

## Review

# Non-compaction of the ventricular myocardium: a cardiomyopathy in search of a pathoanatomical definition

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**Summary.** Ventricular non-compaction is a rare cardiomyopathy characterized by numerous, excessively prominent ventricular trabeculations and deep intertrabecular recesses communicating with the ventricular cavity. The lesion is postulated to result from an intrauterine developmental arrest that stops compaction of the myocardial fiber meshwork. This cardiomyopathy affects the left ventricle, with or without concomitant right ventricular involvement. The disease is now seen with increasing frequency and it is clinically diagnosed by imaging techniques such as echocardiography or cardiac magnetic resonance. Current diagnostic criteria are considered too sensitive, particularly in black individuals. Therefore, this condition has generated considerable controversy and demands a new definition. Non-compaction cardiomyopathy shows variability of hereditary patterns, genetic heterogeneity, diversity in associated phenotypes and a wide spectrum of clinical presentation and pathophysiological findings. Non-compaction can be simply a variant of normal maturation of the ventricular myocardium with only the most severe forms producing a distinct clinical-pathological entity. Ventricular non-compaction most probably is a secondary consequence of an underlying molecular derangement produced by a pathogenetic mutation. It is likely that surgical pathologists will find this entity more frequently due to involvement in transplantation teams.

**Key words:** Non-compaction cardiomyopathy, Left ventricular non-compaction, Congenital heart disease, Heart failure, Cardiac transplantation

## Introduction

Ventricular non-compaction is a rare form of cardiomyopathy characterized by an excessive prominent trabecular meshwork and deep intertrabecular recesses communicating with the ventricular cavity but not the coronary circulation (Freedom et al., 2005). The prevalence in adults is less than 0.3% (Ritter et al., 1997; Oechslin et al., 2000). This lesion uniformly affects the left ventricle, with or without concomitant right ventricular involvement although distinguishing this from normal anatomy is more difficult (Varnava, 2001). Ventricular non-compaction may be associated with structural defects or may be isolated. In children, accompanying heart defects have been described in 14% of cases (Pignatelli et al., 2003) and classified as non-isolated cases. In adults the process is often limited to patients without associated cardiac defects. Therefore the isolated form is more common in adults.

Although this condition was brought to attention by Chin et al. (1990), Dusek et al. (1975) are credited with being the first to describe a series of cases of “spongy myocardium,” some of which now would be classified as non-compaction cardiomyopathy.

Different synonyms have been used for this abnormality including myocardial dysplasia (Allenby et al., 1988), spongy myocardium (Dusek et al., 1975; Steiner et al., 1996; Shah et al., 1998), ventricular non-compaction (Chin et al., 1990), myocardial dysgenesis (Amman and Sherman, 1992), ventricular hypertrabeculation (Stöllberger and Finsterer, 2004), and persistence of myocardial sinusoids (Engberding and Bender, 1984; Jenni et al., 1986).

Ventricular non-compaction was recognized as a separate form of cardiomyopathy and included as an unclassified cardiomyopathy according to the World Health Organization classification of cardiomyopathies

(Richardson et al., 1996). Ten years later a so-called contemporary classification of cardiomyopathies included left ventricular non-compaction among primary and genetic cardiomyopathies (Maron et al., 2006).

In recent years, the clinical interest in non-compaction of the ventricular myocardium has increased notably; however, the disease is still widely unknown, and knowledge about its specific characteristics is incomplete and sometimes confusing.

Pathological series are limited (Burke et al., 2005). On the other hand, the disease is now seen with increasing frequency and it is clinically diagnosed by imaging techniques such as echocardiography or cardiac magnetic resonance. Diagnosis has now moved from the autopsy room to the radiology service. The current improved quality of echocardiography and magnetic resonance equipments and the use of contrast media have allowed a better visualization of the heart. Current diagnostic criteria are considered too sensitive, particularly in black individuals and in elite, competitive sportsmen. Therefore, this condition has generated considerable controversy and demands a new definition with more restrictive diagnostic criteria to avoid false positive identifications (Anderson, 2008; Kohli et al., 2008; Monserrat Iglesias, 2008; Sen-Chowdhry and McKenna, 2008).

The aim of this article is to make a contribution of our experience and a review of the pathological literature in an attempt to better characterize the disease as a morphological entity.

### Morphogenesis of the ventricular non-compaction

During the early stages of development, the myocardium of the rapidly growing heart forms a loose network of interwoven fibers or trabeculae separated by deep recesses that link the myocardium with the ventricular cavity. The trabeculae are restricted to the free wall and the lower part of the ventricular septum, sparing the regions of the atrioventricular canal and outflow tract septum. The formation of these trabeculations serves to increase the myocardial surface area and facilitates myocardial nourishment by exchange diffusion from the cardiac lumen before the coronary circulation is established (Bartram et al., 2007). During the fifth to eighth week of fetal life, the development of the coronary vasculature is established. Once this vasculature is completed, the nutrient supply through the active circulation from the subepicardium is paralleled by gradual compaction of the myocardial trabeculae. Thus, there is a decrease of the inner, trabeculated myocardial layer and an increase in thickness of the outer, compact myocardial layer. Following the direction of coronary arterial development, this process advances from the epicardium toward the endocardium and from the base of the heart to the apex. The intertrabecular spaces transform into capillaries within the coronary circulation. The trabecular compaction is fairly rapid, occurring between the 10th and 12th week (Sedmera and

McQuinn, 2008). In the mature, normal heart a few residual trabeculations remain, more in the right ventricular myocardium.

Based on embryologic data, myocardial non-compaction is a congenital malformation resulting in a failure of normal embryonic myocardial maturation. The extension of the myocardial non-compaction within the ventricle is determined by the time of arrest of this process (Bartram et al., 2007). Since the compaction process concludes in the ventricular apex, this segment is always involved in non-compaction cardiomyopathy. Some authors have used the designation of myocardial sinusoids to refer to the deep intertrabecular recesses, but this is incorrect as these recesses do not communicate with the subepicardial coronary arteries (Freedom et al., 2005).

Yet other authors consider non-compaction cardiomyopathy a condition acquired postnatally, at least in some patients. This cardiomyopathy would thus be the result of processes such as dissection of the myocardium, frustrated myocardial hypertrophy, myocardial tearing caused by dilation, a metabolic defect, or compensatory hypervascularization (Stöllberger and Finsterer, 2004). However, there is much evidence to support the concept that non-compaction represents a failure to resorb the trabeculated part of the ventricular wall during normal embryological development.

### Diagnostic criteria using imaging techniques

Three echocardiographic definitions have been used for the diagnosis of ventricular non-compaction.

Chin et al. (1990) defined this cardiomyopathy by a ratio of  $X/Y \leq 0.5$  (where  $X$ =distance from the epicardial surface to the trough of the trabecular recess; and  $Y$ =distance from the epicardial surface to the peak of the trabeculation). These criteria focus on trabeculae at the left ventricle apex and left-ventricular free-wall thickness at end-diastole.

Jenni et al. (2001) established the following four criteria: (i) a two-layer structure of the myocardium, with a thin compacted layer (C) and a thick non-compacted layer (N) measured in end systole. The cardiomyopathy is defined by a ratio  $N/C \geq 2$  in adults and at least 1.4 in children; (ii) the absence of co-existing cardiac structural abnormalities; (iii) numerous, excessively prominent trabeculations and deep intertrabecular recesses; and (iv) recesses supplied by intraventricular blood on colour Doppler.

Stöllberger et al. (2002) proposed the following two criteria: (i) more than three trabeculations protruding from the left ventricular wall, apically to the papillary muscles, visible in a single image plane; and (ii) intertrabecular spaces perfused from the ventricular cavity, visualized on colour Doppler imaging.

However, prospective diagnosis by echocardiography is not always made (Stöllberger and Finsterer, 2006), and some authors are only able to make the

## Non-compaction cardiomyopathy

diagnosis using cardiac magnetic resonance imaging (Ivan et al., 2005).

Biagini et al. (2006), reported that isolated ventricular non-compaction can co-exist with restrictive, hypertrophic and dilated forms of cardiomyopathy. They concluded that taking into account the spectrum of cardiomyopathies that may accompany left ventricular non-compaction this process is a heterogeneous condition.

In an adult population referred to a heart failure clinic, Kohli et al. (2008) demonstrated an unexpectedly high percentage of patients fulfilling echocardiographic criteria for non-compaction cardiomyopathy. 24% of the study sample satisfied at least one set of the diagnostic criteria, while only 7% fulfilled all three, suggesting a poor correlation between the three echocardiographic definitions. On the other hand, 5 out of 60 (8%) healthy controls also satisfied one or more sets of criteria. Surprisingly, 4 of these 5 controls fulfilling these criteria were Afro-Caribbean. The authors concluded that current diagnostic criteria are too sensitive, particularly in black individuals. Therefore, a definition of the range of normal morphology and function in different racial groups is necessary.

On the other hand, Belanger et al. (2008) through a morphometric study demonstrated that patients with increasing severity of non-compaction had significantly decreased ejections fractions.

Figure 1 shows a two-dimensional echocardiogram of a patient with left ventricular non-compaction.

### Pathology

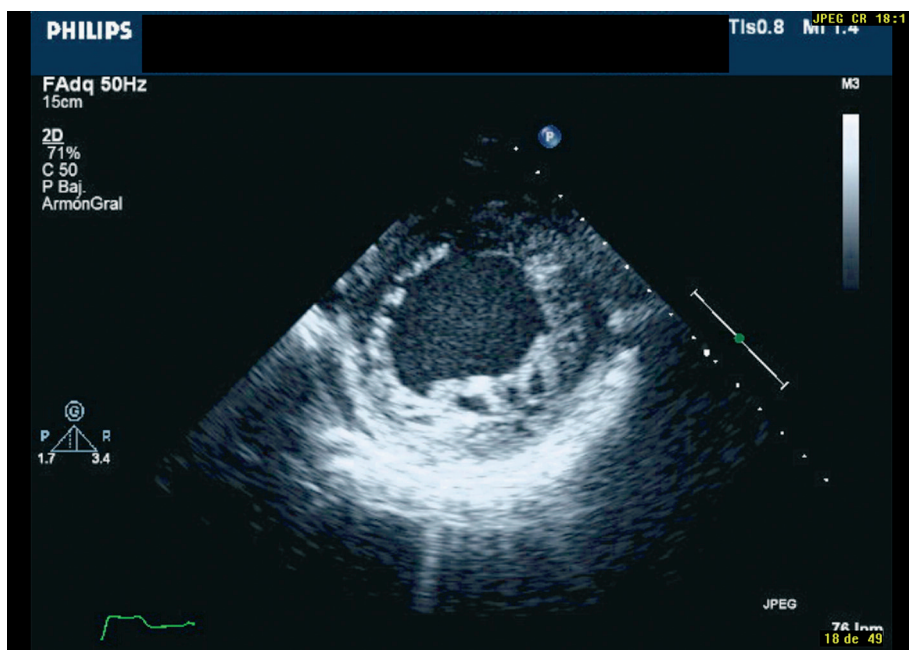
This review is based on five cases that met the

criteria for non-compaction cardiomyopathy. They were a newborn and four adults aged 57, 51, 45 and 21 at explant or death.

Grossly, one of the characteristics of the left ventricle wall in this cardiomyopathy is a two-layer myocardium, which is thin and compacted next to the epicardium, and thick non-compacted near the endocardium. The luminal surface of the left ventricular wall shows an excessive number of abnormally conspicuous trabeculations with deep intertrabecular recesses, most prominent in the mid-ventricular segment and toward the apex. On cut short-axis sections, the appearance varies from anastomosing trabeculae to a relatively smooth endocardial surface, with narrow openings of the recesses to the ventricular lumen (Burke et al., 2005).

The trabeculae can be broad and anastomosing, coarse, resembling multiple papillary muscles, smaller, forming interlacing muscle bundles, or compressed, with virtual recesses identified primarily histologically and relatively smooth endocardial surface (Fig. 2).

Microscopically, in the non-compaction layer there are anastomosing muscle bundles separated by irregularly branching recesses, often with a staghorn appearance, covered by endocardium. Some cases can show a pattern reminiscent of multiple small papillary muscles (Burke et al., 2005). In this non-compaction layer there is commonly thickening of the endocardium, endocardial fibrosis or fibroelastosis, microinfarcts with replacement fibrosis (Finsterer et al., 2002), and in some cases thrombi on the endocardial surface. Myocytes may show disorganized fascicles with focal hypertrophy and nucleomegaly. Subendocardial cells usually display perinuclear or extensive central clearing (Bleyle et al.,



**Fig. 1.** Two-dimensional echocardiogram of a non compacted left ventricle demonstrating extended and prominent trabeculations and deep intertrabecular recesses in a 21-year-old male. Two-layered appearance of the myocardium in a short view of the left ventricle. Courtesy of Dr. Rafael Martín-Durán from the Cardiology Service, Marqués de Valdecilla University Hospital.

1997; Ivan et al., 2005) indicating sublethal ischemic injury of viable myocytes. The ischemic lesions are due to microvascular dysfunction (Jenni et al., 2002). Histological lesions are illustrated in Fig. 3.

Chronic ischemic foci can also be seen in the compaction myocardium.

Burke et al. (2005) established 2 anatomical criteria for the diagnosis of left ventricular non-compaction: (i) absence of well-formed left ventricular papillary muscles; and (ii) total thickness of the ventricle divided by the inner compact ventricular  $> 2$  (i.e.,  $>50\%$  penetration of invaginated endocardial recesses toward the epicardial surface, with histological verification). Because of the normal trabeculation of the right ventricle, right ventricular involvement by this

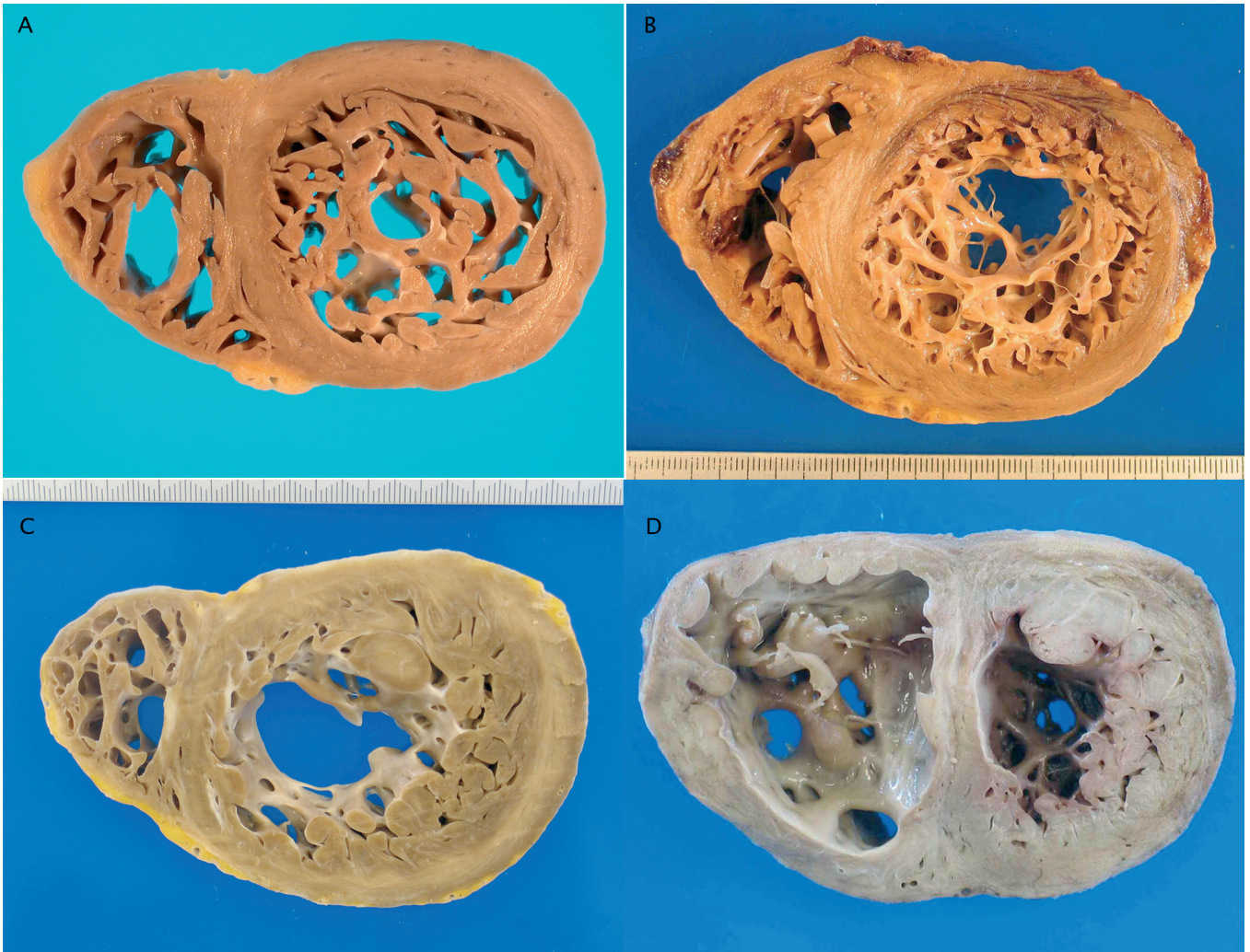
cardiomyopathy requires at least 75% of the ventricular thickness showing increased trabeculations.

There are no differences in gross or histological patterns of the non-compacted regions between the isolated and non-isolated non-compaction cardiomyopathy (Burke et al., 2005).

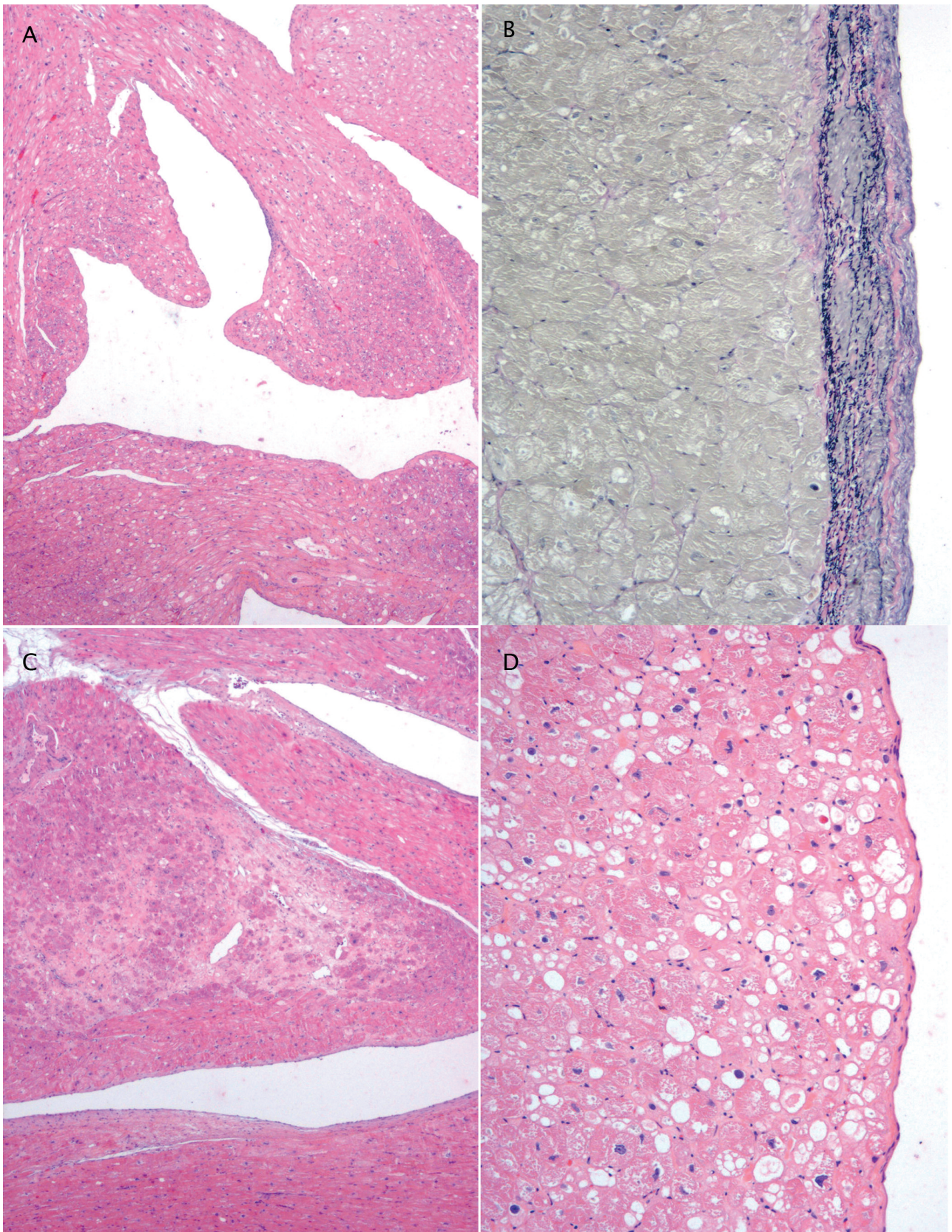
#### Clinical correlation

This rare and unique form of cardiomyopathy is more common in men than in women with male patients accounting for about 71% (Stöllberger et al., 2008).

In the perinatal period this cardiomyopathy manifests as fetal hydrops, neonatal heart failure, or ventricular fibrillation with sudden infant death



**Fig. 2.** Isolated non-compaction cardiomyopathy: macroscopic appearance. **A.** Left ventricular noncompaction showing anastomosing broad trabeculae of the inner part of the left ventricle in a 57-year-old male. **B.** Left ventricular non-compaction presenting extensive interlacing smaller muscle bundles in a 51-year-old male. **C.** Biventricular involvement in a 45-year-old female. Coarse trabeculae resembling multiple papillary muscles can be seen in the left ventricle. The right ventricle is also affected. **D.** Newborn male, left ventricular non-compaction showing coarse trabeculations with compressed invaginations.



**Fig. 3.** Isolated non-compaction cardiomyopathy: histologic features. **A.** Anastomosing trabeculae resulting in large staghorn-like endocardial lined spaces (HE stain). **B.** Endocardial focal fibroelastosis on a trabeculation of the left ventricle (Verhoeff's elastic stain). **C.** Microinfarct with replacement fibrosis (HE stain). **D.** Subendocardial myocytes with perinuclear clearing or extensive vacuolization (HE stain). a, c, x 25; b, d, x 100.

syndrome. There are two groups of patients: one group characterized by early death with progressive systolic dysfunction; and one undulating group characterized by periods of recovery and deterioration, with survival to the adult age.

This cardiomyopathy is complicated by considerable morbidity. Initially, mortality was considered high (Ritter et al., 1997), but with the systematic study of family members, more cases are identified in the early phases of the condition with milder or asymptomatic forms leading to better prognosis in most cases (Murphy et al., 2005). However, prognosis of symptomatic patients remains poor (Pignatelli et al., 2003; Lafiegi et al., 2007).

Subendocardial hypoperfusion and microcirculatory dysfunction cause chronic ischemia associated with progressive myocyte necrosis and fibrosis. This may account for systolic impairment and provide a substrate for arrhythmia with a significant risk of sudden cardiac death. Diastolic dysfunction has been attributed to excessive trabeculation restricting the compliance of the myocardium (Oechslin et al., 2000). Thus, heart failure is a common presentation in these patients. Stasis of blood in the deep intertrabecular recesses leads to thrombosis. The frequency of thromboembolic events can be as high as 24% (Oechslin et al., 2000), manifesting as cerebrovascular accidents, transient ischaemic attacks, mesenteric infarction, or pulmonary embolism.

One intriguing finding of patients with ventricular non-compaction is the presence of associated neuromuscular disorders. The cardiomyopathy may be associated with a known skeletal myopathy (such as Barth syndrome, i.e. mutation in the G4.5 gene in the distal portion of Xq28, Duchenne's, Becker's or myotonic dystrophy) or may be associated with an unclassified myopathy. Stöllberger et al. (2008) reported a frequency of neuromuscular disorders in about 80% of cases. Other authors have not found such a high

frequency.

Dysmorphic facial appearance can be present in some pediatric patients.

### Genetics of ventricular non-compaction

Ventricular non-compaction may be sporadic or familial. Similarly to other primary cardiomyopathies, ventricular non-compaction is frequently a familial disorder. Thus, familial cases make up about 25% (Xing et al., 2006) to 44% (Ichida et al., 1999) of cases. Familial ventricular non-compaction is transmitted as an autosomal dominant trait with incomplete penetrance in the majority of adult patients (Sasse-Klaassen et al., 2003), although autosomal recessive, X-linked recessive and mitochondrial inheritance (Bleyle et al., 1997; Xing et al., 2006; Xia et al., 2008) are also recognized.

The disease-causing genes include: G4.5 (TAZ),  $\alpha$ -dystrobrevin (DTNA), LIM domain binding protein 3 (LDB3/Cypher/ZASP), lamin A/C (LMNA),  $\alpha$ -cardiac actin gene (ACTC),  $\beta$ -cardiac myosin heavy chain (Hoedemaekers et al., 2007) and cardiac troponin T (TNNT2) (Klaassen et al., 2008). LMNA gene was identified in only one family with dilated cardiomyopathy and left ventricular non-compaction (Hermida-Prieto et al., 2004). Monserrat et al. (2007) identified the E101K mutation in the ACTC gene in both patients with hypertrophic cardiomyopathy and patients with left ventricular non-compaction. In addition, in an animal experiment the gene encoding FK506 binding protein 1A (FKBP1A or FKBP12) resulted in a non-compaction cardiomyopathy in mice with associated congenital heart disease (Shou et al., 1998).

Sarcomere protein mutations are more common in adults. Thus, up to 50% of adult patients with this cardiomyopathy have mutations in genes encoding proteins of the cardiac sarcomere (Pantazis and Elliott, 2009). These findings support that sarcomere function is required for proper compaction and that these mutations

**Table 1.** Heart transplantation in adult patients with non-compaction cardiomyopathy.

Authors	Age at transplantation	Gender	Ventricle/s involved	Follow up	Status
Oechslin et al., 2000*	25 years	Male	Left	17 years	Alive
Oechslin et al., 2000*	60 years	Male	Left/Right	9 years	Dead (tumor)
Oechslin et al., 2000*	54 years	Female	Left	8 years	Alive
Oechslin et al., 2000*	39 years	Male	Left	7 years	Alive
Duru and Candinas, 2000	39 years	Male	Left/Right	No data	No data
Conraads et al., 2001	24 years	Female	Left	0.5 years	Alive
Zambrano et al., 2002	35 years	Female	Left	Postop	Alive
Stamou et al., 2004	18 years	Male	Left/Right TVD	2,5 years	Alive
Ivan et al., 2005	37 years	Male	Left	Postop	Postop death
Ivan et al., 2005	21 years	Female	Left	1 year	Alive
Val-Bernal et al., 2006	57 years	Male	Left	3.7 years	Alive
Our case	51 years	Male	Left	Postop	Postop death
Our case	45 years	Female	Left/Right	1 year	Alive
Our case	21 years	Male	Left	26 days	Death (Postop complications)

\*Data kindly provided by Dr. Edwin N. Oechslin on request; TVD, tricuspid valve dysplasia; Postop, postoperative.

## Non-compaction cardiomyopathy

also portend a high risk of developing heart failure in later life (McNally and Dellefave, 2009).

The difference in mode of inheritance suggests a different underlying etiology between children and adult cases (Ichida, 2009).

Increasing evidence has shown that non-compaction cardiomyopathy is, like other primary cardiomyopathies, genetically heterogeneous.

### Review of adult cases treated with heart transplantation

Treatment of isolated non-compaction cardiomyopathy includes heart failure therapy, anti-coagulation, an implantable cardioverter defibrillator or heart transplantation. Once severe congestive heart failure occurs heart transplantation can be an effective treatment for this cardiomyopathy and should be aggressively pursued (Val-Bernal et al., 2006).

Table 1 includes a review of the 11 cases detailed in the literature, and three additional unpublished cases from our institution, of heart transplantation in adult patients with isolated non-compaction cardiomyopathy. Including our own cases, the mean age of the adult patients at transplantation was 37.6 years (range, 18-60 years). The male:female ratio was 1.8:1. Both ventricles were involved in 28.6% of cases. The mean follow-up was 3.8 years (range immediate postoperative period to 17 years). Four patients died one because of a malignant tumor 9 years after transplantation; two of them in the immediate postoperative period; and another patient 26 days after surgery.

Cardiac transplantation allows the study of explanted hearts from affected individuals. Therefore, surgical pathologists will increasingly be involved in the assessment of specimens affected with non-compaction cardiomyopathy.

### Conclusion

Non-compaction cardiomyopathy shows variability of hereditary patterns, genetic heterogeneity, diversity in associated phenotypes and a wide spectrum of clinical presentation and pathophysiological findings.

For many authors, it is unclear whether ventricular non-compaction is a distinct cardiomyopathy or a morphological expression appearing in different diseases. Thus, this process would be a marker of underlying myocardial disease.

Ventricular non-compaction appears to be not an all-or-none process, but a continuous trait within the general population. It is necessary to determine when persistence of the abnormal ventricular layer becomes of clinical significance. Myocardial trabeculation probably has a bell-shaped distribution with the severe condition representing one end of the curve. Non-compaction can be simply a variant of normal maturation of the ventricular myocardium with only the most severe forms producing a distinct clinical-pathological entity.

Ventricular non-compaction most probably is a secondary consequence of an underlying molecular derangement. In the presence of a pathogenic mutation, disturbance to myocyte metabolism and function at a molecular level can induce a maladaptive remodelling response. The functional impact of the mutations recognized in the disease will clarify the cellular and molecular mechanisms underlying the severity of this peculiar cardiomyopathy.

It is expected that surgical pathologists will encounter this entity more frequently due to their involvement in transplantation teams.

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## *Non-compaction cardiomyopathy*

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