REVIEW

Frontiers in cardiovascular medicine

Left ventricular non-compaction revisited: a distinct phenotype with genetic heterogeneity?

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Non-compaction of the left ventricular myocardium (LVNC) has gained increasing recognition during the last 25 years. There is a morphological trait of the myocardial structure with a spectrum from normal variants to the pathological phenotype of LVNC, which reflects the embryogenic structure of the human heart due to an arrest in the compaction process during the first trimester. It must be cautioned not to overdiagnose LVNC: the morphological spectrum of trabeculations, from normal variants to pathological trabeculations with the morphological feature of LVNC must be carefully considered. The classical triad of complications are heart failure, arrhythmias, including sudden cardiac death, and systemic embolic events. Non-compaction of the left ventricular myocardium can occur in isolation or in association with congenital heart defects (CHDs), genetic syndromes, and neuromuscular disorders among others. The clinical spectrum is wide and the outcome is more favourable than in previously described populations with a negative selection bias. Familial occurrence is frequent with autosomal dominant and X-linked transmissions. Different mutations in sarcomere protein genes were identified and there seems to be a shared molecular aetiology of different cardiomyopathic phenotypes, including LVNC, hypertrophic and dilated cardiomyopathies. Thus, genetic heterogeneity, with an overlap of different phenotypes, and the variability of hereditary patterns, raise the questions whether there is a morphological trait from dilated/hypertrophic cardiomyopathy to LVNC and what are the triggers and modifiers to develop either dilated, hypertrophic cardiomyopathy, or LVNC in patients with the same mutation. The variety in clinical presentation, the genetic heterogeneity, and the phenotype of the first transgenetic animal model of an 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.

Keywords   Cardiomyopathy • Non-compaction • Heart failure • Genetics • Echocardiography

Introduction

Non-compaction of the ventricular myocardium (LVNC) has gained increasing awareness and attention and its diagnosis has moved from the autopsy table or previously poorly recognized to a widely recognized cardiomyopathy.[1–3] The exponential increase in publications reflects increasing interest of this fascinating myocardial phenotype.[4] This raises the question whether advances in non-invasive diagnostic technologies led to better delineation of the morphological appearance of the myocardium or whether LVNC is overdiagnosed and the diagnostic criteria are too sensitive. The goal of this article is to review developmental consideration, different diagnostic criteria, genetic considerations, outcomes, and therapeutic implications of this cardiomyopathic phenotype with genetic heterogeneity and to answer the question whether LVNC is a distinct cardiomyopathy or a distinct myocardial phenotype of different underlying diseases.

Historical aspect

Spongy appearance of the myocardium was first identified in a variety of congenital heart defects (CHDs), with the first description published by Grant in 1926.[5,6] It is Dusek et al.,[7] however, who get credited with bringing the entity of spongy myocardium into clinical focus although these early cases are hardly representative of the entity now described as LVNC. The first description of an isolated, rare myocardial anomaly in the absence of any other

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structural heart disease was published by Engberding.[8] The Zurich group confirmed Engberding's findings and published case reports describing echocardiographic, angiographic, and pathological anatomical findings.[9,10] These early reports appreciated the persistence of embryonic myocardial structures, but it was Chin et al.[11] who introduced the term '*isolated non-compaction of left ventricular myocardium*' and recognised the underlying arrest of the normal compaction process during embryogenesis.

Developmental considerations

Understanding of the ontogenetic development of the myocardium is critical to appreciate the morphological appearance of LVNC. There is some controversy whether LVNC is congenital due to an arrest of the normal compaction process of the developing myocardium or LVNC is acquired.

The development of the heart follows the same pattern in all vertebrates from fish to human, where the myocardial maturation undergoes complex changes during the evolutionary development. Landmark articles very nicely illustrate the development of the myocardial architecture which passes through four distinct steps:[6,12] (i) early heart tube, (ii) emergence of trabeculations, (iii) trabecular remodelling, (iv) development of the multilayered spiral system. Emergence of trabeculations and trabecular remodelling are the key steps to understand LVNC.

Emergence of trabeculations

Trabeculations in the human embryo emerge after looping of the primitive heart tube at the end of the fourth week of gestation (length of the embryo ~4 mm) (*Figure 1*).[12] Only early trabeculations effectively increase surface area, enabling the myocardial mass to increase in the absence of an epicardial coronary circulation. The trabeculation patterns are ventricle-specific: the trabeculations in the LV are generally thicker and the corresponding intertrabecular spaces are larger at this embryonic stage. When this myocardial pattern persists postnatally, the morphological appearance strongly resembles the spongy myocardium seen in non-mammalian vertebrates (e.g. reptiles, fish, amphibians).[6]

Trabecular remodelling

Trabecular remodelling starts after completion of ventricular septation (at 8 weeks of gestation in human) (*Figure 1*). Increase in ventricular volumes results in compression of the trabeculations with an increase in the thickness of the compacted myocardium.[12] Rearrangement of the endocardial trabeculations is specific for the ventricles and the species. In the mammalian heart, some of the luminal trabeculations coalesce to produce the anterior and posterior papillary muscles of the mitral valve and apical trabeculations transform into fine honeycomb-like reliefs on the inner ventricular surface.[12] This special aspect must be appreciated when
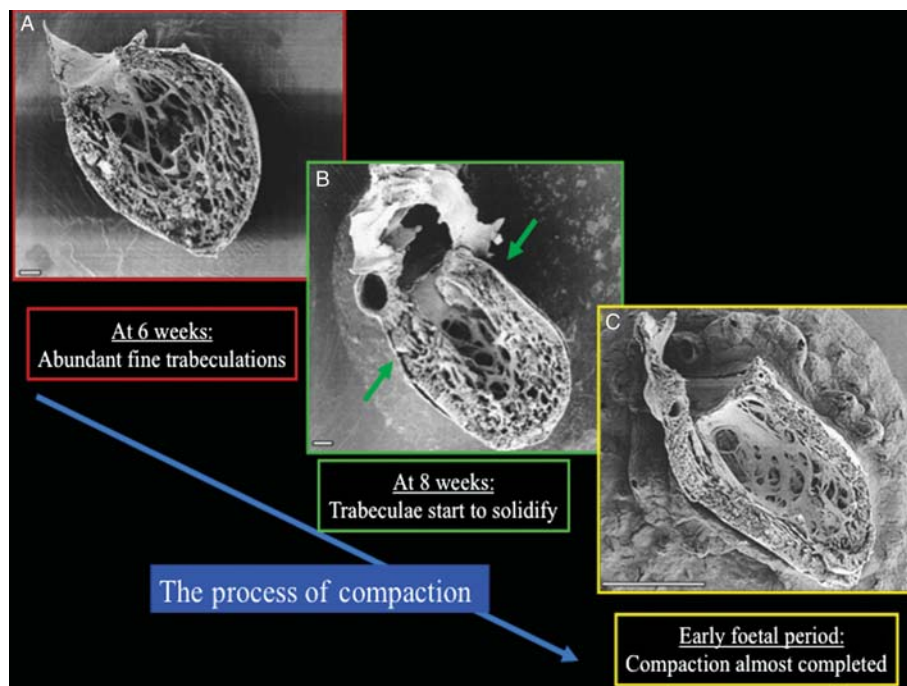
Figure 1 Parietal view of sagitally dissected human embryonic left ventricles showing the process of normal trabecular compaction. (*A*) Abundant fine trabeculations present at 6 weeks. (*B*) The trabeculae start to solidify at the base of the heart, contributing to added thickness of the compacted layer; initiation of this process coincides with the development of the epicardial coronary system. (*C*) The compact layer forms most of the myocardium mass after completion of compaction in the early foetal period. Scale bars 100 μm (A and B), 1 mm (C). Modified reproduction from Isolated left ventricular non-compaction: a distinct cardiomyopathy? Varnava AM *Heart* 2001; **86**:599–600,[47] copyright 2001, with permission from BMJ Publishing Group Ltd.

the morphological appearance of the LV myocardium is described and LVNC is considered.

The compaction process or trabecular remodelling coincides with the invasion of the epicardial coronary arteries and vascularization of the myocardium. It gradually progresses from the epicardium to the endocardium, from the base to the apex and from the septum to the free wall in the LV, and is more pronounced in the LV than in the right ventricle.[12] Thus, the time of arrest of the normal embryonic myocardial maturation determines the severity and extension of LVNC; the ventricular apex is always involved as the compaction process concludes in the ventricular apex.

Non-compaction of the myocardium: congenital or acquired?

Evolutionary changes during morphogenesis strongly suggest that LVNC reflects impaired/arrested compaction of the developing myocardium.[6,7,11,13,14] There is a controversy, however, if LVNC can also be acquired.[15] The discussion against the developmental hypothesis comes from serial echocardiographic studies where LVNC was not diagnosed on initial echocardiogram but was becoming evident in subsequent examinations.

The weight of evidence, based on the developmental changes, strongly supports the hypothesis that LVNC reflects an abnormality in the early myocardial morphogenesis or failure of full maturation of the compacted myocardium.[6] Recent advances in genetics, however, raise the question whether LVNC can also develop postnatally. The morphological features of dilated and hypertrophic cardiomyopathy are not present at birth, but they develop during life. Patients with dilated cardiomyopathy, hypertrophic cardiomyopathy, and LVNC share common mutations in sarcomere protein genes. This common genetic background raises the hypothesis whether LVNC may also develop later in life.

Terminology

Dusek et al.[7] were one of the first who described the morphological appearance of the myocardium in five hearts with different pathologies as postnatal persistence of spongy myocardium with embryological blood supply. Others invoked this concept of evolutionary persistence of the spongy myocardium which resembled a loosely interwoven mesh of trabeculated muscle fibres seen in the embryo and in cold-blooded vertebrates. Many other terms were introduced but were not widely used.

Three terms need further discussion and clarification: non-compaction, hypertrabeculation, and persistent sinusoids. It was Chin et al.[11] who first introduced the term non-compaction. They argued that the descriptive term 'spongy myocardium' has the virtue of precedence. The term non-compaction, however, underscores the hypothesis of an arrest of the normal compaction process of the loosely interwoven mesh of muscle fibres in the embryo. Second, some hearts with 'spongy myocardium' have heavy trabeculations in the affected ventricle, but it does not

follow that every heavily trabeculated ventricle has a 'spongy myocardium'.[11]

The term 'persistent sinusoids' is not correct. Persistent, myocardial sinusoids describe ventriculo-coronary arterial communications or intertrabecular spaces connecting the ventricular cavity with the epicardial coronary artery system through the capillary bed. They are usually seen in pulmonary atresia with intact ventricular septum.[6] The histological appearance is completely different from non-compaction and clinical and developmental data support the evidence of a primary coronary vascular anomaly for the development of persistent myocardial sinusoids. In contrast, the intertrabecular recesses and their troughs are lined with endothelium in the non-compacted myocardium.

The term hypertrabeculation is not correct either. Hypertrabeculation implies an increased number of normally formed trabeculations. The histological appearance of LVNC, however, is far beyond normal.[6,16]

Developmental considerations and evolutionary evidence do not support either the term hypertrabeculation or persistent myocardial sinusoids to describe the distinct morphological feature of non-compaction. Failure of trabecular remodelling is best described by the term 'non-compaction' to illustrate the impaired compaction process and failure of myocardial maturation during embryogenesis.[6,11,12] Scientific statements using the term 'non-compaction' acknowledge myocardial morphogenesis.[1−3]

Classification of cardiomyopathies

The 1995 World Health Organization (WHO)/International Society and Federation of Cardiology Task Force on the definition and classification of cardiomyopathies did not classify non-compaction as a distinct cardiomyopathy but it was rather grouped as an unclassified cardiomyopathy.[3] A causative, genetic approach would be logical because many cardiomyopathies are caused by mutations in genes encoding various cardiac proteins.[17] The American Heart Association recognized the rapid evolution of molecular genetics in cardiology and classified LVNC as primary, genetic cardiomyopathy.[2] In contrast, a position statement of the European Society of Cardiology classified LVNC as 'unclassified cardiomyopathy' because it is not clear whether it is a separate cardiomyopathy or merely a morphological trait shared by many phenotypically distinct cardiomyopathies.[1]

Diagnostic criteria

Normal variants

Characterization of the normal myocardial structure is the first step before definition of a pathological appearance of the myocardium. Boyd et al.[18] reported the frequency and localization of prominent LV trabeculations at autopsy in 474 normal hearts. Prominent trabeculations were observed in 68% of these hearts, and 53% of them exhibited two or more. More than three prominent trabeculations were observed in only 3%, but none of the hearts had more than five. Most of the trabeculations (85%) were septomarginal bundles inserting into both the free wall and the septum.

Echocardiography is the diagnostic modality of first choice to describe myocardial pathologies. However, recent advancements in echocardiography, such as second harmonic imaging, have permitted detection of previously unrecognized anatomical structures of the normal heart. This raises the question whether structures, such as fine trabeculations, are normal, a normal variant or abnormal. The ratio of trabeculated/compacted myocardium was 1.29 ± 0.4 in normal and pathological hearts and much lower than in hearts with non-compacted myocardium.[19] An expert cardiologist and echocardiography operator, however, are qualified to recognize the anatomical trait of LVNC and to separate normal variants of the myocardial appearance from LVNC.

Non-compaction

Chin et al.[11] proposed echocardiographic diagnostic criteria and brought the condition to our attention (Table 1). They quantified the depth of penetration of the intertrabecular recesses relative to the posterior wall thickness at end-diastole and calculated the X-ratio to Y-ratio. This method was validated against a control group of eight subjects with normal echocardiographic studies, which did not disclose the progressive decrease in the X-to-Y ratio from the level of the mitral valve to the apex.

The Zurich group defined echocardiographic diagnostic criteria for isolated LVNC and validated them with patho-anatomical heart preparations (Figure 2).[13] Chin's and Jenni's criteria require a two-layered myocardial structure with a compacted epicardial layer and a much thicker, non-compacted endocardial layer. In contrast to Chin et al., the Zurich group relied on measurements at end-systole to assess the thickness of the two layers best visualized at end-systole. Three additional criteria were added to diagnose isolated LVNC (Table 1). Their diagnostic criteria of LVNC were validated in valvular or hypertensive heart disease or dilated cardiomyopathy (Figure 3). Although some non-compaction criteria were occasionally found in other heart diseases, the combination of all criteria was very specific, and all criteria of non-compaction were rarely met (<5%) in other diseases.[20]

Stöllberger et al.[21] depart from the above diagnostic approach to visualize the two distinct endocardial and epicardial layers (Table 1). The Vienna group modified their diagnostic criteria during the last years and shifted away from their original description. They also prefer to describe the phenotype as 'LV hypertrabeculation' rather than 'non-compaction', although they now add 'non-compaction' to their description.[15,21]

Limitations of echocardiographic criteria

Kohli et al.[22] challenged these three diagnostic criteria (Table 1). There was a poor correlation between the three echocardiographic definitions: 24% of the study population fulfilled one or more echocardiographic definitions for LVNC, while only 30% fulfilled all three criteria. This poor correlation is not surprising: the method of the morphological description differs in the definition of abnormal trabeculations, in the echo planes and in the phase of the cardiac cycle in which the morphology is described (Table 1).[11,13,21,22]

More surprisingly, 8% of apparently healthy individuals also satisfied one or more diagnostic criteria for LVNC; interestingly, four of these individuals were black.[22] This raises the question whether

Table 1 Diagnostic criteria for left ventricular non-compaction

Echocardiography

Chin et al.[11]

    Two-layered structure of the myocardium (epicardial compacted, endocardial non-compacted layer)

    Determination of the X-to-Y ratio (≤0.5)

        X—Distance between the epicardial surface and through of intertrabecular recess

        Y—Distance between epicardial surface and peak of trabeculation

    Acquisition of the images: parasternal short-axis view, measurements of the X-to-Y ratio at end-*diastole*

Jenni et al.[13]

    Thickened myocardium with a two-layered structure consisting of a thin compacted epicardial layer/band (C) and a much thicker, non-compacted endocardial layer (N) or trabecular meshwork with deep endomyocardial spaces; N/C ratio >2.0

    Predominant location of the pathology: mid-lateral, mid-inferior, and apex

    Colour Doppler evidence of deep intertrabecular recesses filled with blood from the left ventricular cavity

    Absence of coexisting cardiac abnormalities (in the presence of isolated LVNC)

    Acquisition of the images: short-axis views, measurements of the N/C ratio at end-*systole*

Stöllberger et al.[15,21]

    More than three trabeculations protruding from the left ventricular wall, located apically to the papillary muscles and visible in one image plane

    Trabeculations with the same echogenicity as the myocardium and synchronous movement with ventricular contractions

    Perfusion of the intertrabecular spaces from the left ventricular cavity

    Ratio of non-compacted to non-compacted segment >2.0 at end-diastole (this criterion was introduced later)

    Acquisition of the images: apical four chamber view; angulation of the transducer and acquisition of pictures in atypical views to obtain the technically best picture quality for differentiation between false chords/aberrant bands and trabeculations

    Diagnostic criteria have changed during the last years

Magnetic resonance imaging

Petersen et al.[26]

    Ratio between the non-compacted and compacted layer >2.3

    Measurement: at end-*diastole*

Jacquier et al.[27]

    Trabeculated left ventricular mass >20% of the global left ventricular mass

    Measurement: left ventricular trabeculation and global/compacted LV mass were defined at end-*diastole*

the current diagnostic criteria are too sensitive, in particular for black individuals, non-compaction is overdiagnosed or the retrospective study design was a limitation (the patients were studied without specific focus on non-compaction).[22] On the other hand, the extent of the myocardial meshwork, with fine trabeculations at one end and LVNC at the other end of the spectrum, may
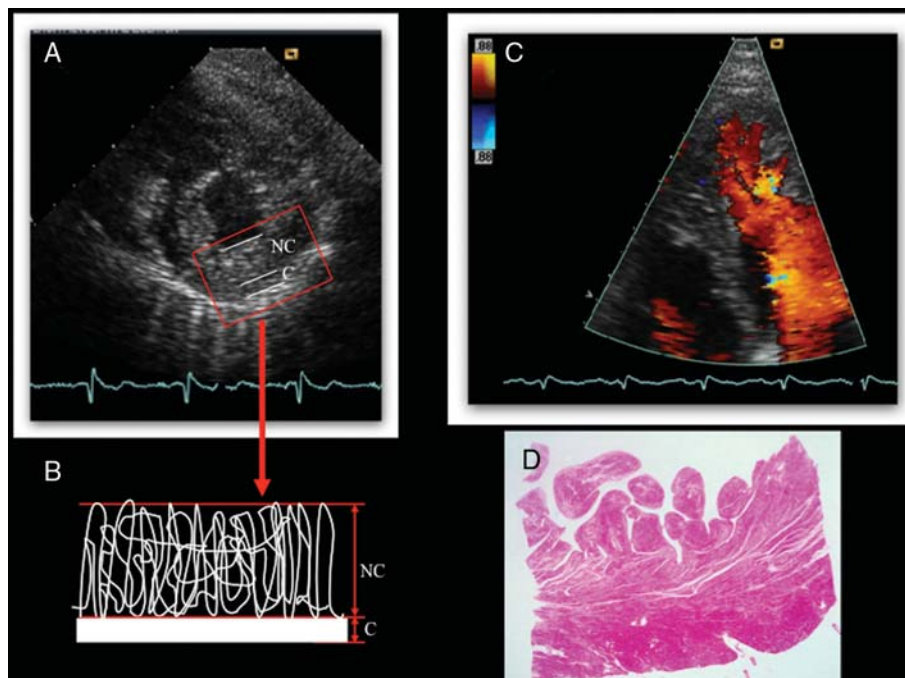
Figure 2 (*A*) Parasternal short-axis view of a patient with isolated LVNC. The end-systolic still-frame shows the two-layered structured of the thickened myocardium. (*B*) To quantify the thickness of the non-compacted layer at the site of maximal thickness, the end-systolic ratio of the non-compacted (NC) to compacted (C) layer is determined. (*C*) Apical four-chamber view (end-diastolic still frame) showing the inter-trabecular recesses filled with blood from the left ventricular cavity. (*D*) Transmural, histological section (haematoxylin and eosin stain). The endocardial, non-compacted layer is covered with endocardium and communicates with the LV cavity. Courtesy of Dr J. Schneider, University Hospital, Zurich.

represent a continuous morphological trait and spectrum. Prominent trabeculations in heart failure patients could be no more than an incidental finding or a normal variant. The most important question remains when fine trabeculations are a normal variant and when they become pathological.

Echocardiographic pitfalls

Echocardiography depends on the skills, experience, and knowledge of the investigator. Oblique images obtained off-axis or images in the parasternal short-axis view, which are not perpendicular to the LV long axis, can produce the morphological appearance of prominent trabeculations and mimic LVNC. It is critical to obtain images that are not foreshortened and are perpendicular to the ventricular long axis. In addition, there are inherent challenges to image the ventricular apex and misdiagnoses are not rare. Contrast echocardiogram is useful to better image intertrabecular spaces (*Figure 4*).

Interpretation of trabeculations adjacent to the papillary muscles and at the apex is challenging and embryogenic considerations must be taken into account when the myocardial pattern is described: some of the luminal trabeculations coalesce to produce the anterior and posterior papillary muscles of the mitral valve and apical trabeculations transform into fine honeycomb-like reliefs on the inner ventricular surface.[6,12] These developmental aspects must be appreciated when LVNC is considered.

New echocardiographic technique, such as tissue Doppler imaging, strain and strain rate, and speckle tracking, may help to evaluate the functional impact of an abnormal myocardial architecture and enable the clinician to distinguish between normally trabeculated myocardium from LVNC.[23,24] Left ventricular twist was determined by speckle tracking echocardiography.[25] Rotation was clockwise at the base and counterclockwise at the apex in all controls and patients with dilated cardiomyopathy. In contrast, the LV base and apex rotated in the same direction in all non-compaction patients. Thus, LV solid body rotation/twist may be a new objective and quantitative, functional diagnostic criterion for non-compaction.[25]

Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging (MRI) has been increasingly used to describe the morphological appearance of the myocardium. Petersen *et al.*[26] tested the accuracy of MRI in distinguishing pathological LVNC from lesser degrees of trabecular layering seen in those with normal hearts, and in those with LV hypertrophy and cardiomyopathies. Areas of non-compaction were common and occurred more frequently in all groups studied in the apical and lateral, rather than in basal and septal segments as reported in echocardiographic studies. A non-compacted to compacted ratio of >2.3 in diastole distinguished pathological non-
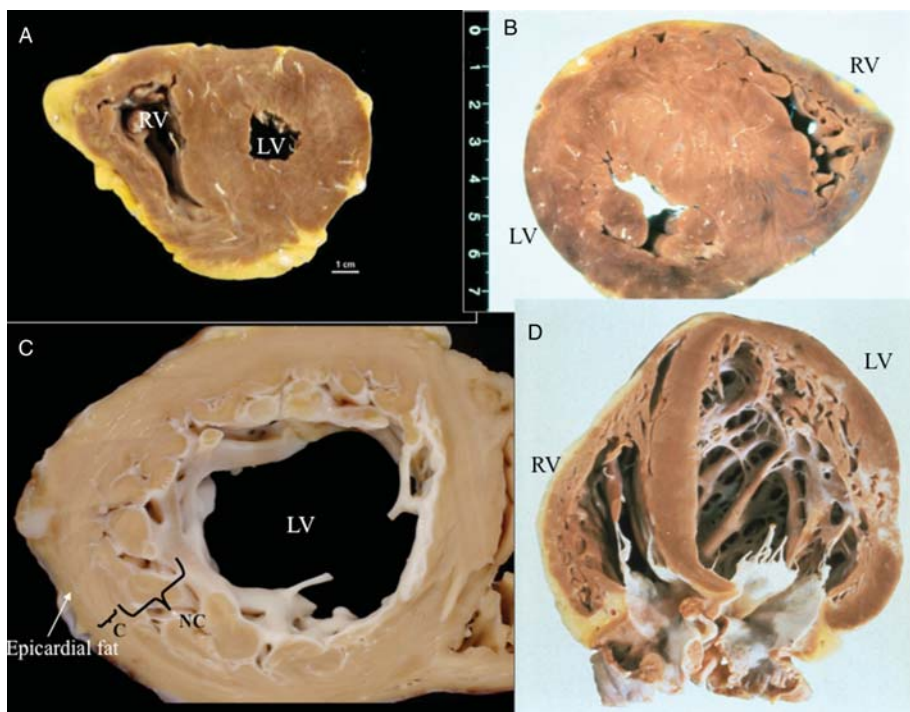
Figure 3 Cross-section views of a normal heart (A), hypertrophic cardiomyopathy (B), and isolated LVNC (C). Transsectional view from anterior on the dorsal half of the heart with severe isolated LVNC (D). The endocardial surface of the specimens (A) and (B) is smooth. (C) demonstrates the two-layered structured of the myocardial wall with an epicardial compacted (C) and a more than twice as thick endocardial, non-compacted (NC) layer. Note marked fibroelastosis of the LV in (C and D). (A and C) Courtesy of Dr P. Vogt, University Hospital, Zurich. (B and D) Courtesy of Dr J. Schneider, University Hospital, Zurich. LV, left ventricle. RV, right ventricle.
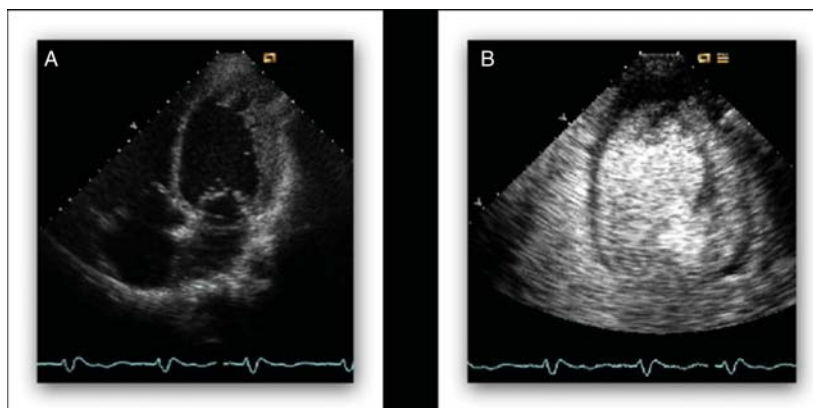

Figure 4 Apical four-chamber view in a patient with isolated LVNC: (A) without contrast; (B) with contrast showing the intertrabecular recesses of the endocardial non-compacted layer.

compaction with values for sensitivity and specificity, and positive and negative predictions of 86, 99, 75, and 99%, respectively.

Jacquier et al.[27] took a different approach to characterize the LV myocardium. Total LV mass and trabeculated LV mass were measured in control subjects, in patients with dilated cardiomyopathy, hypertrophic cardiomyopathy, and LVNC. The percentage of trabeculated LV mass was three times higher in patients with LVNC than in those with dilated and hypertrophic cardiomyopathy

or in controls. Interestingly, the LV compacted mass was the same in patients with dilated cardiomyopathy and LV non-compaction and in healthy controls.[27]

How to diagnose non-compaction of the left ventricular myocardium?

Echocardiography and cardiac MRI studies confirm that the degree of trabeculated LV myocardium is far more frequent than previously thought; this supports the concept of a continuous trait between normal and pathological appearance of the myocardium.[6,19,20,26–28] We require the presence of a thickened myocardial wall with the non-compacted layer being at least twice as thick as the compacted layer (Table 1). Speckle tracking is helpful to describe abnormal LV body rotation/twist.[25] Echocardiography, however, is investigator dependent and has limitations and pitfalls. As the quality of the echocardiographic images improves and more details of the myocardial structure can be imaged, we hypothesize that multimodality imaging, including echocardiography and cardiac MRI, is required to confirm or to exclude LVNC (Table 2). Diagnosis by echocardiography and cardiac MRI must be concordant. This concept may help not to overdiagnose LVNC, but it has to be validated.

Table 2 Diagnostic assessment and therapeutic strategies

Diagnostic assessment	
Doppler echocardiography	Validated echocardiographic criteria (Table 1)
	Speckle tracking (LV solid body rotation/twist)
Cardiac MRI	Ratio between non-compacted and compacted layer >2.3
	Trabeculated LV mass >20% of the global LV mass
Genetic testing	
Neurological assessment	If suspicion of skeletal/mitochondrial myopathy
Family screening (fist-degree relatives)	Doppler echocardiography, (genetic assessment as appropriate)
Electrophysiology study	Symptomatic arrhythmias, syncope
Therapeutic strategies	
Normal LV size/systolic function	Regular follow-up (every 2 years)
Heart failure therapy	As per guidelines for heart failure
Anticoagulation	LVEF <40%
ICD	Secondary prevention/(primary prevention?)
Biventricular pacing	Advanced heart failure/LVEF <35%/ dyssynchrony (as per guidelines)

ICD, implantable cardioverter/defibrillator; EF, ejection fraction; LV, left ventricular; MRI, magnetic resonance imaging.

Differential diagnosis

The differential diagnosis can be challenging and includes apical form of hypertrophic cardiomyopathy, a combination of both apical hypertrophic cardiomyopathy and LVNC, hypertensive cardiomyopathy, endocardial fibroelastosis, abnormal chords, apical thrombus, or tumours among others (Figure 3). Differential diagnosis between dilated cardiomyopathy and LVNC can be a challenge in dilated ventricles. The diagnostic criteria for LVNC, however, are still fulfilled in a dilated LV if the diagnosis is LVNC; this is evident in patients with LVNC during follow-up in whom the first examination revealed normal size and systolic function of the LV.

Genetics of non-compaction of the left ventricular myocardium

Non-compaction of the left ventricular myocardium is a genetically heterogeneous disorder with a sporadic and familial form.[11,29,30] It can be linked to mutations in mitochondrial, cytoskeletal, Z-line, and sarcomeric proteins.[31] Autosomal dominant inheritance seems to be more common than X-linked inheritance.[32–34] Familial recurrence widely varies between 18 and 50% of the cases but there are limitations due to the retrospective study design.[11,30,33,35] Autosomal recessive inheritance was also observed.[36] This high rate of transmission emphasizes the importance of detailed pedigree analysis and justifies screening of all first-degree family members of affected individuals.

Point mutations in *G4.5*/α-dystrobrevin/ *ZASP*

Mutations in the *G4.5* gene, which maps to chromosome Xq28, result in a wide spectrum of severe infantile X-linked cardiomyopathic phenotypes, including Barth syndrome with dilated cardiomyopathy and LVNC in a paediatric population.[32,37,38] However, *G4.5* mutations were not found in our adult population with the autosomal dominant mode of transmission, which suggests that non-compaction presenting in adulthood may be genetically distinct from paediatric cases where the disorder is predominantly X-linked and mutations in *G4.5* prevail.[32,34,37,38]

Mutations in α-dystrobrevin in a family with LVNC and mutations in *ZASP*, a gene encoding for the Z-band alternatively spliced PDZ motif-containing protein, a component of the Z-line in skeletal and cardiac muscle, were described in patients with LVNC and LV dysfunction.[38,39] In contrast, no mutations in *G4.5* and α-dystrobrevin were identified in 47 of 48 patients with isolated LVNC.[40]

Non-compaction associated with chromosomal regions

Loci for LVNC were also described on chromosome 1, 5, and 11 but the specific genes have yet to be identified.[41,42]

Mutations in sarcomere protein genes

Non-compaction of the left ventricular myocardium seems to be within the diverse spectrum of cardiac morphologies triggered

by sarcomere protein gene defects and there seems to be a shared molecular aetiology of different cardiomyopathic phenotypes. Indeed, patients with isolated LVNC, hypertrophic, and dilated cardiomyopathy share common mutations in sarcomere protein genes.[43–45] A novel missense mutation, pE96K, in the cardiac troponin T gene (TTNT2) was described in a family with LVNC.[46] To investigate the pathophysiological implications of the mutations, the researchers generated transgenic mice expressing human wild-type or human troponin T harbouring the pE96K mutation (mut cTNT). Interestingly, mut cTNT mice displayed an impaired LV function and induction of marker genes of heart failure; remarkably, LVNC was not observed. This observation supports the hypothesis that a LVNC phenotype *per se* is not a prerequisite for the deterioration of contractile dysfunction and the development of cardiomyopathy in this specific mutation. In addition, the primary defect in LVNC appears to be cardiomyocyte-autonomous, similar to other genetic cardiomyopathies (e.g. hypertrophic or dilated cardiomyopathy).[46]

Non-compaction: a distinct cardiomyopathy?

The morphological appearance of the myocardium in patients with LVNC is characteristic and suggests a distinct cardiomyopathy.[6,13,47] Genetic testing, however, indicates the lack of a specific genotype–phenotype association and suggests important genetic heterogeneity. Indeed, the same mutations can cause different cardiomyopathic phenotypes: non-compaction can be found with metabolic diseases and genetic syndromes (e.g. Noonan syndrome, Barth syndrome) and is associated with different CHDs (e.g. Ebstein anomaly, pulmonary atresia, aortic stenosis, ventricular septal defect) although some patients with CHD may not represent the classical morphological feature of non-compacted myocardium.[6,41,48]

Despite major advances in the genetic background and understanding of the aetiology of cardiomyopathies, there is a poor understanding between genotype–phenotype correlation and many questions regarding phenotypic expression of the same gene defect are unanswered, yet. There is the reality that a pathogenetic mutation in the same gene results in a different trabecular remodelling or maladaptive remodelling response of the embryonic myocardium, which can cause different phenotypes/cardiomyopathies. This raises the question that at least for certain mutations, hypertrophic, restrictive, dilated cardiomyopathies, and non-compaction are not clearly distinct clinical and pathophysiological entities.[31,49] Is there a continuum from hypertrophic/dilated cardiomyopathy and non-compaction? Indeed, Luedde *et al.*[46] challenged the notion that LVNC phenotype is required for the development of cardiomyopathy. Non-compaction of the left ventricular myocardium may be a secondary consequence of a genetic alteration, which may be well compensated or present with heart failure. The marked variations of phenotypes observed in families indicate that additional, yet unknown modifiers may determine the clinical and pathophysiological appearance of LVNC; the extent of LVNC itself may have a disease-modifying

role.[28,44,46] This hypothesis is further supported by the description of seven different phenotypes of LVNC with different outcome.[50]

The genetic heterogeneity of LVNC, the morphological appearance of LVNC in different metabolic diseases and genetic syndromes, the genetic overlap of different myocardial phenotypes/cardiomyopathies, and the observations from Luedde *et al.*,[46] do not allow us to label LVNC as a distinct cardiomyopathy or a primary myocardial disease.

Multimodality imaging, systematic and comprehensive pedigree analysis, family screening, and genetic testing are required to further characterize the morphological expression and myocardial phenotype of genetic mutations and different underlying diseases, and to better understand the genotype–phenotype correlation. This implies that patients with LVNC and their first degree relatives undergo a comprehensive diagnostic assessment by a multidisciplinary team, including cardiologists and geneticists (*Table 2*).

Epidemiology

The reported prevalence varies considerably and the true prevalence of LVNC is unknown. Once considered a rare form of cardiomyopathy, LVNC is getting increasingly recognized. Major limitations are the retrospective design of most or all of the studies and the different inclusion criteria with a considerable selection bias. Most studies report the prevalence of patients referred to an echocardiography laboratory at a tertiary care centre for the evaluation of symptoms, abnormal clinical findings, or family screening. The prevalence of LVNC referred to echocardiography laboratories is reported to be between 0.014 and 1.3%.[30,51–54]

In a population-based, retrospective cohort study of primary cardiomyopathies in Australian children, isolated LVNC accounted for 9.2% of all cases, identified as the third most frequent cardiomyopathy after dilated and hypertrophic cardiomyopathies,[55] and this proportion was very similar to that calculated from the Texas Children's Hospital echocardiography database (9.5%).[52] Among 960 patients seen in a designated heart failure clinic, heart failure due to ischaemic heart disease, idiopathic dilated cardiomyopathy, and valvular disease was most common, only a minority of this heart failure population (3%) had isolated LVNC.[56]

Clinical presentation and outcome

Initial presentation

The spectrum of the initial presentation is wide and non-specific and depends on many factors: whether LVNC occurs in isolation or in association with a syndrome, CHD, or other diseases, whether LVNC is studied in a paediatric or adult population or whether LVNC is diagnosed in asymptomatic patients during family screening. Clinical symptoms at initial presentation are mainly the result of systolic/diastolic ventricular dysfunction and include non-specific chest pain/discomfort, heart failure symptoms, or arrhythmias.[11,30,35,51–54,57–59]

The electrocardiographic findings are non-specific. In a comprehensive analysis, intraventricular conduction delay (left bundle branch block!), voltage signs of LV hypertrophy, and repolarization

abnormalities were most common, but no electrocardiographic pattern was specific for LVNC at the first presentation.[60] An entirely normal electrocardiogram was present in 13% of the population ($n = 78$); these patients were significantly younger, had less severe structural cardiac abnormalities (except for non-compaction), and were less likely to present with signs of heart failure; some patients were asymptomatic family members of affected patients.[60] Whether these findings have prognostic implications needs to be investigated in long-term controlled studies.

Complications and outcome

The classical triad of heart failure, ventricular arrhythmias, and systemic embolic events constitute typical complications in patients with a more advanced disease (*Table 3*). The outcome also depends on the clinical phenotype.[50] Like in most cardiovascular diseases, we shall never know the natural history of LVNC as the natural history in most patients is modified by interventions, such as heart failure therapy and device implantation. Importantly, outcomes, including morbidity and mortality, vary among the different reports and are not comparable because of the retrospective study design without standardized interventions, selection bias, different patient populations and disease severity among others.[11,30,35,51–54,57–59] Heart failure occurs frequently (>50% of patients) and ventricular tachycardias, cardiovascular deaths, and sudden cardiac deaths are reported by most investigators (*Table 3*); they are less frequently observed in more recent studies[52–54,57–59] than in the initial publications.[11,30] Adverse outcomes have been overestimated in earlier reports because of negative selection bias with inclusion of primarily symptomatic patients referred to a tertiary care centre. In addition, earlier detection due to improvements in recognition, imaging technology, and modern heart failure therapy might have also modified the 'unnatural' history of LVNC in the more recent cohorts with a more favourable outcome than previously reported.[30,54,58,59] Short- and mid-term outcome data in these studies are consistent with that of our experiences in asymptomatic patients (unpublished data).

Mortality did not differ significantly between patients with isolated LVNC and control patients with dilated cardiomyopathy (3-year survival of 85 vs. 83%).[53] This supports the hypothesis that LV dysfunction rather than the phenotype itself (LVNC) poses the patients at risk for morbidity and mortality.[46,53]

Prevention of sudden cardiac death

Life-threatening ventricular tachycardias are reported in 20% or more of the patients and remain a concern for sudden cardiac death in mostly adults with advanced disease (*Table 3*). Patients with LVNC have an arrhythmogenic substrate consisting of subendocardial fibrosis probably due to microcirculatory dysfunction that is not confined to the non-compacted segments.[16,30,61] In a cohort of 12 adults with isolated LVNC and a median follow-up of 36 months who were treated with an implantable cardioverter/defibrillator (ICD) for secondary prevention ($n = 8$), appropriate ICD therapy occurred in 50% of the cases.[62] In contrast, an appropriate ICD therapy was only documented in 25% of the cases with primary prevention. The fact that supraventricular arrhythmias were documented in two-thirds of the patients with an ICD does have important implications regarding the

management strategy and selection of devices with reliable detection enhancements when ICD implantation is considered.[62]

Predictors of outcome

Identification of strong predictors of outcome is important to select effective management strategies. Unfortunately, the different studies are not comparable: the number of patients included in the different studies is small and the population is heterogeneous (paediatric vs. adult population; LVNC in isolation or associated with syndromes, CHD and other disorders) so that the identification of powerful predictors is difficult or impossible. Clinical and echocardiographic predictors are summarized in *Table 4*.[24,30,51,57,59,63]

Management

There is no therapy specific for patients with LVNC. Despite limitations of the published risk factors for adverse outcomes, they are helpful to guide treatment, including medical therapy and device therapy (*Table 4*). Although so far unproven by prospective studies, timely institution of evidence-based standard heart failure treatment in asymptomatic patients with worsening LV systolic function may prevent the occurrence of complications. We apply the current guidelines for the management of heart failure to our patients with LVNC as LV dysfunction rather than the phenotype might pose the patients at risk.[53,64,65]

Anticoagulation?

Prevention of embolic complications is an important management goal and remains a matter of debate in these patients. Biased by early reports with a high rate of embolic events, we were more aggressive to administer anticoagulants independent of ventricular systolic function.[30] As we have never seen thrombo-embolic complications in a patient in sinus rhythm and with normal systolic function, and as the knowledge about the risk of embolic complications has improved in this population, we are less rigorous to initiate anticoagulation therapy. Because deep intertrabecular recesses with slow/sluggish blood flow aggravate the risk of thrombus formation, we recommend anticoagulation (target INR 2.0–3.0) in patients with impaired systolic function (LV ejection fraction <40%), being aware of the absence of any robust data to support this approach. Anticoagulation therapy, however, must be targeted to the individual patient after careful assessment of the benefit and risks.

ICD/biventricular pacing?

As long as there are no robust data whether the current guidelines for device therapy, including ICD and biventricular pacing, apply to patients with LVNC, current practice guidelines are helpful for management strategies.[66,67] The number of patients included in a retrospective study is too small to elaborate hypotheses regarding clinical parameters of patients with isolated LVNC that predict risk for sudden death.[62] It is our practice to perform an EP study in all patients with LVNC and symptomatic arrhythmias or syncope to assess whether ventricular or supraventricular arrhythmias are inducible. In the present state of knowledge, an ICD should be implanted in patients with LVNC presenting with syncope, symptomatic ventricular arrhythmias or with severely impaired LV systolic

Table 3 Clinical characteristics of left ventricular non-compaction

	Chin[11]	Ichida[35]	Oechslin[30]	Pignatelli[52]	Wald[57]	Murphy[58]	Lofiego[59]	Aras[51]	Lilje[54]	Stanton[53]
Isolated form	Yes	Yes	Yes	No[a]	Yes	Yes	Yes	Yes	No[a]	Yes
Number of patients	8	27	34	36	22	45	65	67	66	30
Males, %	63	56	74	56	41	62		66	52	60
Population	Paediatric	Paediatric	Adult	Paediatric	Paediatric	Adult	Adult	Adult	Paediatric	Adult
Median age at diagnosis (range), years	7.3 (11 months–22.5 years)	5 (1 week–15 years)	40 (16–71)	90 days (1 day–17 years)	Mean 3.9 (0–16)	Mean 37 (13–83)	Mean 45 ± 16	41 ± 18 (16–75)	4 (0–21)	Mean 39 ± 19.5 (16–83)
Follow-up (median), years	≤5	≤17 (6)	≤11 (3)	≤12 (3.2)	≤16 (3)	<15 (2.7)	≤16 (21)	≤4 (mean 2.5)	≤4.3 (1)	Mean 2.5 ± 1.2
Familial occurrence, %	50	44	18	19[b]	18[b]	51[c]	31	33	—	—
Localization of non-compacted myocardium (%)										
Apex	Most prominent	100	94	—	Most common	—	Most common	100	—	Most common
Mid-ventricular inferior wall		70	94	—	Most common	—		~90	—	Most common
Mid-ventricular lateral wall		41	100	—	Most common	—		>90	—	Most common
Complications (%)										
Heart failure	63	30	68	>50[d]	91	67	34	34	68	—
VT	38	0	41	3	23	20[e]	6	36	20	27[e]
Systemic embolic events	38	0	21	0	0	4	5	9	14	0
Cardiovascular death (SD)	38 (13)	7 (0)	35 (18)	14 (3)	14 (5)	2 (2)	10 (5)	15 (9)	7 (0)	10
Heart Tx	0	4[f]	12	11	9	0	14	0	0	0

Heart Tx, heart transplantation; SD, sudden death; VT, ventricular tachycardia.
[a]Associated congenital cardiac anomalies included ventricular septal defect, pulmonary valvular stenosis, Ebstein anomaly, left ventricular outflow tract obstruction/hypoplastic left heart syndrome.
[b]Positive family history for cardiomyopathy (dilated cardiomyopathy, hypertrophic cardiomyopathy, and non-compaction).
[c]Family history of dilated cardiomyopathy and left ventricular non-compaction.
[d]Patients with LV ejection fraction <50%.
[e]Non-sustained VT on Holter-ECG.
[f]One patient was a candidate for heart transplantation.

Table 4   Predictors of death or heart transplantation

Clinical predictors[30,51,59]

   Age at initial presentation

   Functional capacity, NYHA class III–IV

   Sustained ventricular arrhythmias

Echocardiographic parameters[24,30,51,57,63]

   Ratio of non-compacted to compacted layers

   Number of affected segments

   LV end-diastolic diameter

   Abnormal lateral mitral tissue Doppler Ea velocity

function (LVEF <35%). Atrial flutter/atrial fibrillation are common and intermittent supraventricular arrhythmias were observed in 66% of patients on interrogation of the device; devices with reliable detection and therapy enhancements should be primarily considered in these patients.[62]

Summary

Knowledge and understanding about aetiology, embryogenesis of the myocardium, genetic background, diagnosis and outcome of LVNC have steadily improved. Non-compaction of the left ventricular myocardium best appreciates evolutionary background and is the appropriate term to describe the distinct morphological appearance of a thickened, two-layered myocardium with an epicardial compacted and a much thicker endocardial non-compacted layer.

Non-compaction of the left ventricular myocardium with poor genotype–phenotype correlation seems to be a distinct myocardial phenotype with genetic heterogeneity: it does not seem to be a distinct cardiomyopathy, but rather a morphological expression of different diseases. Non-compaction of the left ventricular myocardium is within a diverse spectrum of myocardial morphologies/cardiomyopathies triggered by gene defects/mutations: the causal role of LVNC in the pathogenesis of a distinct cardiomyopathy is questionable. Whether LVNC in isolation or in association with other pathologies (e.g. CHD, genetic syndromes) has a similar or completely different molecular/genetic basis, pathobiology, and natural course, and whether different mechanisms, environmental factors, yet unknown modifiers, and pathophysiological mechanisms account for different entities of LVNC despite a characteristic morphological appearance, remain a matter of further research.

Echocardiographers and clinicians have to be cautioned not to overdiagnose LVNC. Non-compaction of the left ventricular myocardium may reflect a morphological trait and there is a grey zone between a normal variant and a pathological myocardial structure with clinical relevance. A comprehensive diagnostic assessment, including multimodality imaging, a systematic screening of first-degree relatives, and a comprehensive clinical, and genetic assessment by a multidisciplinary team may provide the information to determine whether LVNC is just a morphological expression or phenotypic variant of other cardiomyopathies of a primary genetic disorder.

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