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Evaluation and Management of Left Ventricular Noncompaction Cardiomyopathy

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Abstract Left ventricular (LV) noncompaction cardiomyopathy (LVNC) is a form of cardiomyopathy in which trabeculations fail to "compact" with the left ventricular endocardium during fetal cardiac development and is classically associated with subsequent impairment of LV function, significant mortality, ventricular dysrhythmias, and embolic phenomena. As awareness and medical imaging quality have improved, it is becoming easier to identify trabeculations that traverse the LV cavity and serve as a distinguishing feature of this disorder. Differentiating true noncompaction from mild increases in trabeculations requires prudent imaging and clinical correlation. This review seeks to discuss the potential methods of evaluating left ventricular trabeculations, the role of increased trabeculations in cardiovascular disease, and how their presence may affect clinical management.

Keywords Congestive heart failure · Noncompaction cardiomyopathy · Echocardiography · Cardiac magnetic resonance imaging · Embolic events · Sudden cardiac death

Introduction

Left ventricular noncompaction cardiomyopathy (LVNC) is a distinct cardiomyopathy characterized by significant trabeculations, often in the presence of reduced LV systolic function. This form of cardiomyopathy is associated with progressive heart failure, increased mortality, ventricular dysrhythmias, and embolic events [1, 2]. Most believe it results from failure of the compaction process that occurs during the formation of the endocardium during fetal development [3, 4•]. LVNC is often associated with certain clinical syndromes, such as the Barth syndrome [5–7], Charcot-Marie-Tooth disease [8], and Melnick-Needles syndrome [9]. Though different from LVNC, those with other congenital cardiac abnormalities are often noted to have increased trabeculations [10–12]. Trabeculations are often noted in patients with valvular abnormalities or other ventricular diseases, such as hypertrophic cardiomyopathy [13–15]. While trabeculations are mostly an occurrence at the apical and mid levels, they are distinct from the myocardial crypts seen in hypertrophic cardiomyopathy, which are usually located near the LV base [16].

The prevalence of LVNC continues to be debated, but early studies suggested a prevalence of less than 1 %, reflecting the more rare nature of this disorder [1]. Originally described in several European populations [17–19], subsequent studies have shown LVNC in other ethnicities as well [20•, 21, 22•]. Of note, some studies have suggested that individuals of African descent may have more prominent trabeculations, but the true burden and significance of this finding continues to be investigated [21, 22•]. In spite of improved medical therapy, LVNC continues to carry a higher risk of cardiac morbidity and mortality [20•]. In particular, it continues to herald poor outcomes and morbidity in the pediatric populations [23••].

Evaluation

The first widespread imaging modality used to describe left ventricular noncompaction cardiomyopathy was

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echocardiography. As 2-D echocardiography increased in use, several centers, most notably in Europe, reported the presence of significant trabeculations in young adults with advanced heart failure [17, 19]. These case reports evolved into case series and subsequent publications which helped to establish our foundational understanding of LVNC [1, 24]. Echocardiography continues to be the most utilized imaging modality, but cardiac magnetic resonance imaging continues to develop and emerge as a significant tool in visualizing LV trabeculations [25–27]. While imaging features are often the centerpiece of diagnosis, in spite of the presence or absence of these features, for some patients, it may remain a clinical diagnosis, as suggested by Dr. Oechslin [4•].

Chin Criteria

One of the first case series was published based upon data from UCLA. Chin et al. detailed a series of eight patients who had significant morbidity and mortality, the common denominator of which was extensive trabeculation noted in the left ventricle [2]. They described the echocardiography-related findings and presented the *X*:*Y* ratio [2]. The *X* represents the distance from the deepest trough of the trabecular recess to the epicardial surface, and the *Y* represents the distance from the peak of the trabeculations to the epicardial surface (see Fig. 1a). A ratio ≤0.5 would indicate potential LVNC [2]. These measures were obtained at end-diastole in either the parasternal long-axis view or the apical four-chamber view. They also noted that the majority of trabeculations occurred in the apex, a finding which is now well established.

Jenni Criteria

The group from Switzerland led by Dr. Jenni used their clinical experience to develop their own criteria [1, 28]. They published numerous case reports which subsequently evolved into case series. The hallmark of this approach introduced the concept of noncompacted and compacted myocardium. Whereas the Chin criteria focused on the distance between the epicardial surface and certain points within the trabeculations, the Jenni criteria shifted the focus to measuring the thickness of the compacted myocardium and the noncompacted myocardium [1]. These measures were obtained at end-systole from parasternal short-axis images (see Fig. 1b). These measures were then used to generate the noncompacted-to-compacted ratio, which was used to help evaluate whether LVNC is present. Based on their experience, they used a cut point of 2 or higher [1, 28].

However, the Jenni criteria used several measures in addition to the noncompacted-to-compacted ratio to identify cases of LVNC [28]. First, there needs to be a characteristic appearance of numerous, excessively prominent trabeculations and deep intertrabecular recesses, most notable at the LV apex. Second, no other significant congenital cardiac abnormalities were to be present. Third, there needed to be flow demonstrated in the trabecular recesses as indicated by the presence of

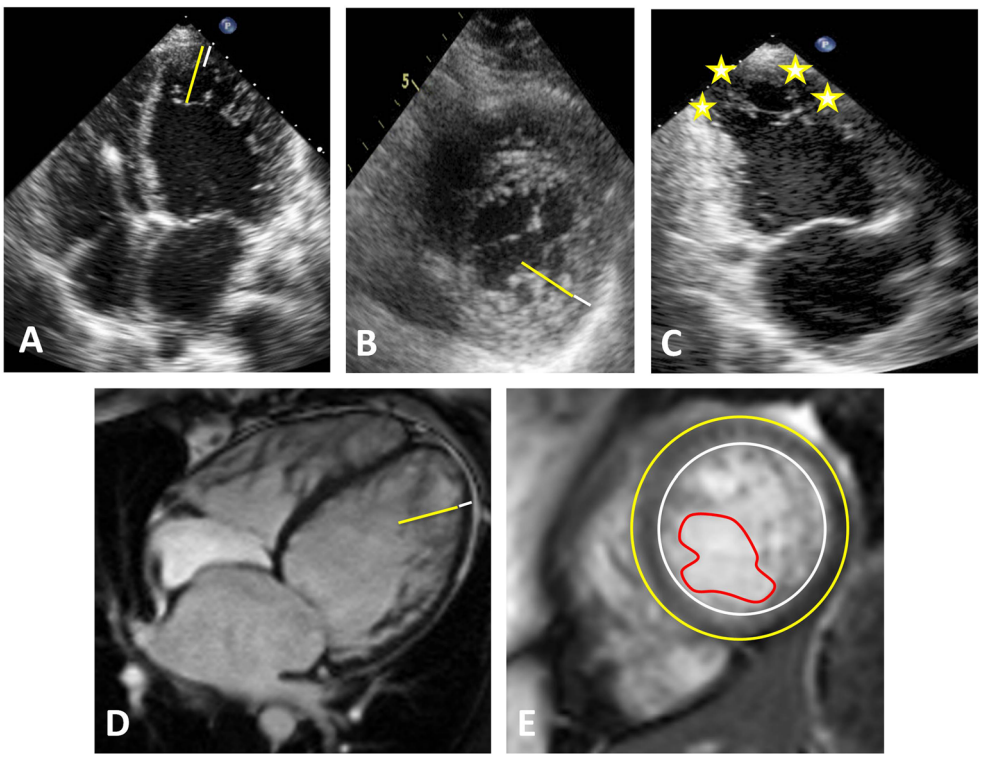

Fig. 1 **a** Chin criteria demonstrating how *X* (*white line*) and *Y* (*yellow line*) of *X*:*Y* ratio are obtained. **b** Image shows collection of noncompacted layer (*yellow line*) and compacted layer (*white line*) from short-axis image at end-systole for the Jenni criteria to calculate the noncompacted-to-compacted ratio. **c** Image demonstrating application of the Stollberger criteria (*stars* indicate trabeculations). **d** MRI image showing the noncompacted (*yellow line*) and compacted (*white line*) layers at end-diastole to calculate the noncompacted-to-compacted ratio for the Petersen criteria. **e** Short-axis image of MRI demonstrating how to measure the trabecular mass (*area contained between the red and white lines*)

color Doppler echocardiography. Finally, the bilayered noncompacted-to-compacted ratio ≥2 with extensive trabeculations and meshwork present helped to further identify those with potential LVNC. The Jenni criteria remain the most validated tool in assessing whether LVNC is present [29]. Based on their experience, the prevalence of LVNC was less than 0.05 %. Subsequent studies have demonstrated the feasibility of using the Jenni criteria with cardiac MRI [30•].

Stollberger Criteria

The Stollberger criteria emerged shortly after the introduction of the Jenni criteria [31]. They are based on autopsy studies from the mid-1980s [32]. These studies showed that over 90 % of hearts at autopsy have less than three trabeculations. To translate this to cardiac imaging studies, Drs. Stollberger and Finsterer set a cut point of three trabeculations being visible in the long-axis views (see Fig. 1c). Interestingly, Stollberger et al. found an association between apical trabeculations and more global myopathies [31]. As with the Chin criteria, the Stollberger criteria are usually assessed at end-diastole. However, more recently, they have discussed the utility of the criteria at both end-systole and end-diastole [33]. Based on the aforementioned autopsy studies, approximately 4 % of the general population would meet this criteria.

Petersen Criteria

With the emergence of cardiac magnetic resonance imaging, Petersen et al. set out to build upon the previous work to translate those results to more advanced cardiac imaging [26]. Using a case–control design, Petersen et al. measured the noncompacted-to-compacted ratio at end-diastole from the long-axis apical views (see Fig. 1d) [26]. With receiver operating curves, the cut point with the optimal sensitivity and specificity for identifying those with previously diagnosed LVNC was a ratio of 2.3 [26]. A minor limitation is that only seven cases of diagnosed LVNC were available for inclusion. In most instances, the other qualifying factors as identified from the Jenni criteria, such as apical predominance, trabecular recess flow, and absence of coexisting congenital cardiac disease, are applied. In most studies describing the Petersen criteria, particularly with events, the diagnosis had previously been established with the Jenni criteria with echocardiography prior to the MRI evaluation. Little data exists to determine if isolated application of the Petersen criteria alone can be used to make the diagnosis of LVNC. Using the Petersen criteria, Kawel et al. demonstrated that over 40 % of individuals without cardiovascular disease have at least segment with a noncompacted-to-compacted ratio >2.3 [34••].

Jacquier Method

Cardiac magnetic resonance imaging represents the gold standard in both assessing left ventricular ejection fraction and left ventricular mass. Based on these techniques, Jacquier et al. developed a method to quantify trabecular mass [35]. Using the short-axis cine images, they measured the trabecular area of each particular slice (see Fig. 1e), multiplied by slice thickness to generate a trabecular volume per slice, and summed the trabecular volume from base to apex. The trabecular volume was converted to mass. They then devised a ratio of trabecular mass to total LV mass. The trabecular mass and total LV mass were calculated at end-diastole. Using receiver operating curves, they identified the optimal sensitivity and specificity for identifying LVNC to be a ratio ≥20 % [35]. One of the challenges to using this method is identification of the papillary muscles. Oftentimes, individuals with LVNC lack fully identifiable papillary muscles, and in their place, they have an elaborate meshwork of trabeculations and poorly developed papillary muscles. Using a slightly modified approach, Stacey et al. were able to demonstrate that the Jacquier method is associated with clinical events commonly ascribed to LVNC [30•].

Challenges in Cardiac Imaging

In spite of such a variety of criteria available, the diagnosis of LVNC remains challenging and may often be a clinical diagnosis. Frequently, a combination of criteria helps to confirm the diagnosis and separate LVNC from other manifestations of cardiac pathology (see Table 1). While initial studies suggested LVNC as a more rare etiology, newer criteria are increasingly being found in individuals without overt cardiovascular disease. Recent studies using short-axis MRI imaging showed that in a population without cardiac disease, virtually none of the participants had an end-systolic noncompacted-to-compacted ratio >2 and only 1 % had an end-diastolic ratio >2.3 from the short axis [36••]. These findings are different from those of Kawel et al., which found almost 43 % of their study population without cardiovascular disease had at least one segment with a ratio >2.3 measured at end-diastole [34••].

How trabeculations are measured has a significant bearing on the results obtained. The short-axis assessment often parallels the experience and findings of initial cohorts, but the long-axis measurement appears to identify significant trabeculations, even when no overt cardiovascular disease or poor prognosis is

Table 1 Sensitivity and specificity of noncompaction criteria for isolated left ventricular noncompaction

	IVNC sensitivity (%)	IVNC vs DCM specificity (%)	IVNC vs HHD specificity (%)	IVNC vs AR specificity (%)	NC vs MR specificity (%)	NC vs AS specificity (%)
Two-layered structure	100	74	95	9	90	93
Perfused recesses	95	52	91	90	91	95
Meshwork	68	97	95	90	91	93
Hypokinesis	79	0	45	60	95	68
Hypertrabeculation	11	100	100	100	100	98

The presence of a meshwork in the apex or in inferior/lateral segments was significantly increased with 68 % in IVNC compared with DCM, HHD, and AS (each $P<.002$) and AR and MR (each $P=.004$). However, more than three distinct trabeculations were rare-even in IVNC where it occurred in only 11 %. Reprinted from [29], with permission from Elsevier

AR aortic regurgitation, *AS* aortic stenosis, *DCM* dilated cardiomyopathy, *HHD* hypertensive heart disease, *IVNC* isolated left ventricular noncompaction, *MR* mitral regurgitation, *NC* noncompacted

present. One of the limitations of the long-axis view is the inability to exclude papillary muscles. Most likely, the inclusion of papillary muscles due to volume averaging may lead to overestimation of trabeculations. Conversely, short-axis views can be used below the papillary muscles, and even at the papillary muscle level, the papillary muscles are often easily seen and excluded. Unless prospectively obtained, most long-axis views are not optimized to exclude the view of the papillary muscles.

Imaging quality is critical in evaluating for LVNC. In particular, visualization of the endocardial border improves the ability to discriminate between the compacted and noncompacted layers. In many centers, when echocardiography yields less than ideal images, the next step may be magnetic resonance imaging. For centers with limited availability in cardiac magnetic resonance imaging, a contrasted echocardiographic examination may assist in identifying the endocardial border [37, 38].

Management

Many initial studies identified an association between poor prognosis and the presence of symptoms, most likely related to severe LV dysfunction. Although not necessarily based on published evidence, most centers today use the left ventricular ejection fraction to assist in management decisions. The LV endocardium is responsible for more of the myocardial contraction than the epicardium [39]. Intuitively, with the presence of LVNC representing a defect in the formation of the LV endocardium, one would suspect that LV systolic function (and consequently ejection fraction) would be compromised. Therefore, in situations where the LV ejection fraction and strain are normal, follow-up can be determined based on the presence, absence, or subsequent development of heart failure-related symptoms, dysrhythmias, or embolic disease. In the situation where LV systolic function is normal and subsequently compromised from another etiology, such as infarction or some other myocardial insult, it remains unclear whether trabeculations may be a complicating factor which increases the risk for morbidity and mortality. Conversely, when the LV ejection fraction is reduced, patients are often symptomatic. In this circumstance, those with LVNC should receive aggressive guideline-based heart failure therapy, consideration for an implantable cardiac defibrillator, particularly if significant ventricular ectopy is present, and finally, anticoagulation may be needed to reduce the risk of subsequent embolic events.

Heart Failure Management

Since LVNC was first identified, there has been a substantial evolution in the medical management of congestive heart failure. Most of the patients identified and followed by Chin et al. and Jenni et al. were done so from the 1980s to the early 1990s [1, 2]. It was at this time that angiotensin-converting enzyme inhibitors were first noted to improve mortality in congestive heart failure and their use was subsequently incorporated into routine clinical care for those with congestive heart failure [40]. Shortly after this, beta-blockers emerged as a tool for clinicians to use in the chronic management of congestive heart failure [41]. The combination of these two agents alone resulted in at least a 25–30 % reduction in mortality from congestive heart failure, often by preventing further progression of the heart failure. As a result, today, most with LVNC and a reduced LV ejection fraction or congestive heart failure receive guideline-based heart failure therapy [42]. Some

recent studies have suggested that, in spite of these advances, LVNC continues to carry a poor prognosis [20•, 23••].

Some investigators have posited that LVNC most likely represents a subgroup of nonischemic dilated cardiomyopathies [43, 44]. In most publications, those with LVNC are noted to have increased volumes. While their heart failure management would parallel those with dilated cardiomyopathy, LVNC does differ in certain respects from nonischemic dilated cardiomyopathy. First, LVNC has a higher risk of developing malignant ventricular dysrhythmias, and second, LVNC has a stronger association with embolic events.

Ventricular Dysrhythmias

One of the most common presentations in the early cohorts for LVNC was syncope [1, 2]. A disproportionate number of those early cohorts died as a result of sudden cardiac death [1]. Case reports and small series involving arrhythmias continue to substantiate this concern related to LVNC [45–47]. In most of these circumstances, individuals with LVNC exhibit a reduced LV ejection fraction which increases their risk for arrhythmias and sudden cardiac death [23••]. However, there are several anatomic considerations which appear to further increase these risks. Histologic studies show that the trabeculations have significant fibrosis [2, 28]. This fibrosis, in conjunction with its relative isolation from the remaining compacted myocardium, may serve as a nidus for the development of reentrant pathways capable of producing and sustaining malignant ventricular dysrhythmias. Because of these risks, guidelines provide electrophysiologists with the license to place implantable cardiac defibrillators into those with LVNC. In those patients with LVNC who have had an implantable cardiac defibrillator placed, they are more likely to receive a shock for ventricular dysrhythmias, but given the concomitant prevalence of supraventricular rhythm disturbances, reliable detection methods should be used to prevent inappropriate shocks [48].

Embolic Events

Another common presentation for those with LVNC in the early cohorts was embolic phenomenon, even in younger individuals [1, 2, 49–52]. Intuitively, possessing deep trabecular recesses adjacent to wall segments with depressed systolic function and sluggish blood flow could contribute to thrombus formation and subsequent embolization. Hence, some investigators have suggested that anticoagulation should be considered for those with deep recesses and compromised LV systolic function [53].

Different centers use different indications for anticoagulation, but most use a threshold of LV ejection fraction of 35–45 %. Conversely, if systolic function was normal, most trabecular recesses would be obliterated with systole and would not be a source of slow blood flow to increase the risk of thrombus formation. In those with dilated cardiomyopathy, their risk of embolization independent of atrial fibrillation was significantly less than that seen in LVNC [54]. For those with LVNC who develop atrial fibrillation, anticoagulation with warfarin or a newer oral anticoagulant should be strongly considered [55].

Genetic/Familial Testing

Given its association with several congenital syndromes and myopathies, many wonder about the role of genetic/familial testing for the families of those diagnosed with LVNC. In one study which evaluated the asymptomatic relatives of those with LVNC, it suggested that increased trabeculations are a very common finding, even in asymptomatic individuals [56•]. Importantly, they do not share the same prognosis and outcome as those with symptomatic LVNC. While it is not unreasonable to screen family members, it must be stressed that functional status, LV function, and symptoms are most important in addressing prognosis, even in the setting of increased trabeculations. With a diverse range of genes being linked to LVNC, there is probably no direct role for genetic testing at this time, unless indicated by factors that would point to a more global abnormality, such as Barth syndrome [5, 6]. Finally, with much data being derived from populations with neuromuscular diseases, it is not unreasonable to investigate for a global myopathic process if indicated by the patient's symptoms and presentation.

Conclusion

LVNC represents a unique phenotype with increased risk for progressive heart failure, sudden cardiac death, ventricular dysrhythmias, and embolic events. While the incidence is uncommon, the management should include optimized medical therapy for heart failure, implantable cardiac defibrillator if systolic function is reduced or ventricular dysrhythmias are present, and lastly, anticoagulation should be considered in those with LVNC when the LV systolic function is reduced.

Compliance with Ethics Guidelines

Conflict of Interest R. Brandon Stacey, Augustus J. Caine, Jr., and W. Gregory Hundley declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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