

## MYOCARDIAL DISEASE

## Non-compaction cardiomyopathy

Ana G Almeida, Fausto J Pinto

► Additional references and videos are published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/heartjnl-2012-302048>).

Cardiology Department, CCUL, University Hospital Santa Maria/CHLN, Lisbon, Portugal

**Correspondence to**

Professor Fausto J Pinto, Cardiology Department, CCUL, University Hospital Santa Maria/CHLN, Av Prof Egas Moniz, Lisbon 1649-028, Portugal; faustopin@gmail.com

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Non-compaction cardiomyopathy (NCM) is a myocardial disorder, which is thought to occur due to the failure of left ventricle (LV) compaction during embryogenesis, leading to distinct morphological characteristics in the ventricular chamber.<sup>1</sup> It was first described about 80 years ago, in association with complex congenital heart diseases. More recently, Chin *et al*<sup>2</sup> reported the isolated form of non-compaction LV, and since then many other reports have been published. The involvement of the right ventricle in the non-compaction process has been increasingly identified and the condition is now included among the cardiomyopathies. The nomenclature of this entity has been variable, being known as 'spongy myocardium' or 'persistent embryonic myocardium', but more frequently known as 'LV non-compaction' or NCM. Therefore, the latter term will be the one used in this article.

The characteristic features of NCM have been described as including a two-layered ventricular wall, comprising a thinner compact epicardial layer and an inner non-compacted layer, with prominent trabeculations associated with deep, intertrabecular recesses that communicate with the ventricular cavity but not with the coronary circulation.<sup>2-3</sup> The *in vivo* diagnosis requires the detection of these typical characteristics using imaging techniques.<sup>2-3</sup> However, there has been considerable controversy regarding the differentiation from normal LV trabeculation and the relationship with other cardiomyopathies, such as dilated and hypertrophic cardiomyopathies, which may share the same genetic basis and be associated with NCM.

The prevalence of NCM varies considerably among different series and is still unknown. Several limitations for this assessment are the different diagnostic criteria, the heterogeneous populations, and the retrospective design of most studies. The reported prevalence of NCM in patients referred to echocardiography laboratories ranges between 0.014–1.26%,<sup>4</sup> while in a population based retrospective study in children NCM accounted for 9.5% among cardiomyopathies,<sup>5</sup> and in a large cohort of an adult heart failure population a prevalence of 3% was recognised.

Other areas of controversy have been identified. Although it has been shown that a genetic basis is involved in the pathogenesis of NCM, the relationship between genotype and phenotype is not clear. Also, clinical features are heterogeneous and range from asymptomatic to symptomatic patients with progressive deterioration in cardiac function resulting in heart failure, thromboembolic events, arrhythmias, and sudden cardiac death.<sup>4</sup> Moreover, to date, the prognosis and the best management strategy have not been agreed upon.

Medical societies have also classified NCM within different disease subcategories. Almost two decades ago, the World Health Organization included NCM among the primary cardiomyopathies. More recently, the American Heart Association statement on cardiomyopathies classified NCM within the genetic cardiomyopathies, while the European Society of Cardiology working group on myocardial and pericardial diseases considered NCM to be among the unclassified familial cardiomyopathies, stating that it is as yet unclear whether non-compaction is a separate cardiomyopathy or simply a trait shared by different cardiomyopathies.

In this article we will present the pathophysiological concepts, the clinical picture and the diagnostic criteria for NCM, as well as the available data on prognosis and therapy. The present uncertainties and future directions will also be discussed.

**DIAGNOSTIC CRITERIA****Echocardiography**

Generally, NCM is considered to be present when there is a two-layered myocardium with a thin compacted epicardial layer and a thick endocardial layer, with prominent trabeculations and recesses. However, LV trabeculation is a normal constituent of the LV chamber and prominent trabeculation can be found in normal subjects. Differentiation of NCM from normal patterns may be difficult and criteria vary according to different authors (box 1).

Chin *et al*,<sup>2</sup> who reported for the first time the isolated form of non-compaction LV based on a series of patients studied by echocardiography, recommended the assessment of the ratio of X/Y dimensions obtained in diastole—where X is the distance from the epicardial surface to the trough of the trabecular recesses, and Y the distance from the epicardial surface to the peak of the trabeculation. An X/Y ratio of up to 0.5 would be required for the diagnosis.<sup>2</sup>

Given the difficulty of measuring the two layers in diastole with ultrasound, Jenni *et al*<sup>3</sup> proposed another set of criteria, validated pathoanatomically, which requires a ratio of the end-systolic non-compacted/compacted layer of at least 2.0 in adults or 1.4 in children. Three additional criteria must be also fulfilled: colour flow Doppler evidence of deep intertrabecular recesses that fill with blood directly from the LV cavity; predominant localisation of non-compaction in the lateral, apical or inferior walls of the LV; and the absence of coexisting cardiac abnormalities.

Stöllberger *et al*<sup>6</sup> departed from the above diagnostic approaches, naming the disease phenotype as 'LV hypert trabeculation', defined by the presence of more than three coarse, prominent trabeculations

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**Box 1 Diagnostic criteria used in non-compaction cardiomyopathy****Echocardiographic criteria**Chin *et al*<sup>2</sup>

- ▶ Ratio of X\*/Y† <0.5
- ▶ Acquisition: evaluates the trabeculations at the left ventricle (LV) apex, using the short axis and apical views and the free wall, at end-diastole

Jenni *et al*<sup>3</sup>

- ▶ Bilayered LV myocardium, with a thin compacted layer and a thick non-compacted layer, with trabeculations and deep recesses; ratio non-compacted/compacted >2.0
- ▶ Evidence of intratrabecular recesses filled by blood flow from the LV cavity
- ▶ Absence of coexisting cardiac structural abnormalities
- ▶ Predominant localisation of non-compaction in the lateral, apical or inferior walls of the LV
- ▶ Acquisition: short axis view; end-systolic acquisition

Stöllberger *et al*<sup>6</sup>

- ▶ Three trabeculations protruding from the LV wall, apically to the papillary muscles, visible in one image plane
- ▶ Intertrabecular spaces perfused from the ventricular cavity as visualised on colour Doppler imaging
- ▶ Trabeculations with the same echogenicity as the myocardium and moving synchronously with ventricular contractions
- ▶ Acquisition: oblique views to differentiate false chords, aberrant bands and trabeculations

**Cardiac magnetic resonance criteria**Petersen *et al*<sup>8</sup>

- ▶ Ratio non-compacted/compacted >2.3
- ▶ Acquisition: end-diastolic

Jacquier *et al*<sup>9</sup>

- ▶ Trabecular LV mass >20% of global LV mass
- ▶ Acquisition: end-diastolic

\*X, distance between the epicardial surface and trough of a trabecular recess; †Y, distance between the epicardial surface and peak of the trabeculation.

located apically to the papillary muscles and surrounded by intertrabecular spaces perfused from the ventricular cavity. Previous reports had shown that only 4% of normal hearts had more than three trabeculations and none had more than five. More recently, these authors have proposed an approach combining Jenni's and Stöllberger's criteria, which would support the diagnosis as definite, probable or possible.

Kohli *et al*<sup>7</sup> have challenged all the above criteria and found a poor correlation between them, with 24% of the study population fulfilling one or more criteria for NCM, and only 30% presenting all

three. Moreover, 8% of apparently healthy individuals also fulfilled one or more criteria for NCM; among this group four patients were black. Over diagnosis may occur, suggesting the need for careful consideration of normal variations.

**Cardiac magnetic resonance**

Petersen *et al*<sup>8</sup> have assessed the accuracy of cardiac magnetic resonance (CMR) in distinguishing pathological non-compaction from lesser degrees of trabeculation seen in normal hearts, in hearts with LV hypertrophy, and those with cardiomyopathies. Areas of non-compaction were common in all groups and more frequently found in the apical and lateral segments, rather than the basal and septal segments. A diastolic non-compacted to compacted ratio >2.3 identified pathological non-compaction with values for sensitivity, specificity, and positive and negative predictions of 86%, 99%, 75%, and 99%, respectively.

Using CMR, Jacquier *et al*<sup>9</sup> found that the percentage of trabeculated LV mass was three times higher in patients with NCM than in those with dilated and hypertrophic cardiomyopathy or in controls, and proposed a diagnostic criterion for the disease—namely, when the non-compacted mass is  $\geq 20\%$  of the total LV mass.

However, the proposed imaging criteria remain doubtful when distinguishing NCM from normal LV. In fact, the 'perfect diagnostic tool', which should act as a reproducible genetic marker, is still lacking.

**Diagnosis of non-compaction cardiomyopathy (NCM): key points**

- ▶ Echocardiography is the first line diagnostic modality.
- ▶ Contrast echocardiography may be useful in cases with unclear diagnosis.
- ▶ Cardiac magnetic resonance (CMR) is the best option for diagnostic confirmation.
- ▶ Speckle tracking echocardiography describes the abnormal left ventricle mechanics in NCM.
- ▶ The presence of late gadolinium enhancement CMR has been associated with more severe clinical disease.
- ▶ Imaging methods are essential for diagnosis, but definite criteria are still lacking.

**AETIOLOGY AND PATHOPHYSIOLOGY**

In humans, the embryonic myocardium is composed of a loose meshwork of interwoven fibres separated by deep recesses, which communicate with the LV cavity, allowing an increase in the myocardial surface area and the exchange diffusion from the cavity. From the 5th–8th week of embryogenesis, LV trabecular compaction occurs simultaneously with the invasion of the myocardium by the developing coronary vasculature coming from the

epicardium. This process coincides with myocardium maturation, and is possibly stimulated by hypoxia in the outermost subepicardial layer of the compacting myocardium.<sup>1</sup> The LV compaction progresses from the heart base to the apex and from the epicardium to the endocardium. NCM is hypothesised to result from the arrest of trabecular compaction during this phase of embryogenesis.

Cessation of compaction would result in a two-layered myocardium, consisting of a compacted epicardial layer and a non-compacted layer composed of a loose network of interwoven fibres, of prominent trabeculations, and deep endomyocardial recesses which communicate with the LV cavity but not with the coronary circulation. It has been proposed that the temporal variability of the myocardial maturation failure might explain the large spectrum of the pathological and clinical expression of NCM.

Histopathology has shown continuity between the endothelium of intertrabecular recesses and that of the endocardium, distinguishing NCM from persistent sinusoids. Other findings have included loosely organised myocytes and endocardial and subendocardial replacement fibrosis consistent with ischaemic necrosis.

Ischaemia is likely to play an important role in the pathophysiology of NCM. CMR, single photon emission CT (SPECT), and contrast echocardiography have demonstrated subendocardial, subepicardial, and transmural myocardial perfusion defects in association with regional myocardial dysfunction. A positron emission tomography (PET) study has also shown reduced perfusion reserve in both non-compacted and compacted segments, suggesting microvascular dysfunction.<sup>10</sup> It is possible that underlying capillary abnormalities—associated with increased stress on the thinner compacted layer—causes perfusion abnormalities.<sup>3</sup> On the other hand, ischaemia and focal necrosis may both contribute to LV dilatation and dysfunction and may represent a substrate for arrhythmias. Diastolic dysfunction has also been reported in patients with NCM, possibly caused by the mechanisms of both ischaemia and fibrosis.<sup>4</sup>

#### Pathogenesis of NCM: key points

- ▶ Cessation of left ventricle (LV) compaction at 5th–8th week of embryogenesis is suggested as the primary event.
- ▶ Heterogeneous genetic mutations have been identified in familial and sporadic cases.
- ▶ Associated modifier factors are suggested to intervene in the non-compaction arrest.
- ▶ Microvascular dysfunction and ischaemia are likely to be involved in the pathogenesis and cause arrhythmias and LV dysfunction.
- ▶ Myocardial fibrosis has been confirmed and may determine LV dysfunction.

#### GENETICS

Several studies suggest that non-compaction of the LV myocardium is a genetically heterogeneous disorder,<sup>11–12</sup> with a familial and a sporadic form. Studies of the familial form have shown that NCM may be transmitted as an autosomal dominant inheritance with incomplete penetrance, as an autosomal recessive, and as X-linked traits. Sporadic cases of NCM, which seem to be common, and de novo mutations have also been recognised. To date, several disease loci have been identified.

The genetic basis of NCM was first recognised in the Barth syndrome, characterised by dilated cardiomyopathy associated with NCM. It is an X-linked disease with mutations in the *G4.5* gene, located at Xq28, which encodes the tafazzins (a family of proteins) with acetyltransferase functions in the mitochondria. This mutation was also demonstrated in an X-linked severe neonatal NCM, allelic with the Barth syndrome.

Another mutation, in the  $\alpha$ -dystrobrevin gene, was identified subsequently in patients with NCM and associated with congenital heart diseases.<sup>13</sup>  $\alpha$ -dystrobrevin is a cytoskeletal protein component of the dystrophin associated glycoprotein complex, which links the extracellular matrix to the dystrophin cytoskeleton of the muscle fibre. A significant variability in the phenotype and severity of disease has been found in association with this mutation. Mutations in the Z-line protein Cypher/ZASP have been identified in association with NCM and dilated cardiomyopathy. This protein is found in the cytoplasm of cardiac and skeletal muscle and appears to play an important role in the maintenance of the normal myocyte architecture.

An NCM phenotype has been reported in association with a mutation in the Lamin A/C protein, which has been linked to dilated cardiomyopathy, conduction system diseases, and muscular dystrophy.

Recently, NCM has also been linked to sarcomere gene mutations, which can cause hypertrophic cardiomyopathy, and which may be more prevalent than previously suspected. In a study of 247 families with cardiomyopathy, a mutation in the  $\alpha$ -cardiac actin gene, essential for cell maintenance, was associated with NCM, apical hypertrophic cardiomyopathy, and septal defects. In a large study of patients with features of NCM, nine heterozygous mutations were identified in 11 of 63 probands in genes encoding  $\alpha$ -myosin heavy chain (MYH7),  $\beta$ -cardiac actin (ACTC), and cardiac troponin T (TNNT2), with 100% penetrance in the family members.<sup>14</sup> A recent study identified a mutation in the sarcomeric TPM1 gene, at 15q22.1, in a family with NCM and a history of sudden death. This suggests the possible importance of genotyping for outcome prediction.

Some studies have suggested that the phenotype for isolated NCM may appear during adult life in patients with myocarditis or muscular dystrophy. Nevertheless, these cases were not followed serially

with an imaging modality and the significance of the LV hypertrabeculation described is still unclear.

In spite of recent advances, only a proportion of patients with NCM can be successfully genotyped, making diagnostic confirmation often difficult.

#### Genotype–phenotype features of NCM: key points

- ▶ In all age groups, heart failure, thromboembolic events, and ventricular arrhythmias are the most common features.
- ▶ Patients and relatives with the phenotype may be asymptomatic.
- ▶ Identified genetic mutations are heterogeneous.
- ▶ Mutations associated with NCM have been found to be associated with other cardiomyopathies.

### CLINICAL PRESENTATION, OUTCOME, AND DIAGNOSIS

#### Presentation and outcome

The triad of heart failure, ventricular arrhythmias, and systemic embolic events comprise the typical complications in patients and may occur at any age. However, the initial presentation is variable and the patient may be asymptomatic (frequently diagnosed during a family screening) or present any of the clinical features and complications, including sudden death (table 1).

In its severe neonatal form, NCM may manifest as heart failure or ventricular arrhythmias which may lead to sudden death.<sup>2</sup>

Studies of older children and adults have reported a high incidence of severe manifestations<sup>4 15–19</sup> such as LV dysfunction, thromboembolic events (probably originating in the deep intertrabecular recesses), arrhythmias, and sudden death. Other studies, however, have found a much lower incidence of complications, suggesting sub-clinical or milder cases<sup>5 20</sup> (table 1).

There is no agreement so far on the natural history and outcomes in NCM because most studies are retrospective and use distinct methods. Heart failure seems to occur frequently (in over 50% of symptomatic patients) and most researchers also report ventricular arrhythmias, cardiovascular deaths, and sudden cardiac death. A recent registry of a large population of adult patients with NCM found heart failure in 74%, LV systolic dysfunction in 88%, strokes in 10%, and syncope episodes in 9%,<sup>16</sup> suggesting the need for long term surveillance of NCM patients. Other series have found a more benign prognosis. Murphy *et al*<sup>20</sup> describe a mean freedom from death or transplantation of 97% at 46 months in adults with NCM.

Predictors of death and heart transplantation have been difficult to assess due to the variability of the phenotype and the underlying pathophysiological scenarios. However, the presence of heart failure, history of sustained ventricular tachycardia or systemic thromboembolism seem to be associated with an unfavourable prognosis among other phenotypes with distinct outcomes.<sup>17 18</sup> In a recent study, mortality did not differ significantly between patients with isolated NCM and control patients with dilated cardiomyopathy,<sup>21</sup> suggesting that LV dysfunction rather than the phenotype itself is the risk-increasing mechanism. However, this finding has not been confirmed by others.<sup>19</sup>

#### Diagnosis Echocardiography

Cardiac ultrasound is a first line technique for diagnosing NCM, since it is a bedside modality that is readily available. This modality allows the detection, location, and confirmation of the more widely used criterion, the ratio of non-compacted and compacted myocardium, measured from end-systolic short axis images. If the ratio is  $>2$ , the criterion for NCM is fulfilled<sup>3</sup> (figures 1 and 2, see online supplementary video 1).

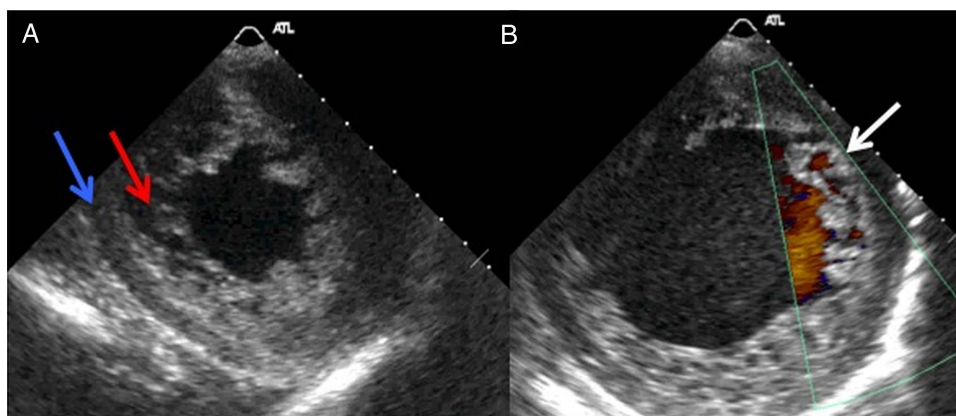
The inherent limitation of evaluating the LV apex and, often, other LV walls poses a diagnostic issue. If the image quality is poor, NCM can be confused with apical cardiomyopathy,<sup>22</sup> thrombus or

**Table 1** Clinical characteristics and outcomes of non-compaction cardiomyopathy

Author	Chin <sup>2</sup>	Ichida <sup>15</sup>	Oechslin <sup>4</sup>	Murphy <sup>20</sup>	Lofiego <sup>17</sup>	Aras <sup>19</sup>	Stanton <sup>21</sup>	Greutmann <sup>18</sup>
Patients (N)	8	27	34	45	65	67	30	132
Type of population	Paediatric	Paediatric	Adult	Adult	Adult	Adult	Adult	>14 years
Family history (%)	50	44	18	51*	31	33	–	23
Follow-up	≤5 years	≤17 years	Mean 44 months	Mean 46 months	Mean 46 months	Mean 30 months	Mean 2.5 years	Mean 2.7 years
Heart failure (%)	63	30	68	67	34	34	–	13
Embolic events (%)	38	0	21	4	5	9	0	4
Ventricular tachycardia (%)	38	0	41	20†	6	36	27†	4
Cardiovascular death or transplantation (%)	0	11	47	2	24	15	10	23
Sudden death (%)	13	0	18	2	5	9	10	9

\*Non-compaction and dilated cardiomyopathy.

†Non-sustained ventricular tachycardia.



**Figure 1** Echocardiographic short axis apical views of the left ventricle in a patient with non-compaction cardiomyopathy and a G4.5 mutation. (A) End-systolic image, showing the compacted layer (red arrow) with 6.3 mm thickness and the non-compacted layer (blue arrow) with 14.4 mm (ratio non-compacted/compacted  $>2$ ). (B) Diastolic image depicting Doppler colour flow in the intertrabecular recesses (white arrow).

fibroelastosis. The use of contrast echocardiography, which permits the visualisation of the trabeculations and the recesses that communicate with the cavity, may assist in clarifying the diagnosis (see online supplementary video 2A,B). Additional information with prognostic impact may be derived from the evaluation of LV systolic and diastolic function. More recently, speckle tracking has revealed abnormal LV rotation and twist, and these findings are promising for diagnosis.<sup>2,3</sup>

### CMR

CMR is a high resolution technique without acoustic limitations, which reveals a wider extent of disease, particularly at the LV apex and the poorly observed segments, which are often problematic with echocardiography.

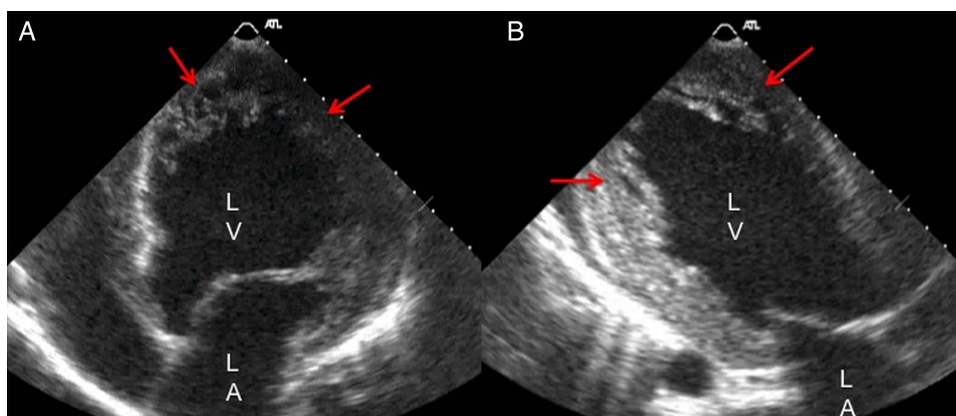
This modality confirms the presence of the anatomic features of NCM, as well as an accurate and reproducible measurement of the non-compacted and compacted myocardial layers. The diagnosis is supported if the end-diastolic thickness of the non-compacted layer is  $\geq 2.3$  times the compacted one<sup>8</sup> (figure 3, see online supplementary video 3).

Additionally, observation and quantification of the apical trabeculations are readily available and permit the use of the additional NCM criterion proposed by Stöllberger *et al.*<sup>6</sup> CMR confirmation of trabeculated LV mass  $>20\%$  of global LV mass fulfils the criterion proposed by Jacquier *et al.*,<sup>9</sup> although the feasibility and reproducibility of this methodology have not been confirmed yet.

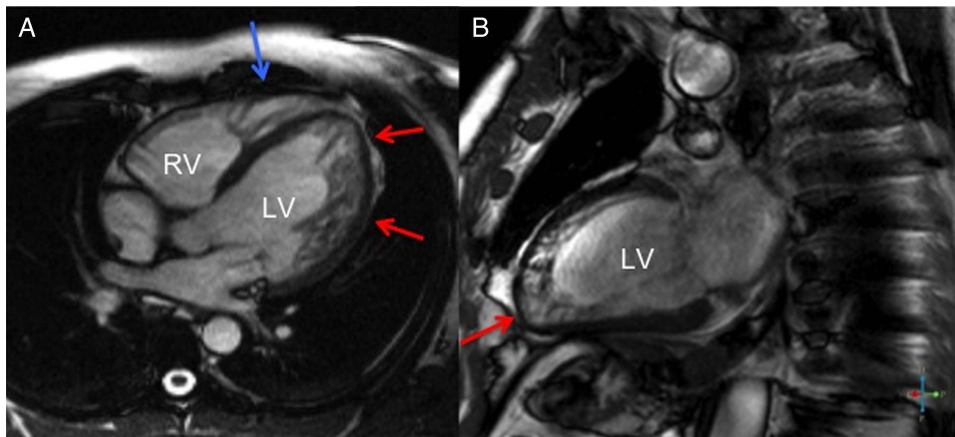
Reliable evaluation of LV function is an additional advantage offered by CMR. Involvement of the right ventricle remains controversial because echocardiography presents inherent difficulties in analysing this chamber, but CMR has been increasingly detecting biventricular NCM.

The combined use of echocardiography and CMR may contribute to lessening the risk of over diagnosing NCM, which can occur with the isolated use of ultrasound, but such an approach has not yet been validated.

Late gadolinium enhancement (LGE) CMR, as a surrogate marker of fibrosis, has been detected in patients with NCM and confirmed by histology. A recent study suggests that the presence and amount of LGE is associated with more severe clinical



**Figure 2** Two dimensional echocardiography of a 16-year-old patient with heart failure and sporadic non-compaction cardiomyopathy. (A) Four chamber view with a dilated left ventricle (LV) and a non-compacted layer at the apical septal segment and the anterolateral wall (arrows). (B) In two chamber view, non-compaction is identified at the apical anterior segment and the inferior wall. Biplane ejection fraction was 36%. LA, left atrium.



**Figure 3** End-diastolic cardiac magnetic resonance representative images from an asymptomatic 36-year-old patient with familial non-compaction cardiomyopathy. (A) Four chamber plane showing the non-compacted left ventricle (LV) myocardium at the apical segment and lateral wall (red arrows) and hypertrabeculated right ventricle, suggestive of biventricular non-compaction (blue arrow); the maximum ratio non-compacted/compacted layer is 4.5. (B) Two chamber plane, depicting the non-compacted myocardium at the apical (red arrow) and the mid anterior and inferior segments. RV, right ventricle.

disease and lower LV ejection fraction,<sup>24</sup> and may represent a prognostic marker for future systolic dysfunction. LGE was found in both compacted and non-compacted myocardium, suggesting that NCM is a diffuse cardiomyopathic process (figure 4).

### ECG

Electrocardiographic changes, when present, are non-specific and include LV hypertrophy and repolarisation abnormalities. Left bundle branch block is relatively common, especially in patients with LV dysfunction. Wolff–Parkinson–White has been frequently detected in paediatric patients and is thought to be involved in the embryogenesis arrest process.<sup>15</sup> However, the ECG may be normal, particularly in young, asymptomatic patients.

### Genetic assessment

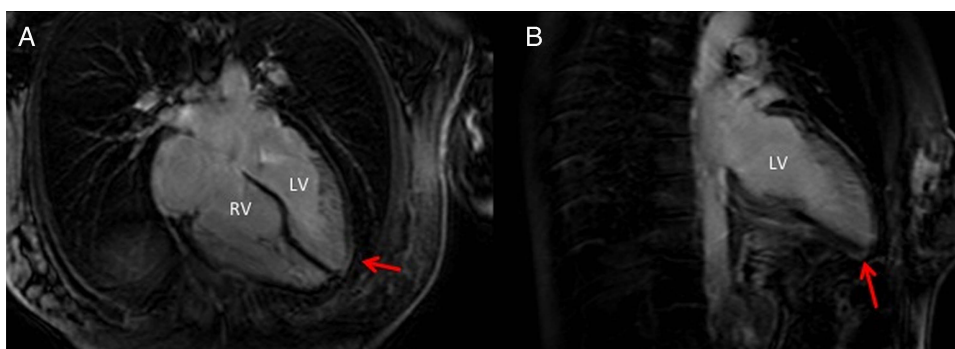
Although knowledge about the genetics involved in NCM remains limited, genetic testing is generally proposed for further characterisation of the myocardial phenotype of genetic mutations and the genotype–phenotype correlation.

According to current guidelines, mutation specific genetic testing is recommended for family members and appropriate relatives, following the identification of an LV non-compaction causative mutation in the index case. Moreover, this testing may be useful for patients where the cardiologist has established a clinical diagnosis of LV non-compaction based on examination of the patient's clinical and family history, and electrocardiographic/echocardiographic phenotype. Following genetic and imaging assessment, the possibility of an early diagnosis of NCM increases, ensuring appropriate monitoring and prophylactic measures.

### MANAGEMENT

Evidence supporting the management of NCM is limited. The main therapeutic objectives are the prevention and treatment of complications, using conventional measures. Thromboembolism, heart failure, and arrhythmias constitute the typical clinical features of NCM to be addressed.

Regarding the true prevalence of thromboembolism, some recent series show a lower frequency compared with previous studies.<sup>20</sup> Accordingly,



**Figure 4** Late gadolinium enhancement (LGE) cardiac magnetic resonance images from a 45-year-old male patient with NCM, associated Wolf–Parkinson–White ECG pattern, and ventricular arrhythmias. Four chamber (A) and two chamber (B) planes show an area of midwall LGE located at the compacted layer of the apical left ventricle (LV) segment (arrows). Increased trabeculation is also visible at the right ventricle (RV).

anticoagulation for prevention of thromboembolism is probably only indicated in cases of LV dilatation and dysfunction, or when a previous history of embolic events is present, although to date no data are available to support these options. For symptomatic ventricular arrhythmias, particularly the ones associated with LV dysfunction, the treatment should follow current guidelines, using antiarrhythmic agents or implantable cardioverter-defibrillators.

Finally, LV dysfunction and heart failure should be treated similarly to dilated cardiomyopathy, using a variety of pharmacological therapies in accordance with guidelines. Heart transplantation has been performed in individual cases, as reported by transplantation clinics, and used as a therapeutic option in non-compaction.

### ASSOCIATION AND OVERLAPPING WITH OTHER CONDITIONS

Chin *et al* described for the first time the isolated form of LV non-compaction.<sup>4</sup> Decades earlier, the association of the phenotype with congenital heart diseases had been recognised and hypothesised to be caused by the additional overload imposed on the LV by the congenital defects.

The association of NCM with neuromuscular diseases has been thoroughly investigated by the Vienna group.<sup>6</sup> In a recent study by these authors involving a large series of patients with NCM, neuromuscular disorders were detected in up to 65% of patients, including metabolic myopathy, Leber's hereditary optic neuropathy, myotonic dystrophy, Becker muscular dystrophy, and Duchenne muscular dystrophy. In this study, the presence of a neuromuscular disease was a predictor of adverse prognosis. However, the exact relationship and pathogenesis of this association remains elusive.

The true significance of non-compaction still remains a matter of debate.<sup>25</sup> Based on the mutations identified so far, which involve cytoskeletal, Z-line, mitochondrial and sarcomeric proteins in the pathogenesis, the pronounced genetic heterogeneity of NCM is clear.<sup>12–25</sup> Interestingly, the NCM phenotype has been recognised in families with hypertrophic cardiomyopathy or dilated cardiomyopathy, sharing the genetic background. Moreover, overlapping phenotypes, which associate NCM with hypertrophic cardiomyopathy or dilated cardiomyopathy, have also been reported.<sup>13</sup> These findings suggest that other factors may play a role in the development of NCM disease during embryogenesis and that NCM could be the final expression of other cardiomyopathies.

### CHALLENGES AND FUTURE DIRECTIONS

One of the most important challenges is the clear differentiation of the NCM phenotype from the normal heart. Although it has been suggested that the proposed echocardiographic and CMR criteria are reliable in diagnosing NCM in patients with full phenotype expression, the current imaging criteria are still imperfect since their true sensitivity

and specificity are unknown, particularly in milder cases of NCM when the distinction from normal is more problematic. CMR has shown increased trabeculation in otherwise normal hearts, particularly in athletes, as well as in hypertensive hearts, with aortic stenosis, hypertrophic cardiomyopathy or dilated cardiomyopathy, and even in healthy volunteers.<sup>8</sup> A spectrum of the extent of the thicknesses of the compacted and non-compacted layers in patients and family members suggests that NCM may be the end point of a bell shaped curve involving the compaction process in embryogenesis, with an early portion of the curve representing the disease condition.<sup>26</sup> Thus, clear and accurate imaging criteria must be defined, mainly in borderline cases, in order to identify the patients and family members affected by NCM who are at risk of complications. Conversely, over diagnosis will involve obvious financial and personal burdens and should be avoided at all cost. Therefore, the accuracy of clinical and diagnostic tests should be assessed in different age groups and ethnicities, possibly leading to more specific criteria.

As discussed above, the pathogenesis of NCM remains challenging. The disease may be secondary to a genetic mutation that induces the myocardial pathology. However, phenotypes are heterogeneous, suggesting the influence of additional modifiers.<sup>13</sup> The evaluation of new genetic mutations and the relationship with phenotypes may shed light on the pathogenesis of this condition, which may have an impact on follow-up and management.

The current awareness of the disease and the availability of high resolution imaging, namely CMR, have increased the number of diagnosed patients. However, the genotype and phenotype heterogeneity suggests the need for multicentre studies involving larger populations, allowing more robust conclusions regarding all the important areas of NCM—namely clinical, genetics, pathogenesis, diagnosis, and management.

### Issues for discussion about NCM

- ▶ The role of genetics on the non-compaction process: the same mutation associated with cardiomyopathies.
- ▶ Which additional modifier factors may intervene in the embryogenesis arrest process?
- ▶ Differentiation of non-compaction patterns from normal left ventricle trabeculations.
- ▶ Which is the perfect diagnostic imaging method and the most accurate diagnostic criteria?
- ▶ The natural history and outcomes of NCM.
- ▶ Do genetics plays a role in the clinical picture and prognosis?
- ▶ To identify appropriate therapeutic strategies for early prevention of complications.

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