Non-compaction of the myocardium is gaining prominence as a rare, distinct cardiomyopathy characterised by the presence of numerous, excessive prominent trabeculations and deep intertrabecular recesses which communicate with the left ventricular cavity. Two decades of research have identified a new disease – firstly, its morphologic and clinical characteristics were described on clinical observational skills and secondly, its genetic background could be elucidated due to modern technologies.

**Classification of Cardiomyopathies**

As classification serves to bridge the gap between ignorance and knowledge, the 1995 World Health Organization (WHO)/International Society and Federation of Cardiology Task Force on the definition and classification of cardiomyopathies defined cardiomyopathies as diseases of the myocardium associated with cardiac dysfunction. The cardiomyopathies were classified by the dominant pathophysiology or, if possible, by aetiological/pathogenetic factors; four categories of distinct and one category of unclassified cardiomyopathies were classified (see Table 1). Unclassified cardiomyopathies include cases that do not fit into any group (e.g. fibroelastosis, systolic dysfunction with minimal dilatation and mitochondrial involvement, etc.). Left ventricular non-compaction (LVNC) has not yet been classified as a distinct entity but rather belongs to the group of unclassified cardiomyopathies, although it clearly departs in its morphology from classified cardiomyopathies.

**Embryology**

In higher vertebrates, the heart develops from a simple tube into a complex organ with four chambers. The development of the myocardial architecture itself passes through several steps. During early embryogenesis, trabeculations emerge in the luminal myocardial layers of the ventricles enabling the myocardium to increase its mass in the absence of epicardial coronary circulation. Trabeculations effectively increase surface area – this developmental step serves to provide adequate oxygenation from the ventricular cavity. With the completion of the ventricular septation (eight weeks in human embryos), the trabeculae start to solidify at their basal area and ends at the apex, adding substantially to the thickness of the epicardial compact layer. This compaction process, coinciding with the invasion of the coronary arteries into the myocardium from the epicardium, is more pronounced in the left ventricle (LV) than in the right ventricle (RV) and results in a more trabeculated endomyocardial surface of the RV. LVNC is supposed to be the result of an arrest or failure of the compaction process of the myocardial trabeculae during endomyocardial embryogenesis; thus, myocardial non-compaction best characterises the basic nature of this disorder and respects its embryogenesis, although in the past other terms (e.g., spongy myocardium) were used.

Non-compacted myocardium was previously described as persistent intramyocardial sinusoids; however, the latter are associated with congenital...
obstructive lesions of the left or right ventricular outflow tract, such as pulmonary atresia with intact ventricular septum. In these patients, regression of the embryogenic sinusoids is impaired during ontogenesis by ventricular pressure overload, which results in deep recesses communicating with both the ventricular cavity and the coronary artery system.

First Descriptions of a New Disease

The first case report about the persistence of left ventricular myocardial sinusoids as an isolated anomaly was published in 1984. In 1985, the description of both the angiographic and the echocardiographic characteristic features published in a German radiology journal was the first important step in the research for identification and diagnosis of a new disease. A year later, Jenni’s group reported a third case of a 21-year-old male patient with progressive heart failure (HF) and cardiomyopathy of obscure aetiology. Two-dimensional (2-D) echocardiography identified a markedly thickened myocardium with prominent trabeculations and intertrabecular recesses (channel-like structures) in the apex and at the posterolateral wall of the severely hypokinet LV. The same structures were visualised by left ventricular angiography and resembled a honeycomb-like inner contour in both ventricles. In this case, autopsy for the first time confirmed the echocardiographic and angiocardio graphic findings.

Diagnostic Criteria for Ventricular Non-compaction of the Myocardium

Meticulous observation and description of the morphologic characteristics allowed establishment of clear-cut echocardiographic diagnostic criteria for LVNC (see Figure 1):

- Co-existing cardiac anomalies have to be absent (by definition).
- The myocardial wall is excessively thickened and presents with a two layered structure – a thin, compacted epicardial layer and a much thicker, non-compacted endocardial layer. The endocardial layer consists of prominent trabeculations and deep intertrabecular spaces, which are in continuity with the left ventricular cavity. The extent of non-compaction is quantified at the site of maximal thickness. For best visual differentiation of the two layers, the thickness of the endocardial and epicardial layers is measured in the parasternal short axis view at end-systole (see Figure 1).
- The non-compacted layer has to be at least twice as thick as the compacted epicardial band.

Table 1: Classification of Cardiomyopathies

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<tr>
<td>Dilated cardiomyopathy</td>
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<td>Hypertrophic cardiomyopathy</td>
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<td>Restrictive cardiomyopathy</td>
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<td>Arrhythmogenic right ventricular cardiomyopathy</td>
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<td>Unclassified cardiomyopathies</td>
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<td>Specific cardiomyopathies</td>
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Figure 1: Non-compaction of the Left Ventricular Myocardium

Parasternal short axis view at end-systole and at midventricular level. Markedly thickened two-layered myocardial wall: a thin, compacted epicardial layer (solid arrowhead) and a non-compacted endocardial layer (dashed arrowhead) consisting of prominent trabeculations and intertrabecular recesses. The non-compacted layer is more than twice as thick as the compacted layer. LV=left ventricle.

The predominantly affected segments (more than 80%) are apical and midventricular of both the inferior and lateral wall.

The deep intertrabecular spaces are filled with direct blood flow from the left ventricular cavity (visualised by colour Doppler imaging). In contrast to myocardial sinusoids, the intertrabecular spaces do not communicate with the coronary circulation.

The LV is divided into nine segments to describe the location of the affected segments — one apical segment, four midventricular and four basal segments (inferior, lateral, anterior and septal segments). Diagnosis of right ventricular non-compaction by echocardiography is not attempted anymore because of the heavily trabeculated right ventricular apex and the difficult differentiation between normal variants and pathologic patterns.

In the past, the diagnosis of this rare cardiomyopathy was frequently missed or delayed due to both the poor awareness of this distinct cardiomyopathy and the lack of clear diagnostic criteria. Secondly, the similarities with well-known cardiomyopathies and with more frequently diagnosed conditions led to misdiagnoses (dilated or hypertrophic cardiomyopathy, heart tumour and thrombus formation in the ventricle). As clear-cut diagnostic criteria now exist, echocardiography has become the method of choice for diagnosing non-compaction of the myocardium. These diagnostic criteria, based only on morphology, may also apply to magnetic resonance imaging (MRI).

Clinical Characteristics

The first 10-year experience of 17 adults with isolated non-compaction of the myocardium was reported in 1996. In the past, the correct diagnosis was frequently missed or delayed for several reasons as previously discussed. HF, ventricular arrhythmias and a history of embolic events were frequent clinical symptoms and findings. In a more recent publication, the long-term follow-up of 34 adults with isolated LVNC was reported. The clinical characteristics and outcome could be better characterised in this largest adult population with isolated non-compaction of the LV.

Morbidity and mortality are high in symptomatic teenagers and adults. Duration of follow-up was 44 ± 39 months (range 0.7–139) and mean age at the time of last follow-up (or before death or heart transplantation) was 46 ± 18 years (range 16–71 years). Major complications are presented in Table 2. HF (53%) requiring hospital admission was the most frequent complication, followed by ventricular tachycardia (41%) and thromboembolic events (24%). Twelve patients (35%) died at 42 ± 40 months (range 0.7–105) after diagnosis and four (12%) had undergone heart transplantation because of end-stage HF (see Table 2). Sudden cardiac death (50%) was the main cause of mortality. The probability of event-free survival (combined endpoint of death or heart transplantation) was 58% at five years. These observations are based mainly on symptomatic patients referred to a tertiary care centre (selection and referral bias).

Due to the risk of familial recurrence, first-degree relatives are screened by echocardiography to identify asymptomatic patients. As a consequence, LVNC is diagnosed in an increasing number of asymptomatic, ‘healthy’ individuals. Their long-term course is yet unknown and the long-term outcome will be better than previously reported. Currently, the authors’ cohort of patients with non-compaction of the left ventricular myocardium consists of more than 90.

Coronary Microcirculatory Dysfunction

After characterisation of the morphologic characteristics and the echocardiographic diagnostic criteria, as well as the clinical presentation and outcome of mainly symptomatic patients with LVNC, it was pertinent to analyse whether coronary microcirculatory dysfunction might be associated with this distinct cardiomyopathy and whether this might contribute to myocardial dysfunction. Quantitative evaluation of regional myocardial perfusion and coronary flow reserve was performed using positron emission tomography (PET) and N-ammonia. Reduced coronary flow reserve is not confined to the non-compacted segments, but extends to most segments with wall motion abnormalities; thus, microcirculatory dysfunction may cause myocardial ischaemia and progressive
ventricular dilatation.16 This observation is consistent with the predominant location of necrosis and fibrosis in the subendocardial, non-compacted layer, but not in the epicardial, compacted layer.13

**Genetics**

Familial recurrence is known and is more frequently encountered in this adult population than has been reported in paediatric populations.3,13,17 Only genetic analysis allows better understanding of this unique cardiomyopathy. In collaboration with the Max-Delbrueck-Centre for Molecular Medicine in Berlin (Dr Ludwig Thierfelder and Dr Sabine Sasse-Klaassen), the authors' pedigree analyses of adults with LVNC suggest an autosomal dominant mode of transmission based on the observation that:

- approximately one-half of descendants from LVNC patients inherit the condition;
- several cases of male-to-male transmission were observed; and
- the disorder occurs in females.18

There is evidence that LVNC is a genetically heterogeneous disorder. A point mutation in the G4.5 gene has been identified in a family with severe infantile X-linked isolated LVNC.19 Mutations in the G4.5 gene were also described as causing Barth syndrome and other forms of infantile dilated cardiomyopathies, suggesting an allelism for these disorders;20,21 however, in the adult population with LVNC, the cardiomyopathy is not caused by mutations in the G4.5 gene.18,19 Adult forms therefore seem to be genetically distinct from paediatric cases where the disorder is predominantly X-linked and mutations in G4.5 prevail.22

With a genome-wide linkage analysis in a family with autosomal dominant LVNC, a locus containing the LVNC disease gene was identified to map to chromosome 11p15.23 On-going research aims to identify the disease gene that will allow genetic screening and provide fundamental insight into the understanding of myocardial morphogenesis in general and the development of this cardiomyopathy in particular.

**Summary**

Two decades of research including clinical observation, meticulous description of the morphology and, finally, modern technologies, i.e. genetic analyses, have resulted in the discovery of LVNC to be a distinct cardiomyopathy. As physicians are becoming more aware of this rare disorder, previously missed patients may be diagnosed and the true prevalence and natural course of LVNC will be better elucidated and understood in the future.