

Non-compaction of the ventricular myocardium

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ABSTRACT: *Non-compaction of the left ventricle (LVNC) is a disorder of endomyocardial morphogenesis that results in multiple trabeculations in the left ventricular (LV) myocardium. This rare disorder is characterized by an excessively prominent trabecular meshwork and deep intratrabecular recesses. This idiopathic cardiomyopathy is characterized by an altered structure of the myocardial wall as a result of intrauterine arrest of compaction of the myocardial fibers in the absence of any coexisting congenital lesion. It can be associated with neuromuscular disorders and can co-exist with other cardiac malformations, and it is accompanied by depressed ventricular function, systemic embolism and ventricular arrhythmia. Echocardiography is the method of choice for diagnosing LVNC, but the correct diagnosis is often missed or delayed due to a lack of knowledge concerning this uncommon disease and its similarity to other diseases of the myocardium and endocardium. There is a two-layered structure of the myocardial wall consisting of a thin compacted epicardial layer and a thick non-compacted endocardial layer with prominent trabeculations and deep recesses. (Heart International 2006; 3-4: 178-83)*

KEY WORDS: *Cardiomyopathy, Left ventricle non-compaction, Left ventricular function*

INTRODUCTION

Isolated non-compaction of the left ventricle (LVNC) is a rare congenital cardiomyopathy. Recognized relatively recently, it has been categorized as "unclassified cardiomyopathy" by the World Health Organization. It is caused by failure of the developing myocardium to become compact, thereby resulting in a "spongy myocardium".

Embryology and development

Isolated LVNC is a rare disorder of endomyocardial morphogenesis characterized by numerous prominent ventricular trabeculations and deep intratrabecular recesses (1). During normal embryonic development, endomyocardial trabeculations emerge from the apical region of the primitive ventricles at day 32 of fetal life (2), and involute by day 70 through a process of resorption and remodeling. LVNC is thought to be a failure of this "compaction" process. It is thought to result from failure

of trabecular compaction of the loose mesh of muscle fibers seen in the early stages of myocardial development. Normally this process is more pronounced in the left than in the right ventricle, resulting in a smooth, flat endocardial surface.

The normal left ventricle has less than three trabeculations per imaging field, mostly confined to the lateral wall (3). In this disorder, however, there are abnormal trabeculations resulting from non-compaction scattered all over the myocardium, but most evident near the attachment of the papillary muscles of the mitral valve (Fig. 1) (4). Right ventricular non-compaction may accompany LVNC in <50% of patients. Due to the difficulty in distinguishing normal variants in the highly trabeculated right ventricle from the pathological non-compacted ventricle, several authors dispute the existence of right ventricular non-compaction (4, 5).

Isolated non-compaction of the ventricular myocardium, first described by Chin et al (1) in 1990, is characterized by persistent embryonic myocardial morphology

found in the absence of other cardiac anomalies to explain the abnormal development. In such cases, the resulting deep recesses communicate with the ventricular cavity only, not the coronary circulation (1).

There is no specific histological finding in LVNC, although fibrosis has been described in numerous reports (6, 7) (Fig. 2). Some reports have observed necrotic myocytes within the prominent trabeculations of patients with non-compaction (5, 6).

Many cases of LVNC are caused by associated anomalies that generate intraventricular pressure overload, as in the case of pulmonary atresia with intact ventricular septum (8) or anomalous origin of the left coronary artery from the pulmonary trunk (9). In these hearts, the deep recesses are in continuity with the ventricular cavity and with the coronary arteries; and therefore, are more accurately described as persistent intramyocardial sinusoids. By contrast, LVNC has no associated cardiac lesions, and persistent sinusoids are not seen.

Genetics

The disorder can be sporadic, but familial recurrence and associated dysmorphism has been reported (8, 9). The familial form has a heterogenous mode of inheritance. In the X-linked form of the disease, the locus has been found on q28, and mutations have been reported in the G4.5 gene (10, 11). This gene is in close proximity to other genes responsible for myopathies, and a number of patients with hypertrabeculations have been found to suffer from neuromuscular disorders such as Emery-Dreifuss muscular dystrophy, Barth's syndrome, Becker's muscular dystrophy, metabolic myopathies, and Roifmann syndrome (12), skeletal abnormalities such as Melnick-Needles syndrome and nail-patella syndrome (13). The facial dysmorphism consists of prominent forehead, strabismus, gothic palate or micrognathia.

In children, LVNC can occur in Barth's syndrome, a rare X-linked multi-system disorder caused by a mutation in the G4.5 gene that encodes the tafazzin family of proteins (14, 15). Mutations in this gene in adult LVNC are rare, however, but mutations have been described in adult LVNC in the genes encoding α -dystrobrevin and Cypher/ZASP (14, 16), integral parts of the complex that link the extracellular matrix of the myocardial cell to the cytoskeleton.

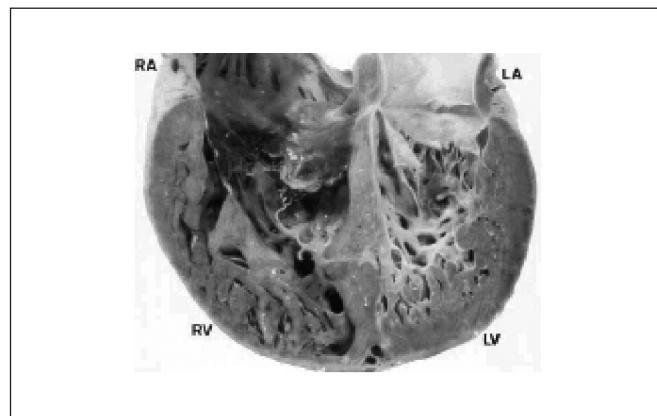


Fig. 1 - Heart of a patient with LVNC.

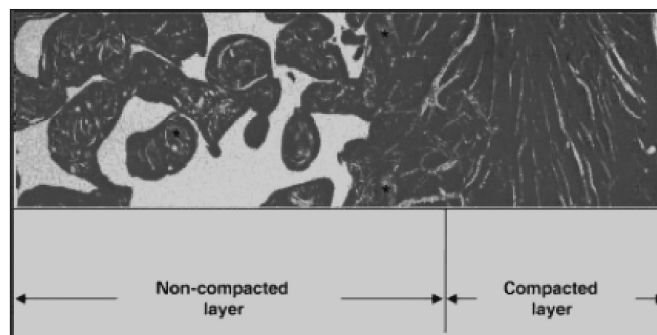


Fig. 2 - Histological features of LVNC.

Epidemiology

In the initial case series of isolated non-compaction (1), the median age at diagnosis was 7 yrs (range 11 months to 22 yrs). Subsequent case reports have described this finding in adults, including the elderly (1, 5, 17-19). In the largest series of patients with LVNC (5), the prevalence was 0.014% of patients referred to the echocardiography laboratory. The true prevalence is unclear since the correct diagnosis is often missed or delayed due to a lack of knowledge concerning this uncommon disease, and its similarity to other diseases of the myocardium and endocardium. Men appear to be affected more than women, accounting for 56-82% of cases in the largest reported series of LVNC (1, 5, 20, 21).

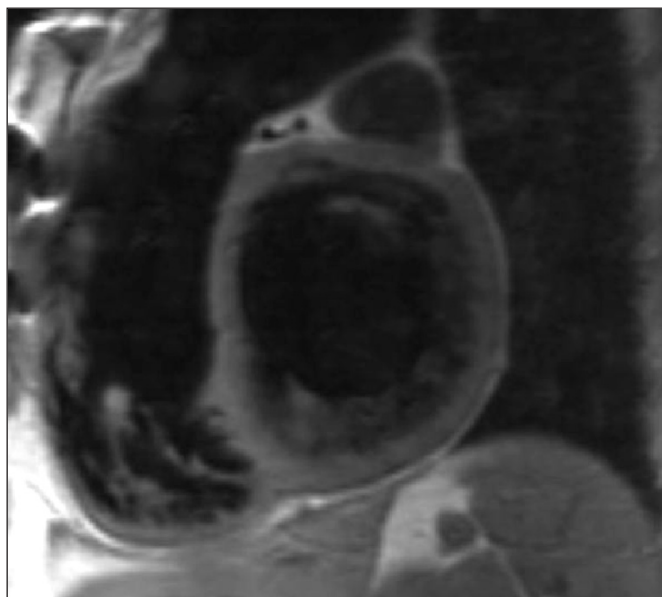


Fig. 3 - MRI of a patient with LVNC.

Clinical features

Clinical severity depends on the extent of non-compacted cardiac segments. Severe systolic heart failure and increased end-diastolic pressure with restrictive cardiomyopathy are seen in >50% of patients. Bundle branch block, atrial arrhythmias and other serious ventricular arrhythmias occur in 40% of cases and can cause sudden cardiac death (11). Thromboembolic complications have also been reported (10, 11).

Diastolic dysfunction in ventricular non-compaction can be related to both abnormal relaxation and restrictive filling caused by the numerous prominent trabeculae (22). The origin of systolic dysfunction in non-compaction is unclear, but there is increasing evidence that subendocardial hypoperfusion and microcirculatory dysfunction play a role in ventricular dysfunction and arrhythmogenesis. Chin et al (1) suggested that subendocardial perfusion might be abnormal in LVNC despite the absence of epicardial coronary artery disease. Due to the numerous prominent trabeculae, subendocardial ischemia can be the result of isometric contraction of the endocardium and myocardium within the deep intertrabecular recesses. Subendocardial perfusion defects have been described in LVNC using cardiac magnetic resonance imaging (MRI) (Fig. 3) (23). Positron emission tomography (PET) (24) and

scintigraphy with thallium-201 (21) have shown transmural perfusion defects correlating with areas of non-compacted myocardium in LVNC.

Abnormalities in resting ECG are found in the majority of patients with LVNC, but findings are non-specific and include left ventricular (LV) hypertrophy, repolarization changes, inverted T waves, ST segment changes, axis shifts, intraventricular conduction abnormalities and AV block (1, 5, 20, 21). Electrocardiographic findings of the Wolff-Parkinson-White syndrome have been described in up to 15% of pediatric patients (21, 25), but it was not observed in the two largest series of adults with isolated non-compaction (5, 20).

Arrhythmias are common in patients with ventricular non-compaction. Atrial fibrillation has been reported in over 25% of adults with LVNC (5, 20). Ventricular tachyarrhythmias have been reported in as many as 47%. Sudden cardiac death accounted for half of the deaths in the larger series of patients with LVNC (1, 20). Although ventricular arrhythmias occurred in nearly 40% of patients in the initial description of LVNC by Chin et al (1), Ichida et al (21) described no cases of ventricular tachycardia or sudden death in the largest series of pediatric patients with LVNC. Paroxysmal supraventricular tachycardia and complete heart block have also been reported in patients with LVNC (20, 21).

The occurrence of thromboembolic events, including cerebrovascular accident, transient ischemic attack, pulmonary embolism and mesenteric infarction, ranged from 21-38% (5, 20). Embolic complications may be related to the development of thrombi in the extensively trabeculated ventricle, depressed systolic function, or the development of atrial fibrillation (20). Interestingly, no systemic embolic events were reported in the largest pediatric series with LVNC (21).

An association between non-compaction and neuromuscular disorders has also been described (3, 26), as many as 82% of patients having some form of neuromuscular disorder. Chin et al described an association between LVNC and facial dysmorphisms, including a prominent forehead, strabismus, high-arching palate, and micrognathia (1).

Diagnosis

Echocardiography is the best means for diagnosing the disorder (4). The combined echocardiographic fea-

tures essential for making a diagnosis include: a two-layered ventricular myocardium consisting of an subendocardial compact layer and a thick non-compacted endocardial layer with prominent trabeculations and intratrabecular recesses; continuity between the LV cavity and the recesses with blood flowing in and out of the ventricular cavity and absence of secondary causes of increased trabeculations (Fig. 4) (13). There is continuity between the LV cavity and the deep intratrabecular recesses that are filled with blood from the ventricular cavity, without evidence of communication with the epicardial coronary artery system (1, 20).

The LV apical and inferior wall segments were involved in all patients in an adult population with LVNC studied by echocardiography (20). The right ventricular apex was involved in 41% of patients. In the largest series of patients with LVNC (5), in addition to the apical and mid-ventricular inferior wall segments, the mid-ventricular lateral wall segment was involved in >80% of patients. Hypokinesis was observed occasionally in normally compacted segments as well as in the non-compacted segments of the left ventricle (5), which may correlate with the observation of microcirculatory dysfunction in both non-compacted and "normal" segments in patients with LVNC.

Chin et al (1) described a quantitative approach for diagnosing non-compaction using a trabeculation peak to trough ratio, but it has not been used widely in clinical practice. Oechslin et al (5) and Jenni et al (4) described the abnormally thickened myocardium as a two-layered structure, with a normally compacted epicardial layer and a thickened endocardial layer. They proposed a quantitative evaluation for the diagnosis of LVNC by determining the ratio of maximal thickness of the non-compacted to compacted layers (measured at end systole in a parasternal short axis view), with a ratio of 2.0 diagnostic of LVNC. This technique allowed the differentiation of the trabeculations of LVNC from that observed with dilated cardiomyopathy or hypertensive cardiomyopathy (4).

Based on echocardiographic studies, its prevalence has been estimated at 0.05% in the general population (20), and the finding of a ratio of 2.0 between the thickness of the non-compacted and compacted myocardial layers in systole is considered diagnostic (4).

Contrast echocardiography can be helpful when standard echocardiographic image quality is limited or

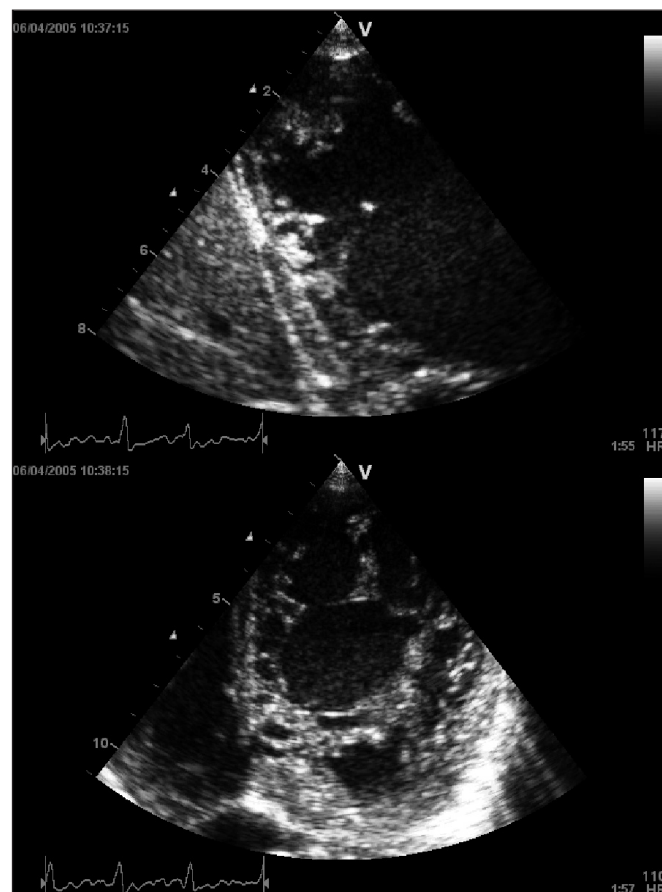


Fig. 4 - Echocardiographic aspect of LVNC.

the diagnosis is questionable (27). Prominent trabeculations, apical hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular dysplasia, endocardial fibroelastosis, cardiac metastasis, and LV thrombus are important differential diagnostic considerations.

Echocardiography can easily diagnose isolated ventricular non-compaction if the echocardiographer is familiar with this congenital disorder, and if clear-cut diagnostic criteria are used. Due to the risk of familial occurrence, first-degree relatives should be screened by echocardiography to identify asymptomatic patients.

Based on the ratio of end-diastolic thickness of the non-compacted to compacted layers of the myocardium, CMR imaging is accurate when diagnosing pathological LVNC (28). The literature supports the clinical use of CMR in diagnosing LVNC, especially for patients with poor echocardiographic windows (29).

Ventriculography and computed tomography can also show the typical morphological features of non-compaction: pathognomonic combination of multiple prominent ventricular trabeculations and of multiple deep intertrabecular recesses communicating with the ventricular cavity.

Prognosis

The current literature suggests that LVNC in adults is rare and associated with a poor prognosis (5, 30). In the largest series to date, 48% of patients died or underwent a heart transplant over a period of 44 months (5). Prognosis in the asymptomatic patients was clearly better than in the symptomatic patients (21).

The prognosis depends on the severity and is generally grim due to cardiovascular complications such as congestive failure (heart failure was caused by systolic and diastolic dysfunction), shock, arrhythmias and fatal thromboembolic events. The high prevalence of thromboembolic events (24% of patients) was consistent and was independent of LV size or function (1). The deep recesses can aggravate the risk of thrombus formation and be an additional factor for this serious complication.

The cause of progressive myocardial failure has not yet been elucidated. The hypertrophic segments are perfused via the epicardial coronary arteries, which have no continuity with the deep recesses communicating with the LV cavity. Thickened endocardium and ischemic lesions in prominent trabeculae surrounded by deep trabecular recesses were documented in histologic specimens, which could be caused by ischemia (20). Indeed, PET demonstrated restricted myocardial perfusion in areas of LVNC (24). Hypothetically, both morphology and vasomotion of the coronary vessels feeding the hypertrophic segments can be abnormal with subsequent ischemia. Progressive ischemia and subsequent scar tissue can be an arrhythmogenic substrate

for ventricular arrhythmias because the well-defined morphologic substrate of LVNC cannot be considered inherently arrhythmogenic. In severe cases, a heart transplant may be the only option (1).

Therapy

There is no specific option for the treatment of non-compaction cardiomyopathy, which is the same as for heart failure. Standard medical therapy for systolic and diastolic ventricular dysfunction is warranted. Some findings have pointed to the efficacy of carvedilol in improving LV function, hypertrophy, and both metabolic and adrenergic abnormalities in isolated LVNC (31). Cardiac transplantation has been used for those with refractory congestive heart failure. A more aggressive approach to the diagnosis and treatment of ventricular arrhythmias may be justified, and assessment for atrial and ventricular arrhythmias by ambulatory ECG monitoring should be performed annually. As more information is gathered about LVNC and the risk of sudden cardiac death, implantable defibrillator technology could have an increased role. Biventricular pacemakers could play a role in the treatment of LVNC patients with heart failure, reduced LV function, and prolonged intraventricular conduction.

Prophylactic anticoagulation may be warranted because of the higher risk of thrombus formation within the intratrabecular recesses.

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