ECRONICON OPEN ACCESS

EC CLINICAL AND EXPERIMENTAL ANATOMY

Review Article

Left Ventricular Trabeculation and Noncompaction Cardiomyopathy: A Review

Perry Wengrofsky[1], Christopher Armenia[1], Filip Oleszak[1], Eric Kupferstein[2], Chandra Rednam[3], Cristina A Mitre[3] and Samy I McFarlane[1]*

[1]Department of Internal Medicine, State University of New York, Downstate Medical Center, Brooklyn, NY, USA

[2]Division of Cardiovascular Disease, Department of Internal Medicine, State University of New York, Downstate Medical Center, Brooklyn, NY, USA

[3]Division of Cardiovascular Disease, Department of Internal Medicine, Brooklyn Campus, Veterans Affairs New York Harbor Healthcare System, Brooklyn, NY, USA

***Corresponding Author:** Samy I McFarlane, Department of Internal Medicine, State University of New York, Downstate Medical Center, Brooklyn.

Received: July 08, 2019; **Published:** July 29, 2019

Abstract

Hypertrabeculation and noncompaction are congenital or acquired abnormalities of myocardial anatomy characterized by prominent trabeculations, intertrabecular recesses, and a thin outer epicardial compacted myocardial layer that are most clinically relevant when presenting as left ventricular noncompaction (LVNC) cardiomyopathy. Manifesting in isolation or in association with development or acquired cardiomyopathies, and primarily extracardiac genetic syndromes, LVNC predisposes patients to major cardiac and systemic complications, including cardioembolic disease, ventricular tachyarrhythmia, and sudden cardiac death. Improvements in cardiac imaging modalities such as echocardiography and magnetic resonance imaging have increased the identification of hypertrabeculation and LVNC, but overall rates of LVNC cardiomyopathy remain very low. We present a review on the embryonic pathogenesis of trabeculations and noncompaction, genetic and epidemiologic profiles of LVNC, clinical manifestations, diagnostic imaging strategies and criteria, and the approach to family medical genetic screening and management of the major complications of hypertrabeculation and LVNC cardiomyopathy.

Keywords: *Trabeculation; Noncompaction; Left Ventricular Noncompaction Cardiomyopathy*

Introduction

Derangements of embryonic cardiac trabeculation and ventricular chamber development and its association with congenital heart disease, namely left ventricular (LV) non-compaction (LVNC), also known as cardiac hypertrabeculation and LVNC cardiomyopathy, are characterized by abnormal ventricular myocardial protrusions with a thin layer of properly compacted myocardium [1,2]. While advances in cardiovascular imaging have improved detection of LV trabeculations, LVNC cardiomyopathy remains a remarkably rare entity with a prevalence less than 0.02% [3,4]. The anatomical organization seen in LVNC, consisting of prominent trabeculations with intertrabecular recesses that are continuous with the LV lumen overlying a thin compacted layer, can also be present in the right ventricle (RV), either in a biventricular or isolated unilateral RV pattern [5]. Given the presence of LV trabeculations across different cardiomyopathies, both familial and sporadic, major national and international cardiology societies have adopted different classifications of the disease [3,4,6,7]. Limited data from randomized controlled trials exist to guide the management of LVNC and LVNC cardiomyopathy, and interventions for the most worrisome associated complications, including thromboembolism and cerebral infarction, heart failure, and sudden cardiac death [8].

We present a review on cardiac embryology and the developmental pathophysiology of trabeculations and noncompaction, recent studies and analyses of the genetic and epidemiologic profiles LVNC, and current recommendations for diagnostic evaluation with imaging modality specific criteria and management of LVNC cardiomyopathy and the major cardiac and systemic complications.

Embryonic trabeculation and compaction

Gross cardiac, atrial, and ventricular chamber development occurs in the early smooth, bilayered, linear heart tube through a pattern of complex morphological changes known as cardiac chamber maturation [1]. The two-layer embryonic heart tube consists of an inner luminal endocardial endothelium with an outer immature myocardial layer of cardiomyocytes, separated by an extracellular matrix [1,9]. Starting at gestational day 23, the embryonic longitudinal heart tube begins the process of "cardiac looping", a steady coordinated planar rearrangement and ballooning of the progenitor heart tube such that it is positioned to differentiate into the cardiac septa, valves, and chambers [10]. As the primitive cardiac chambers continue to align and the outer curvatures of the chambers balloon and dilate, there is concurrent initiation around day 28 - 30 of the physiologic development of myocardial trabeculations into the chamber lumen which function to increase cardiac output and expand surface area for oxygen and nutrient absorption prior to coronary vascularization [1,11].

Trabeculation, along with conduction system development and thickening of properly compacted myocardium, is one of the processes of cardiac chamber maturation, with trabeculation consisting of three sequential stages that ultimately result in the fusion with the compacted myocardium layer and progression of the mature thickened ventricular wall [1,12]. Trabeculations are protrusions from the developing ventricular wall into the ventricular lumen with a structure identical to the embryonic heart tube, myocardial cells lined by the endothelial layer of the endocardium [1].

The initial step is emergence of trabecular ridges, whereby myocardial projections begin to extend into the lumen, protrusions generated from cardiomyocyte invagination and delamination from the compact myocardial layer [1,13]. Emergence is followed by trabeculation, where the budding trabecular projections expand radially and lengthen to form a meshy network of trabeculae, an anatomical cardiomyocyte rearrangement resulting in the majority of myocardial mass contained within the trabecular framework rather than the compact layer of myocardium [1,4]. Trabeculation is followed by remodeling, also known as consolidation or compaction, during which distal ends of trabeculae stop growing, and the proximal or base ends thicken and collapse to visually resemble the underlying compacted myocardial layer, with the spaces between the trabecular buds developing into capillaries [1,14]. Defects at any stage in the emergence, trabeculation, and remodeling junctions of cardiac chamber maturation, can result in the persistence of trabeculations and prohibit proper compacted myocardium proliferation.

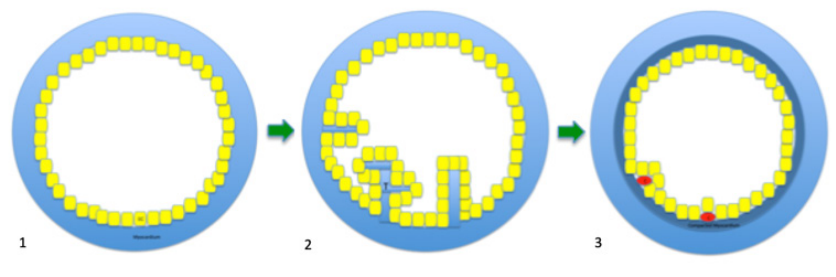

Figure 1: *The primitive embryonic heart tube consists of an inner layer of endocardium made up of endothelial cells (EC, yellow), and an outer myocardial (light blue) layer (1). As cardiac chamber maturation progresses, emergence of trabecular buds and subsequent lumen and radially directed propagation of trabeculae (T, light blue) increases cardiac output and expands surface area for oxygen and nutrient diffusion into the developing endocardium and myocardium (2). Remodeling with consolidation results in thickening of the myocardial layer with compaction of the trabecular network (dark blue), with spaces between the proximal base ends of the trabeculae developing into capillaries (C, red) in parallel to coronary vascularization.*

From a developmental perspective, the later embryonic, pre- and postnatal compacted myocardium is the product of two relatively heterogeneous myocardial sub-layers of the primitive heart tube undergoing different proliferative processes; the distal or subendocardial myocardium that generate trabeculae and eventually undergo remodeling and consolidation, and the proximal or subepicardial myocardium, a thicker and already compacted region of cardiomyocytes [1,15]. While the inner subendocardial myocardium buds trabeculae that thicken, propagate, and subsequently compact, the compact layer proliferates and steadily overtakes the trabeculated myocardium as the primary contractile force [15]. Cardiomyocytes in the outer compact subepicardial layer are less differentiated than cardiomyocytes in the trabeculated regions, and although the oxygen and nutrient absorption is limited by diffusion given the trabeculae and inner myocardial layers, growth of the compact myocardium and thus the entire developing heart is driven by a slower thickening and apposition of increasingly compact layers of differentiating cardiomyocytes [16]. As the cardiomyocytes in the compacted myocardium expand, mature, and differentiate, the compact layer becomes structurally more complex, with compacted cardiomyocytes organized in inter-connected myofibers with fortifying microspatial orientation, previously described as cylindrical geometric patterns like nested doughnuts or warped "pretzels" [15,17-19]. Proliferation and maturation of the compacted myocardium is accelerated by oxygen and nutrient delivery via coronary vascularization originating from the epicardium, further increasing the compacted layer's contribution to the overall ventricular myocardial mass in comparison to the consolidating and remodeled trabecular myocardium [16,20,21].

Noncompaction genetics and embryogenic hypothesis

Although noncompaction of ventricular trabeculations can arise from any disturbance throughout the entire process of cardiac chamber maturation, it is believed that failure in the step of remodeling with consolidation results in noncompaction [22]. Given the autosomal dominant patterns of inheritance in familial cohorts of LVNC, and its appearance as the cardiac manifestation in primarily noncardiac genetic syndromes, the embryogenic hypothesis, which frames LVNC as a genetic disorder resulting in intrauterine arrest of normal ventricular trabecular maturation and compaction, is increasingly supported by observational and experimental data [4,23]. Studies demonstrating associations between LVNC with congenital heart disease, either familial or sporadic, further support the embryonic pathogenesis of noncompaction [4,5,24,25].

Despite the well-studied nature of cardiac chamber maturation, trabeculation, and compaction and the identification of genes and proteins involved in these intricate processes, much of the embryogenic mechanisms remain unexplained [4,5,15]. Furthermore, genes previously implicated in other cardiomyopathies have been associated with LVNC, including genes coding for sarcomere proteins, ion channels, and cellular signaling pathways [5,26-28].

Arbustini., *et al*.'s 2016 review and grouping of LVNC and associated cardiomyopathies emphasizes the highly hereditary nature of LVNC [5]. LVNC appearing in early childhood has been associated with genetic diseases such as Barth syndrome and related tafazzinopathies, X-linked syndromes characterized by mutations in the *tafazzin* gene, with variable cardiac and extracardiac manifestations including LVNC, dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), arrhythmia, neutropenia, and failure to thrive [5,29,30]. Considered an X-linked, mitochondrial disorder, Barth syndrome mutations result in loss of function of Tafazzin, an inner mitochondrial membrane protein essential for high-energy using tissues such as cardiomyocytes [31].

LVNC can be further categorized as LVNC associated with another cardiomyopathy, including DCM, HCM, restrictive cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy [5]. Familial studies of LVNC associated with DCM (LVNC-DCM) and HCM (LVNC-HCM) have elucidated specific pathogenic mutations [32]. Mutations in genes *MYH7*, coding for sarcomere protein cardiac myosin-β, *MIB1*, coding for NOTCH pathway regulator MIB1 (mindbomb homolog 1), and *LMINA*, coding for inner nuclear membrane protein Lamin AC, are associated with LVNC-DCM [5,33-35]. Mutations in *MYBPC3*, coding for sarcomere protein cardiac myosin-binding protein C, are associated with LVNC-HCM [5,32,36]. Genetic changes involving sarcomere proteins identified in LVNC associated with restrictive and arrhythmogenic right ventricular cardiomyopathies have also been associated with LVNC-DCM and LVNC-HCM [5,26,37].

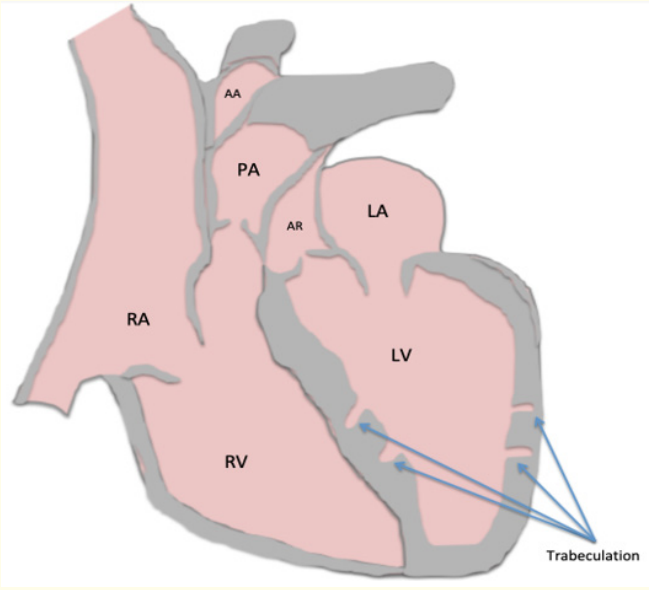

Figure 2: *Trabeculations are myocardial projections into the lumen of the LV cavity. Deep recesses between trabeculations predispose patients to mural thrombi from stasis of blood in the recesses. Key: RA: Right Atrium, RV: Right Ventricle, AA: Ascending aorta, PA: Pulmonary Artery, AR: Aortic root, LV: Left Ventricle, LA: Left Atrium.*

Structural congenital heart disease (CHD) with concomitant LVNC has been demonstrated in sporadic and familial patterns, with CHD appearing in at least one family member [5]. LVNC has been associated with mild, moderate, and severe types of CHD, including atrial and ventricular septal defects, Ebstein's Anomaly and Tetralogy of Fallot, with Hypoplastic Left Heart syndrome and Transposition of the Great Arteries associated with noncompaction patterns in the RV [5,38-41]. LVNC also appears as a cardiac manifestation in cardiac and extracardiac monogenic or chromosomal syndromes, both familial and spontaneous primarily in autosomal recessive distributions like Myotonic dystrophies and Cobalamin C deficiency [5,42,43].

Genetic models have also elucidated many of the functional and signaling proteins involved in trabeculation and highlight the pathophysiology of uninhibited ventricular hypertrabeculation in the development of LVNC. While gain of function mutations in certain genes and resulting hypertrabeculation have not been observed, numerous genes and coded proteins and transcription factors stimulating endocardial-myocardial signaling and trabecular proliferation such as neuregulin, tyrosine kinase receptors ErB2, Angiopoietin-1 (Ang-1), and Ang-1 receptor TIE2 have been identified where loss of function mutations producing poorly initiated, hypoplastic, dysfunctional trabeculations [4,15,44-46]. Bone morphogenetic protein (BMP) signaling is a critical mediator of ventricular trabeculation after successful emergence [15,47]. One particular signal, BMP10, stimulates trabecular growth while inhibiting activation of an inhibitory cell cycle regulator, further promoting trabecular proliferation, with elevated BMP10 levels resulting in noncompacted hypertrabeculated ventricles [15,48]. Similarly, inactivation of cardiac transcription factor Nkx2-5 promotes severe hypertrabeculation [49].

Acquired trabeculation and noncompaction

Increasing clinical evidence of trabeculation and noncompaction in adult life support a dual hypothetical paradigm for LVNC, the embryogenic origin and the acquired, non-embryogenic hypothesis [2,4,5]. While pathophysiologic mechanisms remain unspecified, the prevalence of trabeculations and noncompaction in adult patients with otherwise normal cardiac morphology, wall thickness, and systolic

and diastolic function has led cardiologists to classify LVNC as an isolated, benign, normal anatomical variant [2,4]. Echocardiographic surveys of intensive athletes have demonstrated an increased prevalence of excessive trabeculation, raising questions about trabecular functionality and its presence among the collective physiological, electrical, and structural adaptations seen in the "athlete's heart" [50]. Trabeculation from athletic remodeling are common, but those athletes with structural changes meeting criteria for LVNC cardiomyopathy is significantly less common [50,51]. LV physiology studies in trabeculated athletic heats have shown that trabeculations, particularly in the LV apex, help redistribute wall stress, and generate higher stroke volumes with less wall strain [50,52,53].

The development of acquired and potentially reversible trabeculations and non-embryogenic LVNC in diverse categories of disease expand hypotheses on the pathogenesis and raises questions regarding the role of epigenetic factors and hemodynamics [5].

Gati., *et al.* observed new onset trabeculations in 25% of primigravida women, with longitudinal echocardiographic monitoring demonstrating trabecular reversibility with complete resolution or gradual regression to normal LV morphology in 81.2% of the study population [54]. Sporadic LVNC has been observed in patients with chronic kidney disease, while LVNC has been associated with chronic renal failure secondary to polycystic kidney disease [5,55-57]. LV hypertrabeculation and LVNC have also been documented in patients with hematologic disease such as sickle cell anemia and beta thalassemia [58,59]. While specific pathophysiologic pathways remain unexplained, circulatory changes, most prominently hypervolemia, are a common link between pregnancy, renal insufficiency, and anemia, and point to the role of increased preload in the trabeculation and LVNC [54].

Epidemiology

The increasing identification of hypertrabeculation and LVNC cardiomyopathy, in isolation or in association with other cardiomyopathies, since its original description 1984 by Engberding and Bender that built on the "spongy myocardium" observation of Grant in 1926, has facilitated broad genetic and clinical epidemiologic assessments [60,61].

Although the prevalence of overt LVNC cardiomyopathy is 0.014%, rates of hypertrabeculation and LVNC without overt cardiomyopathy discovered on cardiac imaging have been reported as high as 40% [4,62]. Weir-McCall., *et al.* demonstrated that in a population of nearly 1,500 volunteers with no known history of cardiovascular disease who underwent cardiac magnetic resonance imaging (MRI), 20% of individuals had a long axis (LAX) noncompaction ratio > 2.0, approaching the ratio cutoff of 2.3 required to meet the cardiac MRI LAX diagnostic criteria for LVNC [62].

Hypertrabeculation displayed a balanced gender distribution with a prevalence of 1.1% in males and 1.4% in females [59,62]. A recent meta-analysis by Kayvanour., *et al.* of approximately 7,600 adults showed a male predominance of LVNC of 62% [59]. Ethnic differences in trabeculation have been reported, with African Americans having increased trabecular thickness and mass [63].

Pathophysiology and clinical features

Hypertrabeculation and LVNC can manifest clinically in a variety of ways, including incidentally identified cardiac imaging findings in asymptomatic individuals with or without cardiovascular risk factors, overt LVNC cardiomyopathy with symptomatic heart failure, conduction abnormalities, tachyarrhythmia and sudden cardiac death [2].

Congestive heart failure in the setting of hypertrabeculation and LVNC cardiomyopathy can appear as either heart failure with reduced ejection fraction and systolic dysfunction, or heart failure with preserved ejection fraction and diastolic dysfunction [64]. Trabeculations diminish ventricular compliance, promoting diastolic dysfunction characterized by abnormal relaxation and a restrictive filling pattern from trabeculations protruding into the LV lumen [52,64,65]. LVNC is more typically associated with reduced ejection fraction and marked systolic dysfunction [64,66]. The systolic dysfunction seen in LVNC is attributed to hypoperfusion secondary to subendocardial microvascular abnormalities, circulatory findings identified on positron emission tomography (PET) [64,67,68].

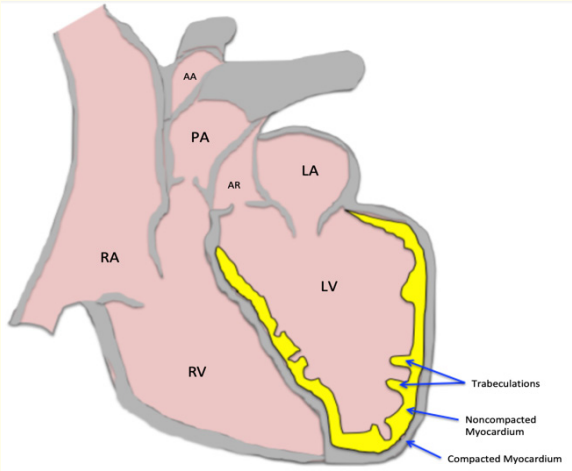

Figure 3: *In LVNC, there is an inner endocardial noncompacted myocardial layer, from which trabeculations protrude into the LV cavity. The outer epicardial myocardial compacted layer is generally thinner than the noncompacted layer. Key: RA: Right Atrium, RV: Right Ventricle, AA: Ascending aorta, PA: Pulmonary Artery, AR: Aortic root, LV: Left Ventricle, LA: Left Atrium.*

Given the close embryonic developmental connection in the cardiac chamber maturation processes of proper remodeling with capillary formation in the former recesses between properly compacted trabecular projections, systolic dysfunction in the setting of persistent trabeculations points to the role of abnormal microcirculation from nonconsolidated trabeculae. Systolic function is also compromised by LV dyssynchrony between the compacted and noncompacted myocardial layers [64,68].

Hypertrabeculation, LVNC, and LVNC cardiomyopathy are typically associated with conduction abnormalities and tachyarrhythmia [69]. Proper embryonic development of the ventricular conduction system, particularly the His-Purkinge network responsible for the quick coordinated depolarization of ventricular cardiomyocytes, is directly connected to proper embryonic maturation and remodeling of ventricular trabeculations and the compacted myocardium [1,70].

Conduction abnormalities seen on electrocardiography (EKG) are identified in over 80% of patients with LVNC, with the most common findings being intraventricular conduction delay, including left and right bundle branch block, AV block, repolarization abnormalities, and electrocardiographic evidence of left ventricular hypertrophy [64,71,72].

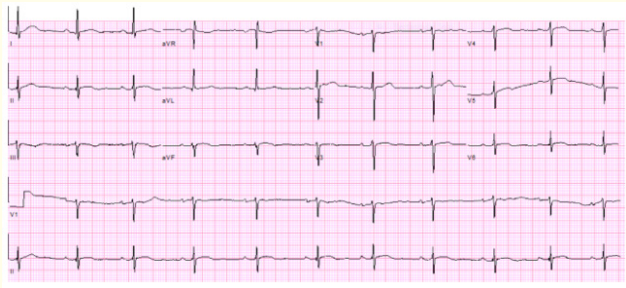

Image 1: *EKG of 32-year-old male patient presenting with acute right-sided neurological deficits, diagnosed with embolic stroke on neuroimaging, with echocardiography subsequently demonstrated LV hypertrabeculation. EKG significant for nonspecific repolarization abnormalities including T wave flattening and inversions in the inferior and lateral leads II, III, aVF, V3-V6.*

The most common repolarization abnormalities seen in LVNC are early repolarization, with a prevalence of approximately 40%, and QTc prolongation, noted in over 50% of patients [71,73,74]. Supraventricular tachyarrhythmias, most frequently atrial fibrillation, have also been reported in LVNC [64,71]. Electrophysiologic abnormalities are strongly associated with LVNC, with repolarization disturbances predisposing patients to malignant ventricular tachyarrhythmias and sudden cardiac death [64,75].

A major clinical outcome associated with LVNC is thromboembolic complications, most importantly cerebrovascular accident (CVA), also known as stroke [2,64,76]. Cardioembolic strokes in the setting of LVNC are secondary to mural thrombi formed in in the recesses between trabeculations in the noncompacted myocardium [2,77]. Non-cerebral systemic embolic complications secondary to LVNC have also been reported, including myocardial, renal, and mesenteric infarction [63,78-80].

Imaging and diagnostic criteria

LVNC is viewed and classified differently by the major American and European cardiology organizations, with the American Heart Association (AHA) led working groups and councils labeling LVNC as a genetic congenital cardiomyopathy, and the European Society of Cardiology as an unclassified familial cardiomyopathy [4,6,7]. According to the 2006 AHA scientific statement, LVNC cardiomyopathy can be diagnosed with echocardiography (ECHO), magnetic resonance imaging (MRI), or LV angiography with ventriculography, but no specific guidelines or imaging criteria recommendations are formally provided [6]. The continued advances in noninvasive imaging modalities, particularly ECHO and cardiac MRI, have led to the proposal and refining of different diagnostic approaches and imaging specific criteria for the evaluation of LVNC with ECHO and cardiac MRI [81]. An additional imaging technique, multidetector computed tomography (MDCT) with angiography, is a helpful noninvasive modality when cardiac MRI is unavailable or a patient has a contraindication [5,81].

Echocardiography (ECHO)

The most generally accepted validated ECHO diagnostic criteria are those outlined in 2001 by Jenni and colleagues [81,82]. Given the difficulty distinguishing the noncompacted and compacted myocardial layers at the end of diastole, the Jenni criteria utilizes the end-systolic ratio between the noncompacted and compacted myocardium, considering a short axis view end-systolic ratio > 2.0 to be diagnostic of LVNC [81,82]. Three additional diagnostic criteria that must be met alongside the end-systolic noncompacted: compacted ratio are the clinical absence of coexisting cardiac abnormalities, ECHO evidence of noncompaction, namely the presence of prominent LV trabeculations (predominantly in the apex and midventricular areas of both the lateral and inferior walls), and multiple deep intertrabecular recesses connecting with the main LV cavity confirmed with color Doppler imaging [81,82].

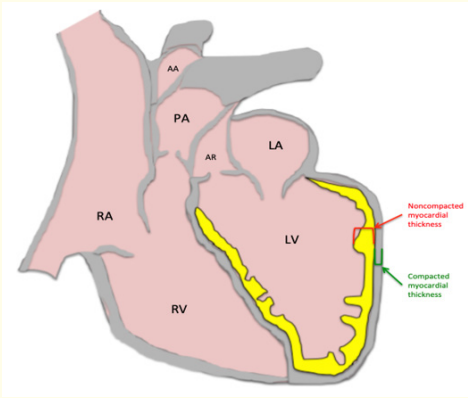

Figure 4: *Thickness of the noncompacted and compacted myocardial layers are used to calculate the noncompacted: compacted ratio in the ECHO and cardiac MRI diagnostic criteria of LVNC. Key: RA: Right Atrium, RV: Right Ventricle, AA: Ascending aorta, PA: Pulmonary Artery, AR: Aortic root, LV: Left Ventricle, LA: Left Atrium.*

Since the validation of Jenni., *et al.'*s approach, multiple additional ECHO diagnostic criteria have been incorporated into the evaluation of LVNC. While the end-diastolic comparison of compacted and noncompacted myocardium was not used by Jenni and colleagues, Stollberger., *et al.*in 2016 utilized an end-diastolic noncompacted: compacted ratio > 2.0 in the apical four chamber view as the diagnostic cutoff for LVNC [81,83]. Gerhard., *et al.* also analyzed the myocardium during systole, defining a systolic thickness of the compacted myocardium < 8 mm as the thickness that could facilitate distinguishing between noncompaction and normal ventricular morphology [81,84].

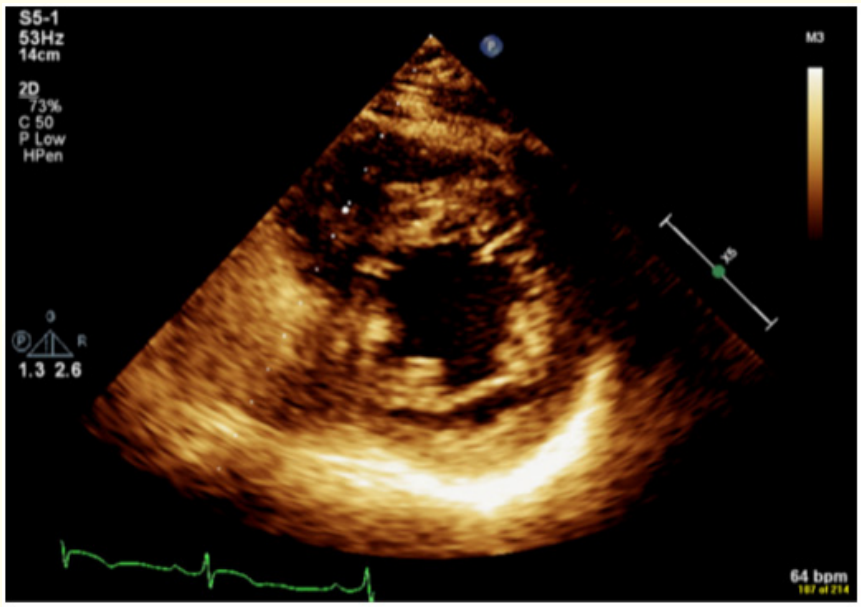

Image 2: *Parasternal short axis ECHO image showing LV hypertrabeculation of aforementioned 32-year-old male patient with embolic CVA.*

Magnetic resonance imaging (MRI)

Cardiac magnetic resonance imaging (MRI) is considered to be superior to ECHO for identification of noncompacted myocardium, with greater image quality and increased sensitivity for identifying trabeculations, particularly at end-diastole [5,81]. The criteria outlined by Peterson., *et al.* in 2005 are the generally accepted cardiac MRI diagnostic parameters for the evaluation of LVNC [85]. The Peterson criteria incorporate both the identification of distinct myocardial layers and the presence of marked trabeculations with deep intertrabecular recesses within the inner noncompacted layer, and an end-diastolic noncompacted: compacted ratio > 2.3 [81,85]. Similar to the evolution of the ECHO LVNC diagnostic criteria, additional cardiac MRI parameters have been introduced for the assessment of LVNC. According to Jacquier., *et al.* an end-diastolic noncompacted myocardial mass value > 20% of the global LV mass is considered to be diagnostic of LVNC [81,86]. The quantitative diagnostic criteria developed by Grothoff., *et al.* considers a trabeculated ventricular mass > 25% of the global LV mass and a noncompacted myocardial mass > 15 g/m^2 [81,87]. Given the superiority of cardiac MRI and its ability to correctly identify and diagnose LVNC that may have been missed on ECHO, it is generally recommended that all patients being evaluated for LVNC undergo cardiac MRI [88,89].

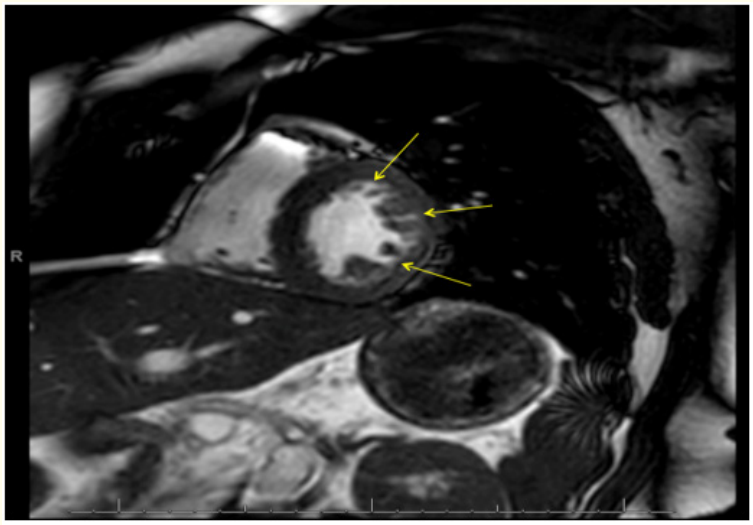

Image 3: *Cardiac MRI axial plane images, demonstrating LV trabeculations with intertrabecular recesses (yellow arrows), of aforementioned 32-year-old male.*

Multidetector computed tomography (MDCT)

MDCT, with angiography, is used less frequently than cardiac MRI for the evaluation of noncompaction, given diminished capacity to characterize myocardial tissue and the associated ionizing radiation exposure [81]. Given reductions in radiation dose and safety for patients with cardiac implantable electronic devices, MDCT provides an additional noninvasive imaging technique for diagnosis [81,90]. MDCT, like cardiac MRI, has been proven superior to ECHO in demonstrating the distribution of noncompacted myocardium in the LV, with the diagnosis of LVNC by MDCT based on the anatomical findings used in the cardiac MRI diagnostic criteria [81,91]. Specific MDCT criteria have been introduced by Melendez-Ramirez., *et al.* classifying a noncompacted: compacted myocardial ratio > 2.2 in at least two segments of the LV to be diagnostic of LVNC [90].

Imaging decision-making

Each noninvasive imaging technique carries its own advantages and limitations, and the different and modality specific diagnostic criteria and clinical indications when being evaluated for additional diagnostic imaging warrants careful and patient-centered decision-making.

Table 1 highlights the major criteria in the diagnostic imaging workup of hypertrabeculation, LVNC, and LVNC cardiomyopathy.

ECHO is the most frequently used noninvasive imaging modality for the identification of LVNC [81]. ECHO can be used in patients with a concerning clinical history, those undergoing screening ECHO for a strongly positive family history, or for clarification of an incidental finding seen on previous ECHO for an unrelated cardiac evaluation. Overall, ECHO possesses a number of limitations in the diagnostic workup of LVNC, including operator dependence, poor visualization of the cardiac apex (the most commonly affected area), and the inability to accurately identify a double-layered myocardium or trabeculations [81,92]. Moreover, the generally accepted ECHO LVNC diagnostic criteria are based on analyses of small patient cohorts, with specifies and sensitivities from randomized controlled trials and larger population based assessments lacking [93]. Use of newer ECHO techniques, such as contrast enhancement, three-dimensional echocardiography, specle tracking, and tissue Doppler imaging can assist in diagnosis and provide insight onto systolic and diastolic function in a hypertrabeculated LV and the general pathophysiology of LVNC cardiomyopathy [81,93].

Imaging Modality	Diagnostic Criteria (Source)	Parameters
ECHO	Jenni., *et al*. [82]	1. Presence of LV trabeculation (mainly inferior and lateral wall apical and midventricular areas) 2. End-systolic noncompacted: compacted myocardial ratio > 2.0 (short axis view) 3. Multiple deep intertrabecular recesses connecting to LV cavity 4. Absence of concurrent cardiac abnormality
	Stollberger., *et al.* [83]	End-diastolic noncompacted: compacted ratio > 2.0 (apical four-chamber view)
	Gebhard., *et al.* [84]	Compacted myocardium systolic thickness < 8 mm (for differentiation of LVNC)
Cardiac MRI	Peterson., *et al.* [85]	1. Visual evidence of two distinct, compacted epicardial and noncompacted endocardial, myocardial layers 2. Presence of prominent trabeculations with deep intertrabecular recesses in noncompacted myocardium 3. End-diastolic noncompacted: compacted myocardial ratio > 2.3
	Jacquier., *et al.* [86]	End-diastolic noncompacted myocardial mass > 20% global LV mass
	Grothoff., *et al.* [87]	Trabeculated LV mass > 25% global LV mass, noncompacted mass > 15 g/m^2
MDCT	Melendez-Ramirez., *et al*. [90]	Noncompacted: compacted myocardial ratio > 2.2 in at least two LV segments

Table 1: *Summary of imaging modality-specific criteria for the diagnosis of LVNC.*

The major advantages afforded by cardiac MRI include a three dimensional approach, a broader cardiac and thoracic view, and superiority in identifying trabeculations and intramural, apical, and intertrabecular thomrbi [81]. The comparative higher cost, longer image acquisition time, and contraindication for patients with implantable defibrillators and pacemakers makes cardiac MRI a second-line diagnostic imaging modality, but certainly provides high quality anatomical assessments in comparison to ECHO [81]. MDCT represents an emerging noninvasive imaging modality with considerably similar image quality to cardiac MRI and provides a second-line imaging option to patients with contraindications to MRI [5,81,94].

Management

Management strategies in LVNC are predicated on genetic screening, prevention, both primary and secondary, of the major complications of LVNC cardiomyopathy, namely stroke and sudden cardiac death secondary malignant ventricular arrhythmias ventricular tachycardia and fibrillation, and guideline directed medical therapy (GDMT) for symptomatic congestive heart failure in the setting of systolic and or diastolic dysfunction [2,5,8,64,71,95,96].

Genetic and family screening

Genetic evaluation, both testing and counseling, is recommended for patients with LVNC, those with one of the genetic syndromes associated with LVNC, and for patients in whom LVNC is incidentally discovered during routine medical screening [5,97,98]. For patients with LVNC, a comprehensive medical genetic physical examination is recommended for assessing possible extracardiac traits known to genetic syndromes associated with LVNC [5]. Family screening in patients diagnosed with LVNC can help determine if the cardiac abnormality is sporadic or familial, as relatives of patients with LVNC can have isolated LVNC, other forms of congenital heart disease, or different classes of cardiomyopathy with or without LVNC [5,98]. For family members in whom hypertrabeculation or LVNC is identified, close clinical surveillance should be recommended [5].

Anticoagulation

Hypertrabeculation and LVNC are associated with an increased risk of cardioembolic events, most prominently stroke, due to the predisposition to mural thrombi forming in deep intertrabecular recesses [2,64]. Multiple case series and prospective cohort studies have produced different outcomes and recommendations for the use of oral anticoagulants for the primary prevention of thromboembolism [77,95,99,100]. Current evidence supports the use of prophylactic anticoagulation for the primary prevention of thromboembolic events in patients with LVNC, reduced ejection fraction < 40%, and/or atrial fibrillation, and patients with intracardiac thrombi identified on ECHO or another cardiac imaging modality [64,95]. For patients with LVNC who do not have a reduced ejection fraction atrial fibrillation, or imaging evidence of intracardiac thrombi, CHADS2/CHADS2-Vasc scoring and discussions on the risk and benefits of anticoagulation should guide further clinical decision-making [8].

Sudden cardiac death

Hypertrabeculation and LVNC are associated with increased risk of conduction abnormalities and tachyarrhythmia and systolic dysfunction secondary to LV dyssynchrony [64,68,69]. Patients with LVNC associated with DCM were shown to have a greater degree of LV reverse remodeling with cardiac resynchronization therapy than patients with isolated DCM [71,96]. Strategies for use of implantable cardioverter-defibrillator (ICD) for patients with LVNC should be based on current ICD primary and secondary prevention guidelines [8,101]. The main indications for ICD implantation for primary prevention of sudden cardiac death that may apply to patients with LVNC are patients with cardiomyopathy and ejection fraction ≤ 35% and high-risk hypertrophic cardiomyopathy with LVNC [101]. Given the risk of ventricular fibrillation and tachycardia in LVNC, patients who develop malignant ventricular tachyarrhythmia should undergo ICD implantation for secondary prevention [101].

Current and Future Perspectives

Multiple completed and ongoing clinical trials examining hypertrabeculation and LVNC and have highlighted genetic, physiologic, and prognostic characteristics.

A large French series of LVNC conducted by Habib et al. identified that patients with LVNC required close follow up due to the increased risk of severe complications, transplantation, or death [102]. Analysis of dose-response relationship between vigor of physical activity and degree of LV trabeculation in a British cohort showed that trabeculation is not influenced by degree of training intensity [103].

Given the diverse genetic profiles in LV hypertrabeculation and LVNC cardiomyopathy, early incorporation of genetic testing into clinical care can provide future opportunities to tailor management to each formulation of LV hypertrabeculation and LVNC [104]. Ongoing studies include genomic and proteomic analyses, studies to identify genetic variation, and novel biomarkers to better improve the diagnosis and prognosis of LVNC [105]. Additional studies investigating metabolomic profiles and pediatric cardiomyopathy genetic testing in LVNC. These studies aim to provide important clinical information on risk stratification and development of novel, genetically tailored treatment strategies [106,107]. These ongoing trials as well as future ones will continue to add to the embryonic, pathophysiologic, diagnostic, and management understandings, thus enhancing our ability to early diagnose and provide targeted therapy for hypertrabeculation and LVNC patients.

Conclusion

While hypertrabeculation can be seen in intensive athletes and patient populations with certain hematologic and intravascular volume expanding conditions, LVNC and LVNC cardiomyopathy represent clinically rare entities. Hypertrabeculation and noncompaction are cardiac image descriptions of LV morphology, with these findings generally observed in congenital heart disease and other acquired cardiomyopathies. Given the complexity in diagnostic imaging identification and the manifestation of hypertrabeculation and LVNC

in isolation or in association with genetic syndromes and congenital heart disease, certain predisposing medical comorbidities, and cardiomyopathies, larger clinical, genetic, and epidemiologic registries and prospective studies are needed to build consensus on the diagnostic criteria and proper labeling of LVNC cardiomyopathy.

Acknowledgement

This work is supported, in part, by the efforts of Dr. Moro O. Salifu M.D., M.P.H., M.B.A., M.A.C.P., Professor and Chairman of Medicine through NIH Grant number S21MD012474.

Bibliography

1. Samsa LA., *et al.* "Embryonic Cardiac Chamber Maturation: Trabeculation, Conduction and Cardiomyocyte Proliferation". *American Journal of Medical Genetics Part C: Seminars in Medical Genetics* 163.3 (2013): 157-168.

2. Towbin JA., *et al.* "Left Ventricular Non-compaction Cardiomyopathy". *Lancet* 386 (2015): 813-825.

3. Tamborini G., *et al.* "Incidence and Characteristics of Left Ventricular False Tendons and Trabeculations in the Normal and Pathologic Heart by Second Harmonic Echocardiography". *Journal of the American Society of Echocardiography* 17.4 (2004): 367-374.

4. Arbustini E., *et al.* "Left Ventricular Noncompaction: A Distinct Cardiomyopathy or a Trait Shared by Different Cardiac Diseases?" *Journal of the American College of Cardiology* 64.17 (2014): 1840-1850.

5. Arbustini E., *et al.* "Left Ventricular Noncompaction: A Distinct Genetic Cardiomyopathy". *Journal of the American College of Cardiology* 68.9 (2016): 949-966.

6. Maron BJ., *et al.* "Contemporary Definitions and Classifications of the Cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure, and Transplantation Committee; Quality of Care Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention". *Circulation* 113.14 (2006): 1807-1816.

7. Elliot P., *et al.* "Classification of the Cardiomyopathies: a Position Statement from the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases". *European Heart Journal* 29.2 (2008): 270-276.

8. Bennett CE and Freudenberger R. "The Current Approach to Diagnosis and Management of Left Ventricular Noncompaction Cardiomyoapthy". *Cardiology Research and Practice* (2016): 5172308.

9. Kloesel B., *et al.* "Cardiac Embryology and Molecular Mechanisms of Congenital Heart Disease – A Primer for Anesthesiologists". *Anesthesia and Analgesia* 123.3 (2016): 551-569.

10. Espinoza J., *et al.* "Changes in Fetal Cardiac Geometry with Gestation: Implications for Three-and Four-Dimensional Fetal Echocardiography". *Journal of Ultrasound in Medicine* 26.4 (2007): 437-444.

11. Jensen B., *et al.* "The Hypertrabeculated (noncompacted) Left Ventricle is Different from the Ventricle of Embryos and Ectothermic Vertebrates". *Biochimica et Biophysica Acta* 1863.7 (2016): 1696-1706.

12. Zou J., *et al.* "Neddylation Mediates Ventricular Chamber Maturation Through Repression of Hippo Signaling". *Proceedings of the National Academy of Sciences of the United States of America* 115.17 (2018): E4101-E4110.

13. Paun B., *et al.* "Quantification of the Detailed Left Ventricular Trabecular Morphogenesis in the Mouse Embryo". *Medical Image Analysis* 49 (2018): 89-104.

14. Kruithof BP., *et al.* "Remodeling of the Myocardium in Early Trabeculation and Cardiac Valve Formation; A Role of TGFβ2". *The International Journal of Developmental Biology* 57.11-12 (2013): 853-856.

15. Risebro CA and Riley PR. "Formation of the Ventricles". *Scientific World Journal* 6 (2006): 1862-1880.

16. Sedmera D., *et al.* "Developmental Patterning of the Myocardium". *The Anatomical Record* 258.4 (2000): 319-337.

17. Wessels A and Sedmera D. "Developmental Anatomy of the Heart: A Tale of Mice and Man". *Physiological Genomics* 15.3 (2003): 165-176.

18. Jouk PS., *et al.* "Three-dimensional Cartography of the Pattern of the Myofibers in the Second Trimester Fetal Human Heart". *Anatomy and Embryology* 202.2 (2000): 103-118.

19. Ohayon J., *et al.* "Fibre Orientation in Human Fetal Heart and Ventricular Mechanics: A Small Perturbation Analysis". *Computer Methods in Biomechanics and Biomedical Engineering* 2.2 (1999): 83-105.

20. Oechslin E and Jenni R. "Left Ventricular Non-compaction Revisited: A Distinct Phenotype with Genetic Heterogeneity?". *European Heart Journal* 32.12 (2011): 1446-1456.

21. Kawel-Boehm N., *et al.* "Hypertrabeculated Left Ventricular Myocardium in Relationship to Myocardial Function and Fibrosis: The Multi-Ethnic Study of Atherosclerosis". *Radiology* 284.3 (2017): 667-675.

22. Towbin JA and Jefferies JL. "Cardiomyopathies Due to Left Ventricular Noncompaction, Mitochondrial and Storage Diseases, and Inborn Errors of Metabolism". *Circulation Research* 121.7 (2017): 838-854.

23. Asfalou I., *et al.* "Left Ventricular Noncompaction – A Rare Form of Cardiomyopathy: Revelation Modes and Predictors of Mortality in Adults Through 23 Cases". *Journal of the Saudi Heart Association* 29.2 (2017): 102-109.

24. Stahli BE., *et al.* "Left Ventricular Non-compaction: Prevalence in Congenital Heart Disease". *International Journal of Cardiology* 167.6 (2013): 2477-2481.

25. Ramachandran P., *et al.* "The Impact of Concomitant Left Ventricular Non-compaction with Congenital Heart Disease". *Pediatric Cardiology* 37.7 (2016): 1307-1312.

26. Klaassen S., *et al.* "Mutations in Sarcomere Proteins Genes in Left Ventricular Noncompaction". *Circulation* 117.22 (2008): 2893-2901.

27. Milano A., *et al.* "HCN4 Mutations in Multiple Families with Bradycardia and Left Ventricular Noncompaction Cardiomyopathy". *Journal of The American College of Cardiology* 64.8 (2014): 745-756.

28. Luxan G., *et al.* "Mutations in the NOTCH Pathway Regulator MIB1 Cause Left Ventricular Noncompaction". *Cardiomyopathy* 19.2 (2013): 193-201.

29. Clarke SL., *et al.* "Barth Syndrome". *Orphanet Journal of Rare Diseases* 8 (2013): 23.

30. Jefferies JL. "Barth Syndrome". *American Journal of Medical Genetics Part C: Seminars in Medical Genetics* 163C.3 (2013): 198-205.

31. Arbustini E., *et al.* "Cardiac Phenotypes in Hereditary Muscle Disorders: Journal of The American College of Cardiology State-of-the-Art Review". *Journal of The American College of Cardiology* 72.20 (2018): 2485-2506.

32. van Waning JI., *et al.* "Cardiac Phenotypes, Genetics, and Risks in Familial Noncompaction Cardiomyopathy". *Journal of The American College of Cardiology* 73.13 (2019): 1601-1611.

33. Yang J., *et al.* "Whole-exome Sequencing Identify a New Mutation of MYH7 in a Chinese Family with Left Ventricular Noncompaction". *Gene* 558.1 (2015): 138-142.

34. Luxan G., *et al.* "Mutations in the NOTCH Pathway Regulator MIB1 Cause Left Ventricular Noncompaction Cardiomyopathy". *Nature Medicine* 19.2 (2013): 193-201.

35. Parent JJ., *et al.* "Left Ventricular Noncompaction in a Family with Lamin A/C Gene Mutation". *Texas Heart Institute Journal* 42.1 (2015): 73-76.

36. Ma Z., *et al.* "Contractile Deficits in Engineered Cardiac Microtissues as a Result of MYBPC3 Deficiency and Mechanical Overload". *Nature Biomedical Engineering* 2.12 (2018): 955-967.

37. Vatta M., *et al.* "Mutations in Cypher/ZASP in Patients with Dilated Cardiomyopathy and Left Ventricular Noncompaction". *Journal of the American College of Cardiology* 42.11 (2003): 2014-2027.

38. Hirono K., *et al.* "Familial Ebstein's Anomaly, Left Ventricular Noncompaction, and Ventricular Septal Defect Associated with MYH7 Mutation". *The Journal of Thoracic and Cardiovascular Surgery* 148.5 (2014): e223-e226.

39. Di Salvo G., *et al.* "Tetralogy of Fallot, Down's Syndrome, Left Ventricular Noncompaction, and Multiples Thrombi". *Journal of Cardiovascular Echography* 25.4 (2015): 108-110.

40. Gardner MM and Cohen MS. "Clinical Findings in Right Ventricular Noncompaction in Hypoplastic Left Heart Syndrome". *Congenital Heart Disease* 12.6 (2017): 783-786.

41. Kharge J., *et al.* "An Unusual Case of Congenitally Corrected Transposition of the Great Arteries Associated with Noncompaction-like Remodeling of the Morphological Right Ventricle". *Echocardiography* 28.10 (2011): E212-E214.

42. Finsterer J., *et al.* "Sudden Cardiac Death in Neuromuscular Disorders". *International Journal of Cardiology* 203 (2016): 508-515.

43. Tanpaiboon P., *et al.* "Noncompaction of the Ventricular Myocardium and Hydrops Fetalis in Cobalamin C Disease". *JIMD Reports* 10 (2013): 33-38.

44. Rasouli SJ and Stainier DYR. "Regulation of Cardiomyocyte Behavior in Zebrafish Trabeculation by Neuregulin 2a Signaling". *Nature Communications* 8 (2017): 15281.

45. Cherian AV., *et al.* "N-cadherin Relocalization During Cardiac Trabeculation". *Proceedings of the National Academy of Sciences of the United States of America* 113.27 (2016): 7569-7574.

46. Qu X., *et al.* "Tie2 Regulates Endocardial Sprouting and Myocardial Trabeculation". *JCI Insight* (2019): 5.

47. Han P., *et al.* "Coordinating Cardiomyocyte Interactions to Direct Ventricular Chamber Morphogenesis". *Nature* 534.7609 (2016): 700-704.

48. Chen H., *et al.* "BMP10 is Essential for Maintaining Cardiac Growth During Murine Cardiogenesis". *Development* 131.9 (2004): 2219-2231.

49. Choquet C., *et al.* "Deletion of Nkx2-5 in Trabecular Myocardium Reveals the Development Origins of Pathological Heterogeneity with Ventricular Non-compaction Cardiomyopathy". *PLOS Genetics* 14.7 (2018): e1007502.

50. Abela M and D'Silva A. "Left Ventricular Trabeculations in Athletes: Epiphenomenon or Phenotype of Disease? ". *Current Treatment Options in Cardiovascular Medicine* 20.12 (2018): 100.

51. Brosnan MJ and Rakhit D. "Differentiating Athlete's Heart from Cardiomyopathies – The Left Side". *Heart, Lung and Circulation* 27.9 (2018): 1052-1062.

52. Halaney DL., *et al.* "The Effect of Trabeculae Carnae on Left Ventricular Diastolic Complicance: Improvement in Compliance with Trabecular Cutting". *Journal of Biomechanical Engineering* 139.3 (2017): 031012.

53. Paun B., *et al.* "Relationship Between the Left Ventricular Size and the Amount of Trabeculation". *International Journal for Numerical Methods in Biomedical Engineering* 34.3 (2018): e2939.

54. Gati S., *et al.* "Reversible de novo Left Ventricular Trabeculations in Pregnant Women: Implications for the Diagnosis of Left Ventricular Noncompaction in Low-risk Populations". *Circulation* 130.6 (2014): 475-483.

55. Markovic NS., *et al.* "Isolated Ventricular Noncompaction in Patients with Chronic Renal Failure". *Clinical Nephrology* 70.1 (2008): 72-76.

56. Fukino K., *et al.* "Noncompaction of the Ventricular Myocardium and Polycystic Kidney Disease: A Case Report". *American Journal of Kidney Diseases* 67.6 (2016): 945-948.

57. Moon JY., *et al.* "Noncompaction of the Ventricular Myocardium Combined with Polycystic Kidney Disease". *Heart Vessels* 21.3 (2006): 195-198.

58. Piga A., *et al.* "Left Ventricular Noncompaction in Patients with β-thalassemia: Uncovering a Previously Unrecognized Abnormality". *American Journal of Hematology* 87.12 (2012): 1079-1083.

59. Kayvanpour E., *et al.* "Clinical and Genetic Insights into Non-compaction: A Meta-analysis and Systematic Review on 7598 Individuals". *Clinical Research in Cardiology* (2019).

60. Engberding R and Bender F. "Identification of Rare Congenital Anomaly of the Myocardium by Two-dimensional Echocardiography. Persistence of Isolated Myocardial Sinusoids". *American Journal of Cardiology* 53.11 (1984): 1733-1734.

61. Floria M., *et al.* "Left Ventricular Non-compaction – Challenges and Controversies". *Maedica (Buchar)* 9.3 (2014): 282-288.

62. Weir-McCall JR., *et al.* "Left Ventricular Noncompaction: Anatomical Phenotype or Distinct Cardiomyopathy". *Journal of the American College of Cardiology* 68.20 (2016): 2157-2165.

63. Caine A., *et al.* "Racial Differences in Left Ventricular Trabeculations By Cardiac Magnetic Resonance Imaging". *Journal of the American College of Cardiology* 65.10 (2015): A1094.

64. Udeoji DU., *et al.* "Left Ventricular Noncompaction Cardiomyopathy: Updated Review". *Therapeutic Advances in Cardiovascular Disease* 7.5 (2013): 260-273.

65. Agmon Y., *et al.* "Noncompaction of the Ventricular Myocardium". *Journal of the American Society of Echocardiography* 12.10 (1999): 859-863.

66. Arenas IA., *et al.* "Echocardiographic and Clinical Markers of Left Ventricular Ejection Fraction and Moderate or Greater Systolic Dysfunction in Left Ventricular Noncompaction Cardiomyopathy". *Echocardiography* 35.7 (2018): 941-948.

67. Soler R., *et al.* "MRI of Subendocardial Perfusion Deficits in Isolated Left Ventricular Noncompaction". *Journal of Computer Assisted Tomography* 26.3 (2002): 373-375.

68. Takahashi N., *et al.* "Clinical Usefulness of Gated Technetium-99m Sestamibi Myocardial Perfusion Single-photon Emission Computed Tomography with Phases Analysis for the Management of Patients with Isolated Ventricular Noncompaction". *Journal of Cardiology Cases* 11.4 (2014): 101-104.

69. Akhbour S., *et al.* "Electrocardiographic Findings in Correlation to Magnetic Resonance Imaging Patterns in African Patients with Isolated Ventricular Noncompaction". *The Anatolian Journal of Cardiology* 15.7 (2015): 550-555.

70. Xi Y., *et al.* "Loss of Function of hNav1.5 by a ZASP1 Mutation Associated with Intraventricular Conduction Disturbances in Left Ventricular Noncompaction". *Circulation: Arrhythmia and Electrophysiology* 5.5 (2012): 1017-1026.

71. Miyake CY and Kim JJ. "Arrhythmias in Left Ventricular Noncompaction". *Cardiac Electrophysiology Clinics* 7.2 (2015): 319-330.

72. Steffel J., *et al.* "Electrocardiographic Characteristics at Initial Diagnosis in Patients with Left Ventricular Noncompaction". *American Journal of Cardiology* 104.7 (2009): 984-989.

73. Caliskan K., *et al.* "The Prevalence of Early Repolarization in Patients with Noncompaction Cardiomyopathy Presenting with Malignant Ventricular Arrhythmias". *Journal Cardiovasc Eletrophysiol* 23.9 (2012): 938-944.

74. Zhou H., *et al.* "Prolonged QTc Indicates the Clinical Severity and Poor Prognosis in Patients with Isolated Left Ventricular Non-compaction". *The International Journal of Cardiovascular Imaging* 33.12 (2017): 2013-2020.

75. Mavrogeni SI., *et al.* "Sudden Cardiac Death in Athletes and the Value of Cardiovascular Magnetic Resonance". *European Journal of Clinical Investigation* 48.7 (2018): e12955.

76. Stollberger C., *et al.* "Frequency of Stroke and Embolism in left Ventricular Hypertrabeculation/noncompaction". *American Journal of Cardiology* 108.7 (2011): 1021-1023.

77. Stollberger C and Finsterer J. "Left Ventricular Hypertrabculation/noncompaction and Stroke or Embolism". *Cardiology* 103.20 (2005): 68-72.

78. Xu L., *et al.* "Acute Kidney Infarction Due to Left Ventricular Thrombus Embolization in Patient with Isolated Left Ventricular Noncompaction. A Case Report". *The Heart Surgery Forum* 20.6 (2017): E252-E255.

79. Pulignano G., *et al.* "Noncompaction and Embolic Myocardial Infarction: The Importance of Oral Anticoagulation". *Revista Portuguesa de Cardiologia* 34.7-8 (2015): 497.e1-4.

80. Blessing E., *et al.* "Isolated Left Ventricular Noncompaction of the Myocardium as a cause of Embolic Superior Mesenteric Artery Occlusion". *Journal of the American Society of Echocardiography* 18.6 (2005): 693.

81. Zuccarino F., *et al.* "Left Ventricular Noncompaction: Imaging Findings and Diagnostic Criteria". *American Journal of Roentgenology* 204.5 (2015): W519-530.

82. Jenni R., *et al.* "Echocardiographic and Pathoanatomical Characteristics of Isolated Left Ventriculat Non-compaction: A Step Towards Classification as a Distinct Cardiomyopathy". *Heart* 86.6 (2001): 666-671.

83. Stollberger C., *et al.* "Refinement of Echocardiographic Criteria for Left Ventricular Noncompaction". *International Journal of Cardiology* 165.3 (2013): 463-467.

84. Gebhard C., *et al.* "Reduced Left Ventricular Compacta Thickness: A Novel Echocardiographic Criterion for Non-compaction Cardiomyopathy". *Journal of the American Society of Echocardiography* 25.10 (2012): 1050-1057.

85. Peterson SE., *et al.* "Left Ventricular Non-compaction: Insights from Cardiovascular Magnetic Resonance Imaging". *Journal of the American College of Cardiology* 46.1 (2005): 101-105.

86. Jacquier A., *et al.* "Measure of Trabeculated Left Ventricular Mass Using Cardiac Magnetic Resonance Imaging in the Diagnosis of Left Ventricular Non-compaction". *European Heart Journal* 31.9 (2010): 1098-1104.

87. Grothoff M., *et al.* "Value of Cardiovascular MR in Diagnosing Left Ventricular Non-compaction Cardiomyopathy and in Discriminating between other Cardiomyopathies". *European Radiology* 22.10 (2012): 2699-2709.

88. Diwadkar S., *et al.* "Echocardiography Fails to Detect Left Ventricular Noncompaction in a Cohort of Patients with Noncompaction on Cardiac Magnetic Resonance Imaging". *Clinical Cardiology* 40.6 (2017): 364-369.

89. Thuny F., *et al.* "Assessment of Left Ventricular Non-compaction in Adults: Side-by-side Comparison of Cardiac Magnetic Resonance Imaging with Echocardiography". *Archives of Cardiovascular Diseases* 103.3 (2010): 150-159.

90. Melendez-Ramirez G -Z., *et al.* "Left Ventricular Noncompaction: A Proposal of New Diagnostic Criteria by Multidetector Computed Tomography". *Journal of Cardiovascular Computed Tomography* 6.5 (2012): 346-354.

91. Hamamichi Y., *et al.* "Isolated Noncompaction of the Ventricular Myocardium: Ultrafast Computed Tomography and Magnetic Resonance Imaging". *The International Journal of Cardiovascular Imaging* 17.4 (2001): 305-314.

92. Hotta VT., *et al.* "Limitations in the Diagnosis of Noncompaction Cardiomyopathy by Echocardiography". *Arquivos Brasileiros de Cardiologia* 109.5 (2017): 483-488.

93. Soliman OI., *et al.* "Diagnostic Uncertainties and Future Perspectives in Noncompaction Cardiomyopathy". *Expert Opinion on Medical Diagnostics* 6.3 (2012): 221-233.

94. Sidhu MS., *et al.* "Defining Left Ventricular Noncompaction Using Cardiac Computed Tomography". *Journal of Thoracic Imaging* 29.1 (2014): 60-66.

95. Kido K and Guglin M. "Anticoagulation Therapy in Specific Cardiomyopathies: Isolated Left Ventricular Noncompaction and Peripartum Cardiomyopathy". *Journal of Cardiovascular Pharmacology and Therapeutics* 24.1 (2019): 31-36.

96. Bertini M., *et al.* "Efficacy of Cardiac Resynchronization Therapy in Patients with Isolated Ventricular Noncompaction with Dilated Cardiomyopathy: A Systematic Review of the Literature". *Journal of Cardiovascular Medicine (Hagerstown*) 19.7 (2018): 324-328.

97. Charron P., *et al.* "Genetic Counseling and Testing in Cardiomyopathies: A Position Statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases". *European Heart Journal* 31.22 (2010): 2715-2726.

98. Hoedemaekers YM., *et al.* "The Importance of Genetic Counseling, DNA Diagnostics, and Cardiologic Family Screening in Left Ventricular Noncompaciton Cardriomyopathy". *Circulation: Cardiovascular Genetics* 3.3 (2010): 232-239.

99. Ritter M., *et al.* "Isolated Noncompaction of the Myocardium in Adults". *Mayo Clinic Proceedings* 72.1 (1997): 26-31.

100. Fazio G., *et al.* "Anticoagulant Drugs in Noncompaction: A Mandatory Therapy?". *Journal of Cardiovascular Medicine (Hagerstown)* 9.11 (2008): 1095-1097.

101. Al Khatib SM., *et al.* "AHA/ACC/HRS Guideline for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society". *Heart Rhythm* 15.10 (2018): e190-e252.

102. Habib G., *et al*. "Isolated Left Ventricular Non-compaction in Adults: Clinical and Echocardiographic Features in 105 Patients. Results from a French Registry". *European Journal of Heart Failure* 13.2 (2011): 177-185.

103. Woodbridge SP., *et al*. "Physical Activity and Left Ventricular Trabeculation in the UK Biobank Community-based Cohort Study". *Heart* 105.13 (2019): 990-998.

104. Ware SM. "Genetics of Pediatric Cardiomyopathies". *Current Opinion in Pediatrics* 29.5 (2017): 534-540.

105. Beijing Institute of Heart, Lung and Blood Vessel Diseases. An Integrative-"Omics" Study of Cardiomyopathy Patients for Diagnosis and Prognosis in China (AOCC) (2019).

106. Beijing Institute of Heart, Lung and Blood Vessel Diseases. Metabolomic Study of All-age Cardiomyopathy (MAC) (2019).

107. Indiana University. Pediatry Cardiomyopathy Mutation Analysis (2019).

Volume 2 Issue 6 August 2019
©All rights reserved by Samy I McFarlane.*, et al.*