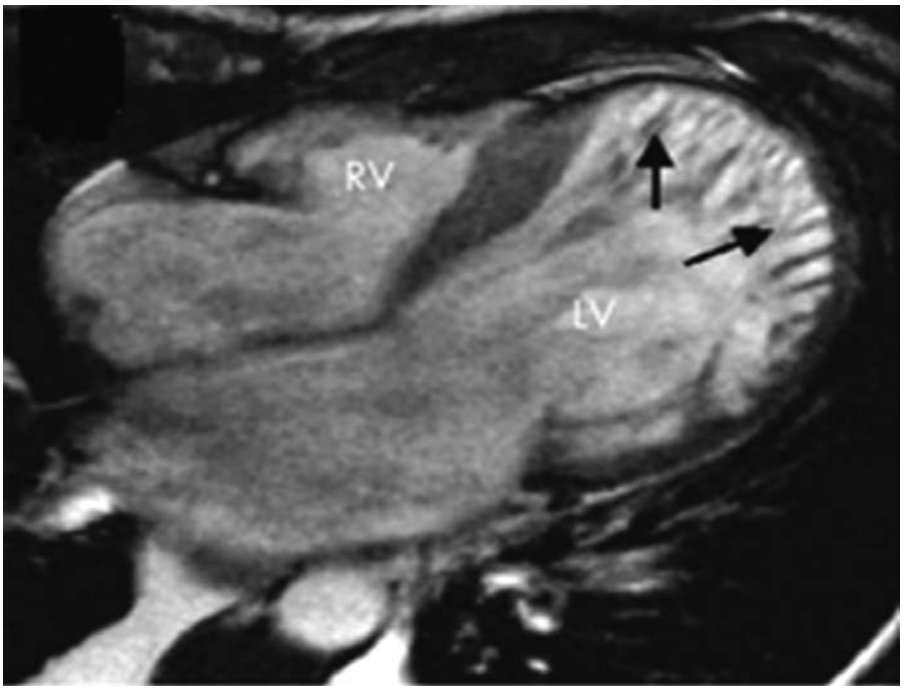

Figure 2. *Magnetic resonance image demonstrating in morphologic detail left ventricular apex trabeculation. LV, left ventricle; RV, right ventricle.*

can be a final option in therapy. There are several major management issues that should be addressed when evaluating the patient with LVNC, such as genetic testing and family screening for LVNC, chronic anticoagulation for prophylaxis of associated thromboembolic events, prophylactic placement of implantable cardioverter defibrillators (ICDs), and prescriptions/restrictions for implementation of physical activity.

Genetic Testing and Family Screening for LVNC

No matter how LVNC is diagnosed clinically, it is a genetically heterogeneous diagnosis. The single gene in which mutations are confirmed to cause LVNC is *TAZ*, an X-linked gene. Mutations in this gene also cause Barth syndrome, which is associated with DCM, with or without LVNC. Clinical genetic testing is available for this gene.

In a recent study, DNA from 63 unrelated adults with LVNC was analyzed for mutations in *MYH7*, *ACTC* (α-cardiac actin), and *TTNT2* (cardiac troponin T). Seven mutations were found in *MYH7*, and 1 mutation each in the other genes (14% yield).[26] This presents compelling evidence that mutations in *MYH7* can cause hereditary LVNC. Further data are needed to reach a firm conclusion on the other newly reported genes. LVNC has been reported in the setting of 14 other genetic syndromes.[27]

The single gene in which mutations are confirmed to cause LVNC is TAZ, *an X-linked gene.*

The role of genetic testing is limited at present by the large number of genes that are occasionally implicated and the cost of genetic testing. The study of 79 cases of LVNC (20 sporadic and 59 familial) for mutations in *TAZ, DTNA, SNTA1, ZASP,* and *FKBP1A* found only 6 mutations (7.6%).[28] Another study found mutations in 14% of 63 families with LVNC.[26] Further studies may be guided by findings in the proband or relatives of those with DCM, HCM, conduction abnormalities, or congenital anomalies. For those with nonsyndromic LVNC, *TAZ* and *MYH7* sequencing may be offered.

Establishing a genetic diagnosis can greatly assist in determining which other family members are at greatest risk, but most families will not attain genetic confirmation of their diagnosis until the science progresses. In addition, as the natural history of LVNC is poorly understood, a positive genetic test result is of limited value in patient management at present. On the other hand, a negative result of a genetic test in an individual from a family with a known gene mutation is reassuring that the individual is unlikely to be at risk for LVNC or its complications. A genetic consultation can be helpful in sorting out these complex issues because LVNC has "incomplete" penetration of the gene mutations and uncertainty of the phenotypic presentation with these mutations. Given the incomplete and evolving genetics, echocardiographic screening should be offered to all first-degree relatives of an affected individual. The value of echocardiographic family screening is supported in a series of 45 patients with LVNC; 25% of asymptomatic relatives had echocardiographic abnormalities that included LVNC, LVNC with systolic dysfunction, and LV enlargement without LVNC.[29]

LVNC and Prophylactic ICD for Prevention of Sudden Cardiac Death

Prophylactic ICD implantation in the absence of documented hemodynamically significant ventricular tachycardia (VT) is not well defined. Patients are often diagnosed with LVNC after presenting with syncope or near syncope associated with nonsustained episodes of VT.[8] Fibrous myocardium, deep trabeculations, and subendocardial ischemia have been hypothesized to predispose patients with LVNC to ventricular arrhythmias.[25] One study enrolled 238 patients with LVNC and evidence of nonsustained VT according to Holter monitoring[30]; of these, 4.2% demonstrated VT, with sustained VT accounting for 2 patients out of the 4.2%. It has also been concluded that ventricular arrhythmias are not commonly associated with LVNC and that ICDs should be reserved for very high-risk cases.[27] However, another study[31] hypothesized that patients with LVNC who have syncope, known arrhythmias, or severely depressed LV function will benefit from ICD implantation. Although the study population was small, 50% of the patients who received an ICD for secondary prevention and 25% who received an ICD for primary prevention were delivered appropriate shocks with device therapy.[29]

The above-mentioned articles focus primarily on ventricular arrhythmias in patients with LVNC and differentiate the clinical approach based upon whether there is normal or abnormal systolic heart function. There is a case in which recurrent sustained ventricular arrhythmias occur in a patient with LVNC, normal coronary arteries, and preserved LV function.[32] This case reifies the heterogeneity of LVNC, how it manifests phenotypically, and why clinical decision making can be uncertain. Use of an ICD for primary prevention (no symptomatic arrhythmias or syncope) is an American College of Cardiology/American Heart Association class IIb indication.[33]

The role of automatic ICD implantation and anticoagulation in patients with LVNC is evolving. Presently, automatic ICD implantation is reasonable and prudent in patients with symptomatic VT, whether LV function is normal or abnormal. The decision in patients with nonsustained VT and syncope must be individualized dependent upon the clinical condition and the mechanism of the presenting condition. The decision to place an ICD has significant clinical implications. Given the lack of congruent literature available on prophylactic ICD placement in patients with LVNC, physicians must individualize the decision on a case-by-case basis and rely on expert opinion as well as their own clinical experience. This individualization of the decision-making process also applies to anticoagulation in patients with LVNC.

Prevention of Thromboembolic Complications

It has been hypothesized that the thromboembolic properties manifested in LVNC occur when blood becomes trapped in the deep intertrabecular recesses that are characteristic of this disease. The risk of LV thrombus formation among LVNC patients, especially those with depressed LV function, is thought to be significant and represents an important clinical decision when treating patients. It is reported that patients with depressed LV function and LVNC are at 10% higher risk for embolic complications than those without LVNC.[17] Clinically, this higher-risk group had depressed LV function and embolic complications, although this was generally not seen in those with LVNC and preserved LV function. Thus, the conclusion was that LVNC and use of anticoagulant therapy should be reserved for those patients with compromised LV function (which then becomes an issue of monitoring for deteriorating LV function).[17]

There is a case of a 44-year-old woman who initially presented with symptoms of stroke and MRI evidence of cerebral infarction. Echocardiographic and MRI images demonstrated LVNC with an ejection fraction (EF) of 45%. Over several months her EF declined with the LV and left atrium dilating.[34] This raises the question of appropriate timing for anticoagulation given that LV function was only mildly depressed at the time of presentation.

Those with LVNC and preserved LV function appear at risk, just perhaps not as great a risk as those with LVNC and compromised LV function. This phenomenon was demonstrated in a 35-year-old woman with echocardiographic evidence of LVNC and preserved LV function whose initial presentation was a devastating cerebroembolic event.[35]

Certainly those with compromised LV function and a diagnosis of LVNC are reported to be at high risk for thromboembolic complications and would most likely benefit from chronic anticoagulation. A more uncertain decision surrounds anticoagulant therapy in patients with LVNC and preserved LV function. There are few data, at this time, on which to base therapeutic treatment decisions and the choice must be based on the discretion of the treating physician.

Exercise Prescription in Patients With LVNC

There are no clinical guidelines or recommendations in the medical literature for exercise prescription or

restriction in those with LVNC. Given the potential for an arrhythmic death, exercise prescription should be conservative, although exercise advice must be individualized. It would seem prudent to discourage athletic activity for patients with LVNC with and without LV dysfunction (similar to the exercise prescription for patients with HCM). Patients with preserved systolic function and no evidence of arrhythmia after careful rhythm monitoring would seem to tolerate activities that do not exceed an aerobic state. LVNC patients with systolic dysfunction, who have received maximal medical therapy and an ICD, should only exercise in programs guided by health care professionals proficient in advanced cardiac life support. Unsupervised activities should be limited to low-impact aerobic activities such as walking.

Future Directions in the Assessment and Management of LVNC

Given the variable clinical presentation of LVNC, continued research on the role of various imaging modalities and gene mutations is needed to develop reliable diagnostic criteria as a prerequisite for appropriate risk stratification and management. LVNC is most likely a genetically determined cardiomyopathy; therefore, the evolution of the understanding of genetics in HCM[36] suggests that continued research on gene mutation discovery and patient outcomes will improve our understanding of the diagnosis, prognosis, and therapy of LVNC.

To better understand the natural history of LVNC and its modification by therapy, registries that monitor therapy and outcomes across the heterogenous spectrum from asymptomatic mild forms to the end stages are urgently needed. ■

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Main Points

- Noncompaction is a rare and primary genetic cardiomyopathy affecting the left ventricle. Because there is considerable overlap with dilated cardiomyopathy and hypertrophic cardiomyopathy, the acceptance of left ventricular noncompaction (LVNC) as a discrete disease entity is controversial.
- Diagnosis is traditionally made using transthoracic echocardiography (TTE); however, other imaging modalities, such as cardiac magnetic resonance, cardiac computed tomography, and contrast ventriculography, are showing great promise, particularly in patients in whom TTE is not possible.
- Medical treatment of LVNC mimics that of other cardiomyopathies, and includes the use of angiotensin-converting enzyme inhibitors, β-blockers, and diuretics.
- The single gene in which mutations are confirmed to cause LVNC is *TAZ*, an X-linked gene. Genetic testing is available for this gene; however, the role of genetic testing is currently limited due to the large numbers of genes that can be affected and the high cost of testing. A positive genetic test result is currently of little value with regard to patient management.
- Given the variable clinical presentation of LVNC, continued research on the role of various imaging modalities and gene mutations is needed to develop reliable diagnostic criteria as a prerequisite for appropriate risk stratification and management.

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