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Non-Compact Cardiomyopathy or Ventricular Non-Compact Syndrome?

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Ventricular myocardial non-compaction has been recognized and defined as a genetic cardiomyopathy by American Heart Association since 2006. The argument on the nomenclature and pathogenesis of this kind of ventricular myocardial non-compaction characterized by regional ventricular wall thickening and deep trabecular recesses often complicated with chronic heart failure, arrhythmia and thromboembolism and usually overlap the genetics and phenotypes of other kind of genetic or mixed cardiomyopathy still exist. The proper classification and correct nomenclature of the non-compact ventricles will contribute to the precisely and completely understanding of etiology and its related patho-physiological mechanism for a better risk stratification and more personalized therapy of the disease individually. All of the genetic heterogeneity and phenotypical overlap and the variety in histopathological, electromechanical and clinical presentation indicates that some of the cardiomyopathies might just be the different consequence of myocardial development variations related to gene mutation and phenotype of one or group genes induced by the interacted and disturbed process of gene modulation at different links of gene function expression and some other etiologies. This review aims to establish a new concept of "ventricular non-compaction syndrome" based on the demonstration of the current findings of etiology, epidemiology, histopathology and echocardiography related to the disorder of ventricular myocardial compaction and myocardial electromechanical function development.

KEY WORDS: Non-compact, Ventricle, Cardiomyopathy, Syndrome.

INTRODUCTION

The first case of ventricular non-compaction was described in 1932 after an autopsy performed on a newborn infant with aortic atresia and coronary-ventricular fistula by Bellet and Gouley,[1] a few studies published late reconfirmed this kind of spongy myocardial malformation by ventriculography and pathological anatomy exam.[2-4] The isolated non-compact cardiomyopathy was defined firstly using two-dimensional echocardiography by Engberding and Bender[5] in 1984. Since then, left ventricular non-compaction (LVNC) has gained increasing recognition during the last 30 years.

CLASSIFICATION AND NOMENCLATURE OF LVNC

American Heart Association (AHA) has classified the ventricular non-compaction into the category of genetic cardiomyopathy in 2006.[6] Even though, the argument on the classification of pathological and patho-physiological phenotypes of myocardial malformation exists since then. Some cardiologists regard the non-compact ventricle as a complex development and construction disorder of ventricular myocardial structure and function induced by different etiology and its related pathological mechanism.

The question on the classification of LVNC is primarily raised from the findings of frequently genetic overlap with hypertrophic (HCM) and even dilated cardiomyopathy (DCM) and some systemic myopathies, and also from a number of pathological and patho-physiological variations of myocardial architecture and function express of non-compact ventricle.

As we know that there is a morphological trait of the myocardial structure with a wide spectrum from normal variants to the pathological phenotypes of LVNC, which reflects the embryogenic structure of the human heart due to an arrest in the compaction process during the first trimester with or with-

out other accompanied congenital heart malformations.[7] The proper classification and correct nomenclature of the non-compact ventricles will contribute to the precisely and completely understanding of etiology, such as genetic background, mutation, modulation, pathological phenotypes and its related patho-physiological mechanism for a more personalized therapy of this kind disease individually. Finally, a correct name of this kind of non-compact ventricle will help us to reform the recognition and classification of cardiomyopathy based on not only the discovery of medical imaging but also the genetic background, other etiological and pathological findings and related pathological mechanism.

GENETICS OF LVNC

A number of pathogenic genes of LVNC have been identified in recent years. The common pathogenic gene mutations are: TAZ tafazzin protein-coding genes G4.5, LIM domain binding protein 3 ZASP/LDB3/Cypher, nuclear genes encoding protein fiber layer A/C (LMNA gene encoding lamin A/C), sarcoplasmic reticulum protein-coding genes (MYH7, ACTC, TNNT2, TPM1 genes), alpha 2 dystrobrevin DMPK DTNA, DM protein kinase encoding genes, and such as mitochondrial genes.[8] But the genetic mechanism of LVNC is not fully clear. The earliest research has showed that the LVNC is considered X chromosome recessive, and LVNC pathogenic gene is located at Xq28 G4.5 gene locus on the chromosome. Similarly, LVNC can be caused by one or several gene mutations.[9]

The published results showed that LVNC is complex genetic diversity. It was found interestingly that this location is in proximity to other genes associated with systemic myopathies (Emery-Dreifuss muscular dystrophy, myotubular myopathy, Barth syndrome), which are commonly accompanied by various cardiomyopathies and arrhythmias.[9] In addition, typical LVNC has been described in a patient with Becker's muscular dystrophy,[10] suggesting that LVNC may occur as part of a systemic myopathic process. Although male predominance is the rule in familial cases of isolated LVNC,[11] both sexes are affected in the nonfamilial form of the disease,[12][13] which has not been genetically characterized. Nonspecific dysmorphic facial features (prominent forehead, strabismus, low-set ears, and micrognathia) have been observed in children with LVNC.[1]

HCM related pathogenic genes have been found overlapped with LVNC disease-causing genes. For example, beta myosin heavy chain gene is the common disease-causing gene of familial HCM, and the published research results have shown that there is a highest pathogenic gene mutation rate of MYH7 gene in HCM.

Recently, some research results confirmed the overlap of HCM and LVNC pathogenic genes.[14][15] In the study of LVNC disease-causing genes, Klaassen et al.[15] analyzed 63 patients with LVNC, found the gene mutation in 11 cases, and gene mutations of 7 cases at MYH7. The cause can be thought of HCM MYH7 mutation may be closely related with the occur-

rence of LVNC. In addition, Monserrat et al.[16] found that the mutations of alpha heart actin gene also occurred in HCM, LVNC and interatrial septum defect (ASD) in the detection which has long been regarded as a leading to DCM.

Furthermore, familial occurrence of LVNC is frequent with autosomal dominant and X-linked transmissions. Different mutations in javascript of sarcomere protein genes were identified and there seems to be a shared molecular etiology of different cardiomyopathic phenotypes, including LVNC, HCM, DCM. Thus, genetic heterogeneity, with an overlap of different phenotypes, and the variability of hereditary patterns, raise more questions whether there is a specific morphological trait from DCM/HCM to LVNC and what are the triggers and modifiers to develop either DCM, HCM, or LVNC in patients with the same mutation.[17] The variety in clinical presentation, the genetic heterogeneity, and the phenotype of the first transgenetic animal model of a LVNC-associated mutation question the hypothesis that LVNC be a distinct cardiomyopathy. It seems to be rather a distinct phenotype or phenotypic, morphological expression of different underlying diseases than a distinct cardiomyopathy.[7] All of the genetic heterogeneity, phenotypical overlap and variety in clinical presentation indicates that some of the cardiomyopathies might just be the different consequence of myocardial development variations related to mutation and phenotype of one or group genes induced by the interacted and disturbed process of gene modulation at different links of gene function expression. These genetic findings have enhanced the suspicion that the AHA classifies LVNC as an isolated primary genetic cardiomyopathy.

OTHER ACQUIRED ETIOLOGY OF LVNC

Another important evidence rather than genetics is that precise tissue concentration of retinoic acid has been found that it is indispensable for proper interaction of second heart field cells with cardiac neural crest cells and induction of signalling pathways, and important for normal myocardial growth. Since retinoic acid deficiency during embryogenesis induces non-compaction except gene mutation, it has been confirmed that excess retinoic acid at the stage of heart tube elongation may also cause thinning of the myocardial wall which leads to non-compaction. This kind of cardiomyopathy is more evident in the right ventricle (RV) than in the left ventricle (LV).[18]

It has been reported that LVNC may also be associated with acquired compensation of myocardial damage.[19]

IMAGING CRITERIA OF LVNC

Four morphological criteria of isolated LVNC established by Jenni et al.[20] in 2001 based on the findings of two-dimensional and color Doppler echocardiography as follow: 1) Coexisting cardiac abnormalities were absent (by definition). 2) A two layer structure was seen, with a compacted thin epicardial band and a much thicker non-compacted endocardial layer of trabecular meshwork with deep endomyocardial spaces. A

maximal end systolic ratio of non-compacted to compacted layers of > 2 is diagnostic. 3) The predominant localization of the pathology was to mid-lateral, apical, and mid-inferior areas. Concomitant regional hypokinesia was not confined to the non-compacted segments. 4) There was color Doppler evidence of deep perfused intertrabecular recesses. Based on these criteria, Jenni suggested that isolated LVNC as a distinct cardiomyopathy at that time.

Cardiac magnetic resonance imaging also could provide an accurate and reliable evaluation of the localization and extent of non-compacted myocardium at end-diastole. The end-diastolic ratio of non-compacted to compacted myocardium (non-compact/compact ratio, NC/C ratio) of > 2.5 had high diagnostic accuracy for isolated LVNC in a Chinese adult Han population (n = 30). Chinese researchers reported that the end-diastolic NC/C ratio of > 2.5 had 96.4% sensitivity and 97.4% specificity for identifying patients with isolated LVNC.[21]

Maximal systolic compacta thickness < 8 mm is another specific sign for LVNC and allows the differentiation of LVNC from normal hearts as well as those with myocardial thickening due to aortic valve stenosis. This observation may be particularly useful as an additional diagnostic criterion for preventing the overdiagnosis of LVNC.[22]

Currently six imaging based diagnostic criteria have been established based on echocardiographic and magnetic resonance imaging (MRI) modalities and adopted by cardiologists worldwide. Most of these diagnostic criteria only focused on the visible morphologic trait of myocardial architecture except myocardial dysfunction. Recent pathological and histological findings revealed that the myocardial recesses of LVNC may be large enough to be similar to those of ventricular trabecular hyperplasia due to ventricular outlet stenosis and overload, or may be subtle enough not to be visualized by regular imaging modalities, suggested that the updated imaging diagnostic criteria of LVNC should include the specific criteria of global and regional myocardial dysfunction and the myocardial electro-mechanical remodeling of LVNC, specially in atypical LVNC cases, for a systematical demonstration of pathology and patho-physiology of LVNC from malformation of myocardial anatomical structure to myocardial dysfunction.

In echocardiography, the importance of contrast agents is twofold, as they can be considered essential for a reliable differentiation between the compacted and the non-compacted myocardium, while at the same time allowing accurate measurement of the ratio.[23] The subtle recesses of myocardial non-compaction and regional ventricular systolic and diastolic dysfunction in LVNC patients with HCM could be uncovered by contrast echocardiography. It is demonstrated that contrast echocardiography is superior to standard two-dimensional echocardiography for detecting subtle non-compaction in LVNC patients with HCM.

The global peak systolic longitudinal strain in patients with HCM with non-compaction has been reported a significantly lower absolute value than that in patients without non-compaction and healthy controls, indicating that the total number of segments affected by coexistent subtle non-compaction in patients with HCM was an independent predictor of LV systolic dysfunction.[24]

Other useful diagnostic techniques for LVNC include cardiac magnetic resonance imaging, computerized tomography, and even left ventriculography should be selectively used for more trait information of LVNC in future.[21]

Routinely, the ventricular non-compaction also has been divided into three morphological types:

LVNC: the LV is the most affected site, but RV involvement has been reported in some cases.

Right ventricular non-compaction: although the usual site of involvement is the LV, the RV can rarely be affected, but RV involvement is not uncommon. Among the reported cases in recent years, younger patient with isolated RV non-compaction seems more frequent.[25-27]

Biventricular non-compaction: left and right ventricular non-compaction complicated by severe pulmonary hypertension was reported. Pulmonary hypertension may be a consequence of increased pulmonary venous pressures caused by systolic and diastolic heart dysfunction secondary to LVNC.[28]

Obviously this kind of classification could not help us to fully understand the formation and development of ventricles and its accompanied congenital pathological abnormalities, such as ventricular non-compaction mergered with HCM, DCM and systemic myopathies.

Diagnosing LVNC is a challenge for the medical community because the condition of LVNC shares imaging based morphologic features of HCM and DCM. The diagnosis requires expertise in the broad spectrum of overlapping cardiomyopathies. The demarcation between LVNC and normal or abnormal phenotypic variations is often indistinct.[29]

Based on the above existing research findings, we currently have realized that the main reasons for the diagnostic uncertainty may result in are as follow:

Lack of detailed phenotype evaluation and further analysis of disease genes based on morphology which leading to ill-defined diagnostic criteria of all genetic and genetic related cardiomyopathies.

Lack of comprehensive evaluation of basic non-compact pathological anatomy and patho-physiological abnormalities based on anatomical and functional pathological changes.

Lack of more precise diagnostic information of anatomical and functional features derived from different medical imaging modalities, etc.

Some researchers also concluded that the uncertainty surrounding the diagnosis of LVNC is related to the lack of a "perfect diagnostic tool", such as a reproducible genetic marker.[29]

Unfortunately, there is no such kind of perfect diagnostic tool in real world. Infant and pediatric patient appear to X linkage, is considered possible with the Xq28 G4.5 gene mu-

tations. Autosomal dominant is common pathogenesis in adult patients with LVNC may be associated with autosomal gene mutations. However, in the vast majority of LVNC families and sporadic cases studies have failed to find gene mutation sites, in Xing's report that only 6 of 79 cases of LVNC were found DNA mutations, prompting that LVNC has significant genetic heterogeneity again. Myocardial compaction or densification might not be achieved with multiple pathogenic gene, but the known genes may only be a fraction of all of the pathogenetic genes. Unlike chromosome 21 three body deformity, even if G4.5 (TAZ), alpha-dystrobrevin (DTNA), 11 p15 gene variants were found in the amniotic fluid testing, fetal LVNC cannot be directly determined.[30)31)] So just relying solely on genetic analysis, conducting an early embryos diagnosis of LVNC is not feasible. Potential indication of LVNC must be set up combined with ultrasonic imaging findings in early stages of pregnancy with abnormal construction and dysfunction of LV wall. Once myocardial dysfunction accompanied with myocardial densification was found could help to establish the clinical LVNC diagnosis in time.

PREVALENCE, SPECTRUM, AND FUNCTIONAL CONSEQUENCES OF LVNC

Non-compaction of ventricles may not be a rare phenomenon and is comparable to other more widely recognized but less common causes of heart failure such as peripartum myopathy, connective tissue diseases, chronic substance abuse and HIV disease also.

The published studies have shown that the difference of echocardiographic detection rate of ventricular non-compaction is too large, which indicate that there are a number of unresolved diagnostic problems of ventricular non-compaction. Echocardiography can be assumed overly sensitive and lacking in specificity with the presently defined measurements and ratios used to diagnose LVNC as mentioned above. The available diagnostic criteria show a propensity toward overdiagnosing LVNC.[29)] A 3.7% prevalence of definite or probable LVNC was found in those with left ventricular ejection fraction (LVEF) ≤ 45% and a 0.26% prevalence for all patients referred for echocardiography. This is appreciably higher than prior reports from tertiary centers.[32)]

Conversely, a study showed that 2 blinded reviewers assessed 500 transthoracic echocardiograms for LVNC for adequate study quality, absence of co-existing cardiomyopathy, and LVNC. If present, the ratio of the maximum linear length of NC/C and the planimetered area of LVNC on apical 4-chamber view were measured. Patients were classified by degree of non-compaction measured by either the NC/C ratio or LVNC area as controls, mild, moderate, and severe; 380 patients were included in the analysis and 60 (15.8%) had evidence of ventricular non-compaction. Patients with increasing severity of non-compaction had significantly decreased ejection fractions. These findings indicate that LVNC may be more common

than previously recognized and may exist as a wide spectrum as mentioned before.[33)]

The prevalence of LVNC in the Duchenne Muscular Dystrophy (DMD) population is 28% (27/96). The high prevalence of LVNC in DMD is associated with decreased LV systolic function (EF < 55%, 53.3%, 16/27) that develops over time and may represent muscular degeneration versus compensatory remodeling.[34)]

Non-compaction of the LV myocardium can occur in isolation or in association with coronary artery abnormalities (i.e., coronary artery fistula) due to the close embryogenic spatio-temporal relationships[35)36)] and other combination with cardiac malformations. Usually, LVNC is association with ventricular septal defect, ASD and patent ductus arteriosus etc.,[37)] and associated with Ebstein's anomaly is very rare. Genetic syndromes, neuromuscular disorders and systemic myopathies among others also have been reported.[7)]

Ebstein's anomaly is a rare congenital cardiac disease initially described by Wilhelm Ebstein in 1866. The primary pathology involves significant apical displacement of the septal tricuspid valve leaflet and the presence of a redundant, elongated, anterior tricuspid valve leaflet. This congenital malformation has multiple known associated morphological and electrophysiological cardiac pathologies. Nimeri et al.[38)] have reported a rare case of severe heart failure and complex cardiac anomaly including biventricular non-compaction, Ebstein's anomalies and large patent ductus arteriosus with severe persistent pulmonary hypertension in a 31-weeks-old preterm infant. Another case of Ebstein's anomaly with multiple accessory bypass tracts, dual AV nodal physiology, non-compacted LV myocardium and a patent foramen ovale has been reported subsequently. Indeed, complete evaluation of the left heart is required in cases of Ebstein's anomaly to accurately assess LV myocardial structure and function.[39)]

One case of a patient who underwent cardiac surgery for pulmonary valve stenosis as a child, and presented as an adult with signs and symptoms of severe congestive heart failure was reported. The LV showed an increased trabecular pattern in the region of the apex, the mitral annulus was severely dilated with mitral incompetence, the right ventricular out-flow tract (RVOT) was largely dilated with aneurysm of both pulmonary arteries, and there was evidence of pulmonary valve incompetence. Previously, rare cases have been reported of persistent LVNC in patients with congenital left or RVOT obstruction.[40)]

The related clinical cardiac complications are varied based on different pathological problems and associated with other congenital cardiovascular malformations or manifest as an isolated disease. LVNC can be characterized by a wide variety of clinical presentations that ranges from complete absence of symptoms to congestive heart failure, lethal ventricular arrhythmias and thromboembolic manifestations; the short- and mid-term prognosis is quite severe.[41)]

LVNC is frequently, but not invariably, associated with LV

systolic dysfunction. Factors impacting on regional and global LV function are unknown. In patients with LVNC, disease severity correlates with the degree of LV dysfunction at a regional level. The extent of myocardial non-compaction might be an independent predictor of global LV dysfunction.[42]

A study of a total of 15 patients aged 52 ± 17 years (40% males) with the presentation form of heart failure in 53% of subjects, syncope in 20%, ventricular arrhythmias in 13% and stroke in 7% diagnosed as LVNC at echocardiography laboratory was reported. LV end-diastolic diameter was 66 ± 11 mm and estimated ejection fraction was 27 ± 10%. Apical and/or mid-ventricular segments of the LV were involved in all the cases. Pulmonary hypertension was present in 40%. The average follow-up was 19 months and no patient died during this period. Sixty seven percent of the patients had manifestations of heart failure, 27% presented sustained ventricular arrhythmias and 20% had atrial fibrillation or flutter, whereas 13% had cerebral embolic events. An automated internal cardioverter defibrillator was implanted in 47% of patients.[43]

Another study reported that LVNC is a form of cardiomyopathy with higher prevalence and relatively better prognosis than previously reported. Age at initial presentation, ratio of NC/C, and number of affected segments seem to be major determinants of LV systolic dysfunction, while initial LVEF and last functional capacity predict mortality in this cohort.[44]

LVNC with congenital heart disease is often accompanied by chronic systolic dysfunction. One case involved an adult with a small ventricular septal defect, initially exhibiting mild systolic dysfunction and slightly prominent LV trabeculations progressing over 13 years to severe DCM and overt non-compaction has been reported. The morphological and function progress of this case strongly suggests a correlation between the extent of non-compaction and the degree of systolic dysfunction. The initial presence of a small ventricular septal defect and mild trabeculations highlights the genetic determinants of non-compaction and the importance of closely following patients with mild non-compaction due to the possibility of progression. More sensitive diagnostic criteria are needed to avoid overlooking mild cases, which may show prominent trabeculations without reaching a requisite ratio of compacted to non-compacted tissue.[45]

Contradictorily, a study from Italy showed that ventricular dysfunction seems to be completely independent from the segment numbers of non compacted segments. To identify the correlation between ventricular dysfunction and number of segments involved in non compaction, a consecutive series of 238 patients affected by non compaction were evaluated, from the Società Italiana di Ecografia Cardiovascolare (SIEC) registry. The average age of patients was 41.5 years (range: 1–92 years), 137 were males and 101 females. In 122 cases ventricular systolic dysfunctions with an EF average of 34.6% were found. The number of affected segments by non-compacation and diastolic dysfunction were found to be non-independent predic-

tors of LV systolic dysfunction.[46]

A consecutive series of 50 patients with isolated LVNC from a single institution were reviewed. During the same period, 50 patients with DCM who had prominent trabeculations, who were matched for age, gender, and body surface area, were prospectively included. LV morphology and function were assessed using cardiac MRI. Compared with patients with DCM, patients with isolated LVNC had a significantly lower LV sphericity index and end-diastolic volume index (LVEDVI) and a greater LVEF, number of trabeculated segments, and NC/C ratio. There were no significant differences in stroke volume index, cardiac output, and cardiac index between the two patient groups. In patients with isolated LVNC, the number of trabeculated segments and the NC/C ratio correlated positively with LVEDVI (r = 0.626 and r = 0.559, respectively) and negatively with LVEF (r = -0.647 and r = -0.521, respectively, $p < 0.001$ for all). In patients with DCM, the number of non-compacted segments and the NC/C ratio had no correlation with either the LVEDVI (r = -0.082 and r = -0.135, respectively) or the LVEF (r = 0.097 and r = 0.205, respectively).[47]

These paradoxical results might indicate that the systolic dysfunction of LV is not only related to the numbers and levels of non-compacted segment, but also more closely related to the severity and exact location of abnormal myocardial architecture and electro-mechanical activation in each involved segments.

RV dysfunction was present in half of patients with LVNC. Significant RV dysfunction seems to be a marker of advanced LVNC and may carry a worse prognosis.[48]

Patients with LVNC-DCM had greater LV reverse remodelling after cardiac resynchronisation therapy than patients with DCM. The greater the area of non-compaction (higher number of isolated ventricular non-compacted segments) the greater the chance of achieving cardiac resynchronisation therapy response and greater LV reverse remodeling.[28]

Mitral annulus enlargement and functional impairment were both present in LVNC patients, with a higher incidence and severity of mitral regurgitation. The prevalence and severity of mitral regurgitation were comparable in the LVNC and DCM groups, but higher than in controls and the number of non-compacted segments did not correlate with mitral annulus diameter and area.[49]

LVNC especially could introduce a lethal ventricular arrhythmias has to be considered in young patients presenting with sudden cardiac death a common pathogenesis.[50] In young cases, LVNC could present with aborted sudden cardiac death. Thus, preventive and treatment strategies could be established for this potentially life-threatening condition.[51]

Except ventricular arrhythmias, LVNC may also develop into episode of symptomatic ventricular flutter which requiring electrical cardioversion.[52][53] A family in which two adult members were found to have isolated LVNC, and one case of them associated with ventricular pre-excitation syndrome has been reported.[54]

LVNC also could present with multiple LV intramural thrombi simultaneously.[55][56] The diagnosis of left cardiogenic embolism is primarily based on echocardiographic demonstration of a spongy myocardium with left heart failure and single and multiple LV thrombi.[55]

Sometimes, the patient may also suffer from an acute myocardial infarction, stroke and other systemic embolism due to LV intramural thrombi, which usually complicated with severe LV systolic dysfunction.[40][57][58]

LVNC IN FETAL AND PEDIATRIC POPULATION

The published cases reports of fetal LVNC were reviewed. The prenatal diagnosis of fetal LVNC could be achieved using echocardiography.[59] A case report of fetal hydrops associated with cardiac malformation was detected by routine echocardiography revealed a complete auriculoventricular septal defect, non-compacted myocardium, and a bradycardia of 70–90 beats per minute, which lead to the suspicion of left isomerism. Fetal death occurred at 20 weeks and 3 days. Autopsy was consistent with the prenatal LVNC diagnosis.[60]

The data regarding newborn, infants and childhood LVNC are sparse.[61] A complete clinical history and the echocardiographic study were performed in six child patients with complex congenital heart disease has been reported. The associated congenital heart diseases were: Ulh's anomaly, the absence of right atrioventricular connection, single ventricle, cleft of mitral valve, transposition of the great arteries, double inlet in LV.[62]

Whereas arrhythmias and thrombo-embolic events were rare, chronic heart failure was frequently found. An equally aggressive anticongestive treatment regimen and even heart transplant would seem indicated for LVNC in child patients.[63]

Usually, early onset of symptoms of LVNC in pediatric population is associated with a poor prognosis. When prospectively evaluated, LVNC appears to have been previously under-diagnosed in pediatric population.[64]

Junga et al.[65] reported that restricted myocardial perfusion and decreased flow reserve in areas of ventricular non-compaction occurred in children demonstrated by positron emission tomography. The myocardial perfusion defects in non-compacted areas may be the cause of myocardial damage and possibly form the basis of arrhythmias and pump failure.

The subendomyocardial fibrosis of LVNC has been identified in compact and non-compact myocardium by histological observation and MRI.[29][66] The subendomyocardial fibrosis related ventricular restrictive diastolic dysfunction of LVNC could be revealed by spectral Doppler and tissue Doppler echocardiography and MRI might be the surrogate of subendomyocardial fibrosis.

CONSIDERATION OF RENEWING DIAGNOSTIC CRITERIA AND NOMENCLATURE

The pathological phenotypes definition associated with genetic background might be the key component of more precise clinical diagnostic criteria of ventricular non-compaction for better understanding of patho-physiological mechanism and more personalized therapy.

The global and segmental even transmural electro-mechanical remodeling and a variety of anatomical and function features and complications of so-called atypical ventricular non-compaction should be paid more attention during echocardiography exam for proper and detailed clinical classification.

The trend to using a morphologic/patho-physiologic, instead of a solely morphologic approach holds promise in the quest for an accurate, reliable diagnostic system of LVNC. We must understand the distinction between morphological findings and morphological findings with patho-physiology. Our future understanding of LVNC should depend on an integration of cardiac morphology, physiology, patho-physiology and evolving genetics.[29]

A new concept of "ventricular non-compact syndrome", not just a genetic syndrome, should be established based on the systematical exploration based on the findings from etiology (i.e., genetics, such as gene mutation, modulation and interaction, etc.), pathology, patho-physiology and clinical manifestation, and this will deeply change the profile of so-called "genetic or mixed cardiomyopathy". The priority, we should to do, is to identify the potential sign of adverse clinical prognosis in this kind of genetic or acquired variation of myocardial structure and function development in clinical practice and set up the risk stratification of non-compacted ventricles as early as possible, and give up any useless effort to distinguish LVNC from other cardiomyopathies.

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