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UPDATE
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Left Ventricular Noncompaction, a Recently Recognized Form of Cardiomyopathy

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Left ventricular noncompaction (LVNC) is a recently and increasingly recognized form of cardiomyopathy. It is characterized by the presence of an extensive trabeculated layer of myocardium and multiple deep intertrabecular recesses reinforcing the luminal aspect of the compacted part of the ventricular wall. It is probably secondary to an arrest of the normal process of compaction that occurs early in fetal life. LVNC seems to be a morphologic abnormality with genetic heterogeneity; both familial and isolated cases have been described. A few causal mutations have been discovered. Clinically, LVNC presents with: heart failure (usually severe), systemic embolism, arrhythmia or sudden death. Association of LVNC with other congenital heart and neuromuscular diseases has been reported. The diagnosis is generally made by the echocardiographic demonstration of a thick noncompacted layer with a maximal noncompacted to compacted ratio > 2; flow from the left ventricular (LV) cavity into the intertrabecular recesses; and areas of hypokinesia with depressed systolic and diastolic function. Also, magnetic resonance imaging appears promising to increase the diagnostic accuracy. Prognosis was initially thought to be very poor; but this belief has changed in the last years. There is no specific therapy for LVNC, so patients are treated with digoxin, inhibitors of angiotensin converting enzyme, diuretics and beta blockers. Anticoagulation is recommended after embolic episodes. Cardiac transplantation remains as the last option for cases refractory to medical therapy.
Key Words: Cardiomyopathy - Heart failure - Myocardium - Noncompaction - Echocardiography

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Introduction

A recently recognized form of cardiomyopathy named Left Ventricular Noncompaction (LVNC) is a fascinating disorder characterized by the presence of an extensive trabeculated layer of myocardium and multiple deep intertrabecular recesses reinforcing the luminal side of the compacted portion of the ventricular wall. It is probably secondary to an arrest in the normal process of myocardial compaction during fetal life[1,2]. Although once considered rare, LVNC is now being diagnosed with increasing frequency, from the fetus to the adult, either in isolation or combined with congenital heart disease or neuromuscular disorders[3-5]. Diagnosis has moved from autopsy to recognition during life by non-invasive means: echocardiography and more recently cardiac magnetic resonance imaging[6-8]. Clinical manifestations are highly variable ranging from no symptoms to severe heart failure, systemic embolism, arrhythmia or sudden death.

Definition

In the normal heart, the ventricular walls are made up predominantly of a compacted layer of myocardial fibers set in a matrix of supporting connective tissue[9]. The luminal surfaces of the ventricles show trabeculations that are particularly prominent at the ventricular apexes[10]. Trabeculations are generally coarser in the morphologically right than in the left ventricle. The proportion of the normal ventricular wall formed by trabeculations never exceeds the thickness of the compacted layer in normal ventricles. On the contrary, in patients with LVNC: a) the thickness of the noncompacted myocardium is greater than the compacted layer which in turn is generally thinned; b) an excessive number of conspicuous ventricular trabeculations are visible. These trabeculations are usually confined to the apical and mid

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ventricular myocardial segments of the left ventricle; c) deep intertrabecular recesses receiving flow from the left ventricular (LV) cavity are present[3]. These recesses are covered by endocardium and are directly continuous with the endothelial lining of the LV cavity. The recesses are neither in contact nor communicate with the coronary circulation[11,12]. LVNC has recently been classified as a primary (i.e., predominantly affecting the myocardium) and genetic cardiomyopathy, being neither dilated, restrictive nor hypertrophic[13].

Embryology, Development and Histology

During early embryonic development, the myocardium is a loose network of interwoven fibers separated by deep recesses that link the myocardium with the LV cavity. Gradual compaction of this spongy meshwork of fibers and intertrabecular recesses, or sinusoids, occurs between weeks 5 and 8 of embryonic life, proceeding from the epicardium to endocardium and from the base of the heart to the apex[14-17]. The coronary circulation develops concurrently during this process, and the intertrabecular recesses are reduced to capillaries[18].

LVNC was initially called "persistent spongy myocardium", and associated with other congenital anomalies such as pulmonary atresia with intact interventricular septum, severe obstruction to the LV outflow tract and severe coronary anomalies[6]. In these cases, the abnormal load to the ventricle leads to persistence of the embryonic myocardial sinusoids in communication both with the ventricular cavity and the coronary circulation was present[11,12]. Now we realize that the initial description is far from what we nowadays call LVNC.

Isolated LVNC, first described by Chin et al. in 1990[7] is characterized by persistent embryonic myocardial morphology found in the absence of other cardiac anomalies to explain the abnormal development. In such cases, the deep recesses communicate only with the LV cavity, not the coronary circulation.

Although widely believed to be the mechanism, there has been no proof of an arrest in embryonic endomyocardial morphogenesis. Arguments in favour of the embryonic hypothesis are that many genes are involved in the key phases of myocardial morphogenesis and that in several experiments mice with mutations of these genes developed LVNC[16,19]. This hypothesis has been challenged by the detection of a normal phenotype early life with development of LVNC later in life[20,21]. Secondly, the fact that LVNC occurs more frequently in the LV apex, the part of the ventricle with the thinnest myocardium and the highest wall stress, suggests that LVNC may be an attempt of abnormal myocardium to grow in order to reduce wall stress[22].

Another appealing theory suggests that LVNC is the result of an adaptation to abnormal loading conditions on the ventricle[23]. This theory is supported by the finding that a trabeculated myocardium has markedly different a viscoelastic behavior, influencing the rate and magnitude of contraction and relaxation, than the compact myocardium[24]. Furthermore, the performance of the cardiac ventricle of the icefish, which is of spongy type with myocardial pseudohypertrophy resembles the anatomy and function of the heart in LVNC[25]. The icefish's heart functions as a specialized volume pump that moves large stroke volumes at a low heart rate, but is not able to produce high pressures[26]. In addition, LVNC has been noted in patients with abnormal loading on the ventricles such as Ebstein's malformation, pulmonary stenosis, and critical aortic stenosis[4,27,28].

Histological findings in LVNC are non-specific, they include fibrosis/fibroelastosis, myocardial disarray and increased mitochondrial size[29,30]. For these reasons it may not be justified to perform endomyocardial biopsies which are not helpful at all, and may be dangerous in small patients[4].

Genetics

Both familial and sporadic forms of the disease have been described. Familial forms seem to represent between 20-50 % of the cases[31-33]. X-linked and dominant transmission patterns have been described. Multiple genes responsible for the familial cases have been identified; the mutations in G4.5 of the Xq28 chromosome that encodes for a protein family called tafazzins is associated with Barth syndrome, an X-linked mitochondrial disease affecting cardiac and skeletal muscle[34,35]. Also, mutations in the alpha-dystrobrevin and lamin A/C genes that cause muscular dystrophy have been documented[36]. All these mutations produce a wide phenotypic spectrum of cardiomyopathies, including dilated cardiomyopathy, X-linked infantile cardiomyopathy, and X-linked endocardial fibroelastosis. Vatta et al. have shown that in some patients with either dilated cardiomyopathy or LVNC, a mutation in Cypher-Zasp, a gene encoding a protein that is a component of the Z-line in both skeletal and cardiac muscle may be causal[37]. In adults, an autosomal dominant disorder rarely caused by mutations in G4.5, and hence genetically distinct from the X-linked cases seen in infancy has been recognized[38,39]. So far, it appears that LVNC is a morphologic abnormality with genetic heterogeneity[40].

Epidemiology and Demographics

Although initially considered rare, increasing physicians' awareness about the condition has led to LVNC being more frequently diagnosed. Also, improvements in imaging modalities, specially the development of echocardiographic second harmonic, and the increasing use of cardiac magnetic resonance which allow better visualization of the LV apex and have improved the diagnostic sensitivity. Various echocardiographic studies report that 0.001 to 0.1 % of all investigations corresponds to patients with LVNC. In adults, Ritter found an incidence of 0.05 % of all examinations[41]. In children, a revision of all echocardiograms in a tertiary center showed that 0.01 % had been diagnosed with LVNC and that LVNC accounted for 10 % of pediatric cardiomyopathies[4]. Although these contemporary data suggest that LVNC is an extremely rare form of cardiomyopathy, we must now accept that it is being recognized with increasing frequency, so recently LVNC has been classified as a specific

form of genetic cardiomyopathy [13,42,43].

There seems to be a male to female ratio of nearly 1.8, explainable by the inheritance pattern of familial forms. Age at diagnosis varies considerably according to whether the reporting center serves a pediatric or adult population, with few diagnoses made during fetal life and others at the age of 70-80 years. In pediatric patients most of diagnoses are made in infancy (median 90 days of life). In adults, there is a wide range with slight increase in the frequency of diagnoses between 20 - 40 years. Some patients appear to have an "undulating course" with poor LV function at diagnosis, followed by initial recovery in function that ultimately evolves into end-stage heart failure. In other patients, LVNC initially presents as hypertrophic or dilated cardiomyopathy but a phenotypical switching can occur during follow-up[4].

Clinical Characteristics

Three major clinical manifestations of noncompaction have been described: Heart failure, arrhythmias, and embolic events[4,32,44]. Findings vary among patients, ranging from asymptomatic LV dysfunction to severe, disabling congestive heart failure. Over two thirds of the patients in the largest series with LVNC had symptomatic heart failure[32]. Both systolic and diastolic ventricular dysfunction have been described[33,45]. The origin of systolic dysfunction in noncompaction is unclear, but a body of evidence is accumulating points toward subendocardial hypoperfusion and microcirculatory dysfunction playing roles in ventricular dysfunction and arrhythmogenesis[29,30]. Diminished coronary flow reserve has been demonstrated by PET in both noncompacted and compacted myocardial segments in LVNC.

Arrhythmias are common in patients with LVNC. Atrial fibrillation has been reported in over 25% of adults with LVNC[32]. 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[32].

Abnormalities of the resting ECG are found in the majority of patients with LVNC but findings are non-specific and include LV hypertrophy, repolarization changes, inverted T waves, ST segment changes, axis shifts, intraventricular conduction abnormalities, and AV block. In neonates, biventricular high voltage is frequently seen and highly suspicious of LVNC or storage disease. Oechslin et al described left bundle branch block in 44% of adult patients with LVNC, but the reported incidence in children was much lower in another study. Electrocardiographic findings of the Wolff-Parkinson-White syndrome have been described in up to 15% of pediatric patients, but it was not observed in the 2 largest series of adults with isolated noncompaction[4,32,33].

The occurrence of thromboembolic events, including cerebrovascular accidents, transient ischemic attacks, pulmonary embolism, and mesenteric infarction, ranged from 21% to 38%[32,46]. Embolic complications may be related to development of thrombi in the extensively trabeculated ventricle, depressed systolic function, or the development of atrial fibrillation. Of interest, no systemic embolic events were reported in the 2 largest pediatric series with LVNC[4,33].

Diagnosis

In most cases, the diagnosis of LVNC has relied in two dimensional and color Doppler echocardiography. Several criteria have been applied in an attempt to clarify the diagnosis. The most widely used have been published by Jenni et al, are based on echocardiographic measurements performed on adults[3]. They include: (1) presence of numerous and prominent trabeculations and intertrabecular recesses, specially if localized in the apical or mid myocardial segments; (2) visualization of blood flow in the recesses with color Doppler imaging; (3) absence of any other cardiac abnormality; (4) noncompacted to compacted ratio > 2 at end systole. In children, others have used a noncompacted to compacted ratio > 1.4[4]. See Figures 1 and 2. A magnetic resonance study found a noncompacted to compacted ratio > 2.3 at end diastole had the highest sensitivity, specificity, positive and negative predictive value to discriminate LVNC from prominent trabeculations secondary to LV hypertrophy and athlete's heart[8].. The LV apex and mid inferior, anterior and lateral myocardial segments are more often involved[47]. Depressed LV global systolic function is the rule, with a reported mean ejection fraction of 25-35 % depending on the study. Also, regional hypokinesia not only of the noncompacted but also of the compacted myocardial segments has been described[48]. Concomitant right ventricular involvement is seen in nearly 40 % of the cases[4]; with no case of isolated right ventricular involvement reported until now. Actually, many authors are unsure about whether isolated right ventricular noncompaction can be diagnosed as the right ventricle normally has some degree of noncompaction[1,3].

Echocardiography, nonetheless, is less than perfect for the diagnosis of noncompaction, since the adequacy of the investigation depends very much on the experience and knowledge of the investigator. Echocardiography poses inherent problems in assessing the LV apex, known to be the most

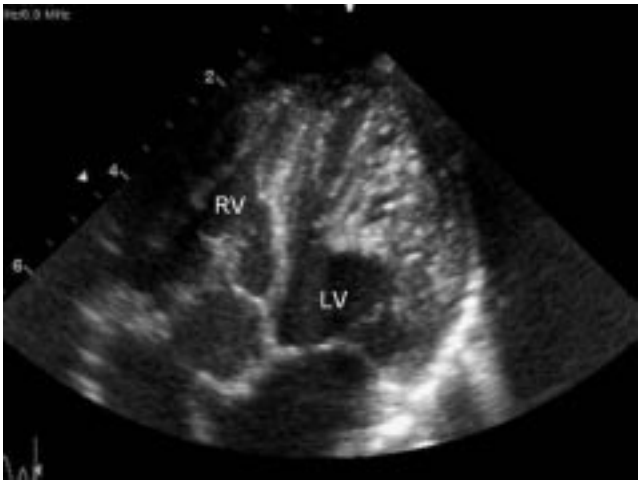

Figure 1. Two dimensional echocardiogram of a patient with left ventricular noncompaction in apical 4-chamber view showing the bilayered arrangement of the myocardium. The inner, thick and hyperechogenic layer is noncompacted, the outer is more echolucent, compacted and thinner than in normal subjects. Trabeculations are prominent and numerous. This appearance is more markedly visible on the lateral wall. LV, left ventricle; RV, right ventricle.

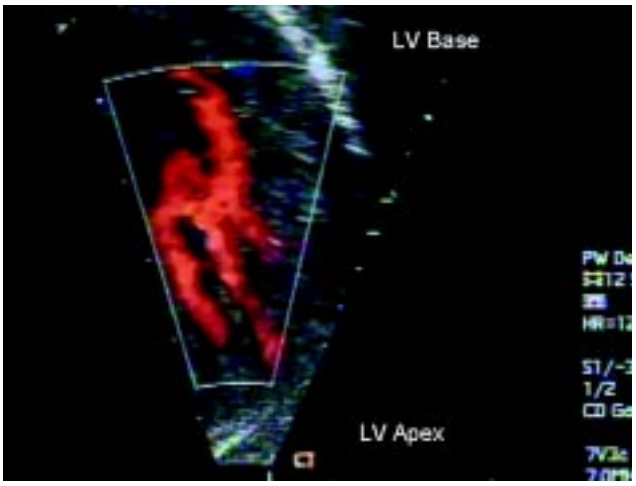

Figure 2. Color Doppler echocardiogram in apical 4-chamber view showing flow from the left ventricular cavity within the deep intertrabecular recesses.

commonly noncompacted area. Furthermore, patients may be misdiagnosed as having apical hypertrophic cardiomyopathy[49]. Contrast echocardiography might improve the sensitivity of diagnosing noncompaction due to improved contrast between myocardium and blood pool in patients with poor acoustic windows. Involvement of the right ventricle also remains controversial, first because of the more trabeculated nature of the right ventricle itself, and second, due to problems with echocardiographic access to the right ventricle behind the sternum.

Magnetic resonance imaging is increasingly used for the diagnosis of LVNC[8,50]. Magnetic resonance cine imaging, by using so-called steady state free precession sequence, is increasingly used because of its ability clearly to visualize the compacted and noncompacted layers (Figures 3 and 4).This technique shows a wider extent of disease, and a greater ratio of noncompacted to compacted myocardium, when compared to echocardiography in cases with LVNC. Interestingly, the noncompacted layer is demarcated internally by an interrupted layer of tissue. The trabeculations hang from this layer towards the compacted layer, appearing like a cascading necklace. In addition, the high spatial resolution of cardiac magnetic resonance imaging demonstrated that ventricles of normal individual, of athletes and of patients with aortic stenosis, dilated and hypertrophic cardiomyopathy have some degree of noncompaction. Furthermore, the localization of the noncompacted myocardium did not help to discriminate among these groups. However, then end-diastolic noncompacted to compacted ratio was always > 2.3 provided a sensitivity, specificity, positive and negative predictive values of 86 %, 99 %, 75 % , and 99 % respectively to differentiate patients with LVNC from all the other investigated groups[8]. It has also been suggested that delayed hyperenhancement imaging might be able to visualize the necrotic or fibrotic myocardium that could be the focus of the ventricular arrhythmia[51]. Another advantage of magnetic resonance imaging is that its intrinsically three-dimensional nature permits the assessment of all cardiac segments. Sequences based on the use of contrast then allow the assessment of myocardial perfusion, and the evaluation of

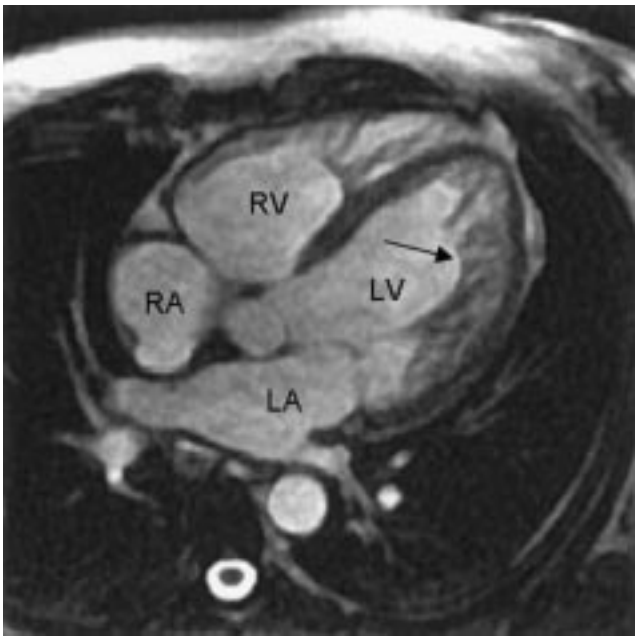

Figure 3. End-diastolic steady state free precession cine magnetic resonance images in horizontal long axis showing (arrow) a large noncompacted layer and a thin compacted layer in the left ventricular lateral wall. In addition, a clear distinction between these two layers can be demonstrated. LV, left ventricle; RV, right ventricle; LA, left atrium; RA, right atrium.

myocardial fibrosis. This modality also allows better visualization of LV thrombus.

Differential diagnoses include: false tendons, prominent trabeculations as normal variants, apical hypertrophic cardiomyopathy, dilated cardiomyopathy, Fabry disease, arrhythmogenic right ventricular dysplasia, endocardial fibroelastosis and LV thrombus. It is essential to reach an accurate diagnosis as prognosis varies widely among all these conditions.

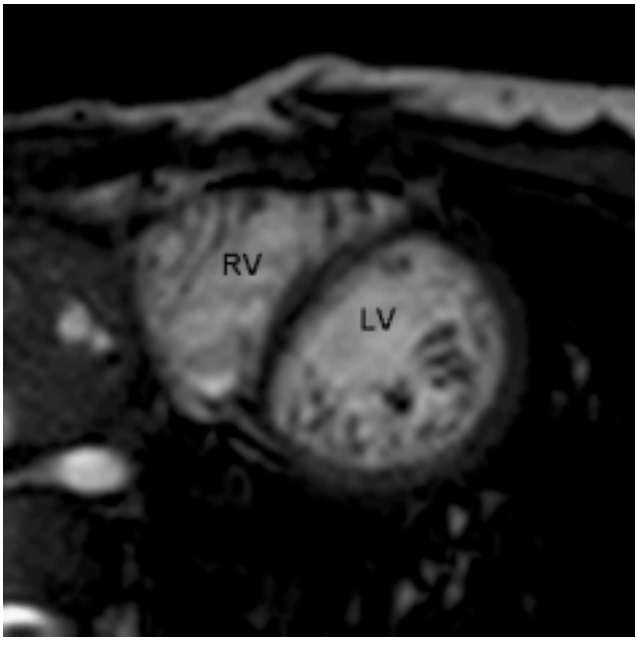

Figure 4. End-diastolic steady state free precession cine magnetic resonance images in short axis view at the apical level showing prominent trabeculations and a thin compacted layer.

An association between LVNC and neuromuscular disorders has also been described, with as many as 82% of adult patients having some form of neuromuscular disorder. For this reason, Stöllberger and Finsterer recommend that all patients diagnosed with isolated LVNC should be screened for neuromuscular abnormalities[47,52].

Management and Outcome

Many of the early clinical reports emphasized the dismal outcomes of patients with isolated LVNC, focusing on the often malignant accompanying arrhythmias [32,41]. Increasing clinical experience has modified to some extent this bleak outlook[4,5]. In some asymptomatic patients, isolated LVNC has been found as an incidental finding. In others it has been recognized in the sixth and seventh decades of life, and beyond. Yet the disorder certainly has the potential for a poor outcome. Even for those patients presenting in the first year of life with depressed LV contractility, with some recovery of ventricular function, recovery can be transient. Oechslin et al reported that certain clinical characteristics were observed significantly more frequently in nonsurvivors compared with survivors with LVNC, including higher LV end diastolic diameter on presentation, New York Heart Association class III-IV, permanent or persistent atrial fibrillation, and bundle branch block[32]. Patients with these high risk features are candidates for early, aggressive interventions, including consideration for AICD implantation and for heart transplant evaluation[53].

There is no specific therapy for LVNC. A variety of medical therapies have been utilized in those symptomatic patients with congestive heart failure, including cardiac glycosides, diuretics, inhibitors of angiotensin converting enzyme, afterload reducing agents, and for those suspected of having an underlying mitochondrial myopathy, a “metabolic cocktail” containing coenzyme Q10, riboflavin, thiamine and carnitine[4]. Beta-blockade has also been used with some success, and some have proceeded to cardiac transplantation. Disturbances of rhythm have been treated in standard fashion, while some have implanted defibrillators for severe ventricular arrhythmias recognized as predisposing to sudden death.

Cerebral vascular accidents certainly contribute to co-morbidity in patients with LVNC. In general, all patients with LVNC receive platelet aggregation inhibitors either aspirin or clopidogrel. Several authors recommend long-term prophylactic anticoagulation for all patients with LVNC whether or not thrombus has been found. Of course, if a patient develops atrial fibrillation or has sustained an unequivocal thromboembolic event, then full anticoagulation is advised.

Because of the familial association described with LVNC, screening echocardiography of first degree relatives is recommended[4]. The increasing awareness about the condition results in some asymptomatic subjects with preserved LV function are diagnosed with LVNC during work up of heart murmurs or while screening before starting competitive sports. This brings up new therapeutic dilemmas as the management and outcome in this group has not yet been determined.

Conclusions

LVNC is a genetically heterogeneous disorder, it mat affect both ventricles, may be isolated or associated with other cardiac malformations. The weigh of evidence suggests that LVNC results from an arrest in the process of LV compaction that normally occurs early in fetal life. However, research is needed to further elucidate the mechanism involved in this process.

Clinical presentation does not differ from the one seen in patients with dilated cardiomyopathy. In children a restrictive physiology is also common. Interestingly, LVNC is often associated with neuromuscular disorders. However, the reasons for this association remain unclear. Prognosis is poor, with progression to severe heart failure and death. Sudden death also occurs reflecting the predisposition to severe ventricular arrhythmias. In severely symptomatic patients, cardiac transplantation is an option if medical therapy fails to stabilize the condition.

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