

## Noncompaction Cardiomyopathy - a Current View

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### Abstract

Isolated non-compaction cardiomyopathy is a rare disease that is likely to develop in the embryonic period. It is caused by the intrauterine arrest of the myocardial compaction process in the beginning of the fetal development. It is characterized by prominent myocardial trabeculations and deep intertrabecular recesses, as well as the thickening of the myocardium into two distinct layers (compacted and not compacted). Even though this disease is said to be prevalent in the pediatric population or together with congenital heart disease, one can understand that this disease occurs in isolation, because the diagnosis is becoming more common in adult patients that have no other heart disease. The clinical manifestations vary greatly, because they range from absence of symptoms to congestive heart failure, arrhythmias and systemic thromboembolism. Echocardiography is the most widely used diagnostic procedure, but the little knowledge about this disease, its similarity to other myocardial diseases and the limitation of the echocardiographic technique used delay the diagnosis. The purpose of this review is to show that other imaging techniques, such as MRI, CT and left ventriculography have emerged as diagnostic alternatives.

### Introduction

The first reported cases of non-compaction cardiomyopathy (NCC) were associated with congenital heart disease with obstructed outflow tract of the left and right ventricle, complex cyanotic congenital malformations and coronary anomalies<sup>1</sup>. The isolated noncompaction cardiomyopathy was reported for the first time by Chin et al<sup>2</sup> in 1990, who described eight cases of the disease<sup>2</sup>.

The non-compaction cardiomyopathy is a rare disorder, which is considered to be a primary genetically-determined cardiomyopathy by the American Heart Association<sup>3</sup> or an unclassified cardiomyopathy according to the World Health Organization. It is characterized by the following aspects:

- Change in myocardial wall due to the prominence of its trabeculations with deep intertrabecular recesses, which may be secondary to the intrauterine arrest of myocardial

### Keywords

Cardiomyopathies; embryonic structures/abnormalities; fetus/abnormalities; heart defects, congenital.

compaction that occurs in the early stages of fetal development. The result is two layers of myocardium, a compacted one and noncompacted layer<sup>4,5</sup>.

- Continuity between the ventricular cavity and the intertrabecular recesses, which are filled with blood from the ventricle and which have no communication with the epicardial coronary system.
- Decrease in the coronary flow reserve measured by PET-CT, observed in most segments that show ventricular wall motion abnormalities<sup>6</sup>.

The prevalence of NCC in the general population has not yet been determined. However, in a population of patients who underwent echocardiographic examination, it was possible to identify 34 cases in 15 years of monitoring, which represented 0.014% of the echocardiograms<sup>7</sup>. However, this is a fact that is probably underestimated, since the image quality of this method has greatly improved in recent years. More recent studies have determined that the prevalence of the disease was of around 18% to 50% among members of affected families<sup>8</sup>.

### Pathogenesis and genetics of the non-compaction

During the embryonic development of the myocardium, there is a meshwork of cardiac muscle fibers loosely interwoven and separated by deep recesses that link the myocardial wall with the ventricular cavity. Approximately between the 5<sup>th</sup> and 8<sup>th</sup> weeks, this sponge-like meshwork of fibers and intertrabecular spaces will become compressed, from the epicardium to the endocardium and from the base to the apex of the heart<sup>4,9</sup>. While the compaction occurs, the coronary circulation develops with the reduction in intertrabecular recesses and the formation of capillaries. This process involves the secretion of endothelial growth factors, such as neuregulins and angiotensins<sup>4,10</sup>.

The cause of the non-compaction is not yet fully understood, but it is believed that pressure overload or myocardial ischemia have a role in the regression of embryonic sinusoids. This process will result in the persistence of intertrabecular spaces and, in some cases, there may be a direct communication with the ventricular cavity and coronary circulation<sup>7</sup>.

With respect to the findings of electron microscopy, there is not a specific histological pattern, although some studies have described the presence of necrosis and fibrosis in the endomyocardial biopsy<sup>11-14</sup>.

Some cardiac abnormalities may be associated with NCC:

- The noncompacted myocardium with sinusoids and fistulas of the right coronary artery may present

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congenital abnormalities in the outflow tract of left and right ventricles<sup>15</sup>.

- Presence of Ebstein's anomaly, bicuspid aortic valve and transposition of great vessels<sup>16,17</sup>. Patients with NCC may also have a ventricular septal defect<sup>18</sup>.
- The NCC can occur in metabolic diseases and genetic syndromes, including the Barth syndrome, the Charco-Marie-Tooth disease and the Melnick-Needles syndrome<sup>19</sup>.

The NCC can be genetically sporadic or familial. In one study, six of 34 patients (18%) had a family history of NCC<sup>7</sup>. Some affected individuals may be detected by tracking the asymptomatic relatives of affected patients.

Different genes have been identified:

- Mutations in the G4.5 gene, found in tafazzins, are responsible for the Barth syndrome.
- A mutation (P121L) in the gene that codes the dystrobrevin alpha, cytoskeletal protein and transcription factor NKX2.5 was found in a family with NCC and congenital heart disease<sup>3,20,21</sup>.
- A mutation of the gene for the cytoskeletal protein, CYPHER/ZASP, was found in one family and in three sporadic cases<sup>22,23</sup>.
- The locus on chromosome 11p15 was seen in a family with autosomal dominant penetrance<sup>24</sup>.
- The E101K mutation of the alpha-cardiac actin has been identified in families with NCC, septal defect and apical hypertrophic cardiomyopathy<sup>25</sup>.

## Clinical manifestations

The clinical manifestations of NCC vary widely (Table 1). Patients may be asymptomatic or show symptoms of heart failure, arrhythmias or thromboembolism<sup>25-27</sup>. In a small series of 16 cases, the average time for the onset of symptoms after the diagnosis was 3.5 years<sup>4</sup>. The frequency of these manifestations was illustrated in a more recent series of 34 patients of the same authors<sup>7</sup>. In this study, at the time of the diagnosis, the clinical manifestations included: dyspnoea - 27 patients (79%); heart failure (HF) functional class III and IV - 12 patients (35%); chest pain - 9 patients (26%); chronic atrial fibrillation - 9 patients (26%).

Most patients with noncompaction cardiomyopathy will develop, over the years, symptoms of ventricular failure. The origin of the dysfunction in these patients is still unclear, but it is believed that the microcirculatory dysfunction and, consequently, the subendocardial hypoperfusion collaborate in a decisive way to these symptoms<sup>2</sup>.

The electrocardiographic findings are often abnormal, but no specific change was identified<sup>7</sup>. The abnormalities that can be described are, basically, branch blocks and arrhythmias, such as atrial fibrillation and ventricular tachycardia. A possible association with bradycardia and Wolff Parkinson White Syndrome was described in 18% of pediatric patients with NCC<sup>20,28,29</sup>.

## Diagnosis

The diagnosis of noncompaction cardiomyopathy is often made by echocardiography. However, other imaging tests such as magnetic resonance imaging, which is the most chosen method, computed tomography and left ventriculography may diagnose or confirm the clinical suspicion.

The main differential diagnoses of NCC include: dilated cardiomyopathy, hypertensive heart disease, apical hypertrophic cardiomyopathy, infiltrative cardiomyopathy and endomyocardial fibrosis.

### A. Echocardiogram

It is used as the initial method in the diagnosis and monitoring<sup>7,30</sup>. The echocardiographic criteria proposed include those based on observational studies of three authors: Chin et al<sup>2</sup> Jenni et al<sup>30,31</sup> and Stollberger et al<sup>32</sup>

#### 1. Criteria proposed by Chin et al<sup>2</sup>

Presence of  $x / y < 0.5$ , where:

**X** = distance from the epicardial surface to the trabecular recess;

**Y** = distance from the epicardial surface to the peak of trabeculations.

These criteria are applied to trabeculations of the left ventricular apex with subxiphoid or apical four-chamber views at the end of the diastole.

#### 2. Criteria proposed by Stollberger et al<sup>32</sup>

- Presence of more than three trabeculations in the left ventricular wall, with the papillary muscles located at the apex, visible in one image plane.
- Intertrabecular spaces, perfused from the ventricular cavity, viewed by color Doppler imaging.

#### 3. Criteria proposed by Jenni et al<sup>30,31</sup>

- Absence of coexisting cardiac abnormalities.
- Segmental thickening of myocardial wall of left ventricle with two layers: a thin epicardial layer and a thick endocardial layer with prominent trabeculations and deep recesses. The ratio of non-compacted myocardium to compact myocardium at the end of systole is  $> 2:1$ ;
- The trabeculae are usually located on the apical/lateral, middle/bottom walls of the left ventricle. Most non-compacted segments are hypokinetic.
- The flow between the intertrabecular recesses can be identified by using the color Doppler method (Figure 1).

The diagnostic criteria commonly used are those proposed by Jenni et al<sup>30</sup> and Frischknecht et al<sup>31</sup>. They are more accurate echocardiographic criteria that are available. The study conducted by Frischknecht et al, who substantiated such criteria, was retrospective and blinded. The study evaluated

**Table 1 - Demographic and clinical characteristics of patients with ventricular noncompaction cardiomyopathy**

	Chin <sup>2</sup>	Ritter <sup>4</sup>	Ichida <sup>26</sup>	Oechslin <sup>7</sup>	Stolberg <sup>22</sup>
Patients	8	17	27	34	62
Males %	63	82	56	74	70
Median age at diagnosis (years)	7	45	5	40	50
Age group (years)	0.9 to 22.5	18 to 71	0 to 15	16 to 71	18 to 75
Monitoring (years)	≤ 5	≤ 6	≤ 17	≤ 11	≤ 6
Facial dysmorphism (%)	38	0	33	0	...
Familial occurrence (%)	50	12	44	18	...
Location of non-compaction segments					
Apex	majority	100	100	94	98
Inferior wall	...	100	70	84	8
Lateral wall	...	...	41	100	19
ECG - abnormal	88	88	88	94	92
Branch block	25*	47	15	56	26
S. Wolf-Parkinson-white	13	0	15	0	3
Ventricular tachycardia	38	47	0	41	18
Atrial fibrillation	...	29	...	26	5
Left ventricular systolic dysfunction	63	76	60	82	58
Congestive heart failure	63	53	30	68	73
Systemic embolism	38	24	0	21	...
Pulmonary embolism	0	6	7	9	...
Ventricular thrombus	25	6	0	9	...
Heart transplant	0	12	4	12	...
Neuromuscular disorders	...	...	...	...	82
Mortality	38	47	7	35	...
Sudden death	13	18	0	18	...

Adapted from Rigopoulos et al<sup>23</sup>.

19 patients with non-compaction cardiomyopathy, 31 with idiopathic dilated cardiomyopathy, 22 with hypertensive cardiomyopathy and 86 with severe heart valve disease with dysfunction. In all the patients with NCC, there was thickening of the left ventricle wall in the two layered structures, as well as recesses perfused and assessed by Doppler in 95% and hypokinetic segments in 89%.

The myocardial wall trabeculations are most commonly located at the apex and on lateral and bottom walls of the left ventricle<sup>33</sup> (Table 2).

### Cardiac magnetic resonance imaging

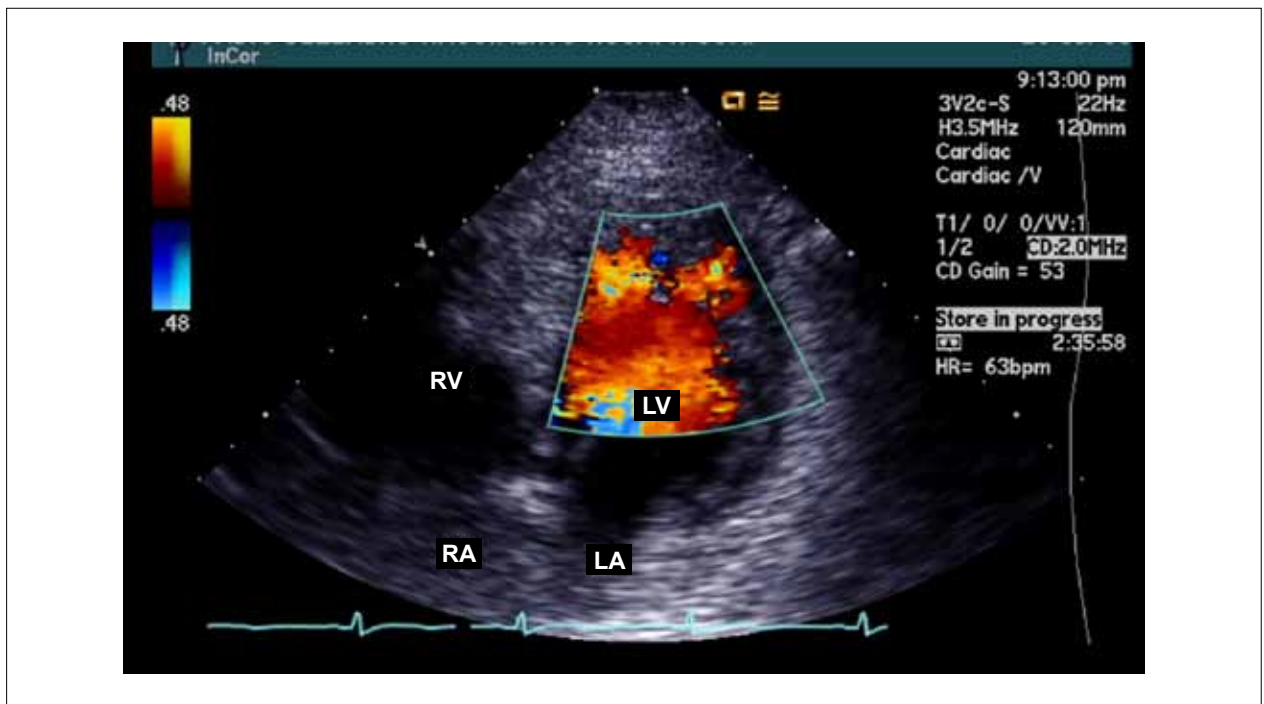
Traditionally, the left ventricular non-compaction is diagnosed by echocardiography, when the ratio of compacted to noncompacted myocardium is more than two. However, the apical region cannot be properly viewed by echocardiography, and this leads to underestimation of the degree of the left ventricular non-compaction. Thus, cardiac resonance has become the method of choice to confirm or rule out the diagnosis of NCC, because it provides a more detailed description of the cardiac morphology in any

image plane (Figure 2). A ratio of compacted myocardium to noncompacted myocardium > 2.3 produces the highest sensitivity (86%) and specificity (99%) in the diagnosis<sup>34,35</sup>. The effectiveness of the diagnosis made by resonance was evaluated by a study with seven patients with NCC, who were compared with 170 healthy patients, athletes, patients with hypertrophic cardiomyopathy, hypertensive heart disease and aortic stenosis<sup>35</sup>, where the following was observed:

1. The noncompaction areas are most commonly found in the apical and lateral portions of the left ventricle<sup>35</sup>.
2. The ratio of noncompacted myocardium to compacted myocardium must be greater than 2.3 during the diastole (sensitivity of 86% and specificity of 99%)<sup>35</sup>.

### Limitations of the diagnostic criteria

There is already enough evidence to support the concept of non-compaction cardiomyopathy as a real illness and which can, in some cases, be associated with other cardiac and systemic anomalies, especially neuromuscular disorders. However, a recent study<sup>36</sup> demonstrated that a large portion of patients diagnosed with systolic heart failure met the



**Figure 1** - Echocardiogram, apical four-chamber view demonstrating intertrabecular recesses and trabeculations in the left ventricle. The flow in the trabeculae can be verified by the color Doppler method.

**Table 2** - Location of trabeculations in patients diagnosed with noncompaction cardiomyopathy

	Pediatric patients Ichida <sup>26</sup>	Adult patients Oechslin <sup>7</sup>	Sengupta <sup>41</sup>
LV apex	100%	94%	100%
Inferior wall	70%	94%	95%
Lateral wall	41%	100%	100%
Basal segments of the LV		< 20%	< 27%

LV - left ventricle.

criteria for NCC, at least when such criteria are applied a posteriori. There was also evidence that 8.3% of the normal controls listed in this study met these criteria, suggesting that prominent trabeculations could be another incidental finding. This is particularly true for black people, who have a higher incidence of hypertrabeculation that meets current diagnostic criteria, regardless of the presence of left ventricular disease.

To avoid an excess of NCC diagnoses, it is recommended that the suspected diagnosis be confirmed with the use of cardiac magnetic resonance imaging, so as to differentiate the trabeculae of aberrant bands, false tendons and abnormal insertion of papillary muscles. Consider the differential diagnosis with thrombi, apical hypertrophic cardiomyopathy, fibroma, obliterative process, intramyocardial hematoma, cardiac metastases and intramyocardial abscesses (Table 3)<sup>37,38</sup>.

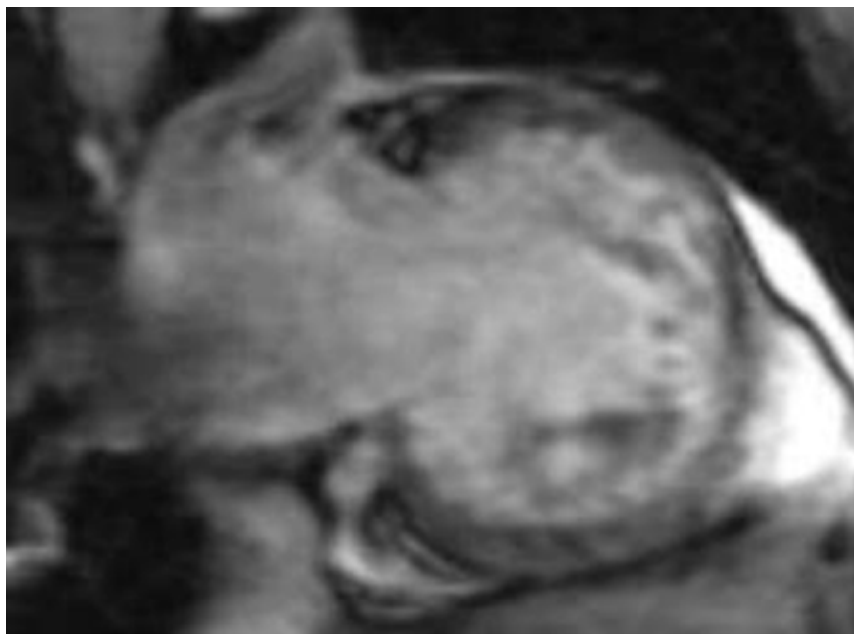
In children, this cardiomyopathy must be differentiated from pulmonary valve atresia with intact interventricular

septum and diseases that may lead to obstruction of the outflow of the left ventricle. Some cardiac tumors such as hemangiomas, which are characterized by the proliferation of blood vessels, may look like recesses<sup>26</sup>.

## Treatment

The main complications related to noncompaction cardiomyopathy are thromboembolism, arrhythmias and progressive heart failure. The prevention of thromboembolic complications has been the subject of intense debate. Some authors recommend prophylactic anticoagulation, in the long term, for all patients diagnosed with ventricular noncompaction, regardless of the ventricular function<sup>4,7</sup>. However, the risk of thromboembolism is probably lower than it was previously believed. As a consequence, some guidelines, including the Brazilian one<sup>39</sup>, recommend anticoagulation to patients with decreased systolic function with ejection fraction below 40%, history of thromboembolism or atrial fibrillation<sup>8</sup>. The use of aspirin is recommended for asymptomatic patients with normal systolic function. With respect to beta-blockers, their use in left ventricular dysfunction caused by noncompaction is performed by extrapolating the indications of management in heart failure. Even though the results are scarce, they should be used together with ACE inhibitors. There is only one study that evaluated the use of beta-blockers in children with NCC<sup>40</sup>.

Due to the increased frequency of ventricular tachycardia and significant risk of sudden death, the evaluation of atrial and ventricular arrhythmias by ambulatory monitoring of ECG should be carried out on an annual basis. In the case of symptomatic



**Figure 2** - ECG gated acquisitions in cine FIESTA, at the end of diastole, in the LV long-axis plane. Note the total wall thickness and increase in the subendocardial trabeculation of the LV. The maximum ratio of non-compacted diastolic myocardial thickness (red tracing/green tracing) was 3.8. The mean ratio was 2.4.

**Table 3 - Alternative diagnoses when aspects of NCC are present on echocardiogram and when such aspects can be confirmed by cardiac MRI**

Athletic heart	Fabry Disease
Cardiac sarcoidosis	Primary amyloidosis
Hypertrophic cardiomyopathy	Cardiac tumors
Friedreich's ataxia	Hyperparathyroidism
Hypereosinophilic Syndrome	Noonan Syndrome
Klinefelter's syndrome	Pompe Disease
Glycogen disorders	Pheochromocytoma

ventricular arrhythmia and in the context of impaired systolic function, the prevention of a sustained event and potentially lethal arrhythmia is indicated by antiarrhythmic agents or implantable cardiac defibrillators, according to international guidelines. The echocardiographic tracing of relatives has been recommended. Due to the high prevalence of neuromuscular disorders reported in patients with NCC, neurological and musculoskeletal evaluations are also recommended.

The reason why there is often a relationship between the noncompaction and neuromuscular disorders is unknown. The prevalence of neuromuscular disorders was of 82% in 49 patients with NCC who were neurologically investigated<sup>32</sup>. In some of these cases, the neuromuscular disorder had not yet manifested itself clinically. In such cases, the diagnosis of NCC can lead to the neurological diagnosis, so it is recommended that patients with NCC undergo neurological examinations,

regardless of whether they have symptoms or not.

Oechslin et al<sup>7</sup> reported that certain clinical characteristics were more frequently observed in patients who died, compared to survivors with NCC, including higher final diastolic diameter of left ventricle, low ejection fraction, functional class III-IV (New York Heart Association), persistent or permanent atrial fibrillation and bundle branch block. Patients with these characteristics are at high risk and they are, at an early stage, candidates for aggressive interventions, including the consideration of an implantable cardiac defibrillator and evaluation for transplant.

The prognosis of patients with noncompaction cardiomyopathy is determined by the degree and progression of heart failure, presence of thromboembolic events and arrhythmias. In an initial series, approximately 60% of patients suffered a sudden death or underwent cardiac transplant, within six years after the diagnosis<sup>4</sup>. Similarly, in another series of 34 adults with isolated NCC, 47% of such patients died or underwent heart transplantation in a follow-up period of  $44 \pm 39$  months<sup>7</sup>. The occurrence of embolic events, ventricular arrhythmias and sudden death appears to be significantly lower in pediatric patients<sup>26</sup> when compared to the subpopulation of adults in the initial description of Chin et al<sup>2</sup>, although approximately 90% of patients monitored over a period of ten years to developed left ventricular dysfunction. Recently, Murphy et al<sup>8</sup> noted improvement in prognosis, compared to what was reported in previous studies. For a mean period of 46 months, one death was found in a cohort of 45 patients with ventricular noncompaction, who were clinically monitored at regular intervals every six months in a specialized center.

## Conclusion

Noncompaction cardiomyopathy is a disease that has been increasingly diagnosed in clinical practice and which may, in some cases, be associated with other cardiac and systemic anomalies, especially neuromuscular disorders. Its clinical presentation is highly variable and it may be asymptomatic in many cases, or it may lead to severe heart failure and sudden death in other cases. The high incidence of noncompaction cardiomyopathy in recent years, mainly due to improvements in echocardiographic techniques and use of cardiac resonance, suggests that hypertrabeculation also occurs in other comorbidities and that it may be falsely diagnosed as ventricular noncompaction. Therefore, we suggest that the diagnosis of suspected myocardial noncompaction should be carefully

evaluated by imaging methods to avoid inappropriate and exaggerated diagnoses.

## Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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## Study Association

This study is not associated with any post-graduation program.

## References

1. Bellet S, Gouley BA. Congenital heart disease with multiple cardiac anomalies: report of a case showing aortic atresia, fibrous scar in myocardium and embryonal sinusoidal remains. *Am J Med Sci.* 1932; 183: 458-65.
2. Chin TK, Perloff JK, Williams RC, Jue J, Mohrmann R. Isolated noncompaction of left ventricular myocardium: a study of eight cases. *Circulation.* 1990; 82 (2): 507-13.
3. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, et al. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. *Circulation.* 2006; 113 (14): 1807-16.
4. Ritter M, Oechslin E, Sutsch G, Attenhofer C, Schneider J, Jenni R. Isolated noncompaction of the myocardium in adults. *Mayo Clin Proc.* 1997; 72 (1): 26-31.
5. Weiford BC, Subbarao VD, Mulhern KM. Noncompaction of the ventricular myocardium. *Circulation.* 2004; 109 (24): 2965-71.
6. Jenni R, Wyss CA, Oechslin EN, Kaumann PA. Isolated ventricular noncompaction is associated with coronary microcirculatory dysfunction. *J Am Coll Cardiol.* 2002; 39 (3): 450-4.
7. Oechslin EN, Attenhofer Jost CH, Rojas JR, Kaufmann PA, Jenni R. Long-term follow-up of 34 adults with isolated left ventricular noncompaction: a distinct cardiomyopathy with poor prognosis. *J Am Coll Cardiol.* 2000; 36 (2): 493-500.
8. Murphy RT, Thaman R, Blanes JC, Ward D, Sevdalis E, Papra E, et al. Natural history and familial characteristics of isolated left ventricular non-compaction. *Eur Heart J.* 2005; 26 (2): 187-92.
9. Taylor GP. Cardiovascular system. In: Dimmick JE, Kalousek DK, eds. *Developmental pathology of the embryo and fetus.* Philadelphia, Pa: Lippincott; 1992. p. 467-508.
10. Zambrano E, Marshalko SJ, Jaffe CC, Hui P. Isolated noncompaction of the ventricular myocardium: clinical and molecular aspects of a rare cardiomyopathy. *Lab Invest.* 2002; 82 (2): 117-22.
11. Finsterer J, Stollberger C, Feichtinger H. Histological appearance of left ventricular hypertrabeculation/noncompaction. *Cardiology.* 2002; 98 (3): 162-4.
12. Conraads V, Paelinck B, Vorlat A, Goethals M, Jacobs W, Vrints C. Isolated non-compaction of the left ventricle: a rare indication for transplantation. *J Heart Lung Transplant.* 2001; 20 (8): 904-7.
13. Daimon Y, Watanabe S, Takeda S, Hijikata Y, Komuro I. Two-layered appearance of noncompaction of the ventricular myocardium on magnetic resonance imaging. *Circ J.* 2002; 66 (6): 619-21.
14. Hamamichi Y, Ichida F, Hashimoto I, Uese KH, Miyawaki T, Tsukano S, et al. Isolated noncompaction of the ventricular myocardium: ultrafast computer tomography and magnetic resonance imaging. *Int J Cardiovasc Imaging.* 2001; 17 (4): 305-14.
15. Lauer RM, Fink HP, Petry EL, Dunn MI, Diehl AM. Angiographic demonstration of intramyocardial sinusoids in pulmonary-valve atresia with intact ventricular septum and hypoplastic right ventricle. *N Engl J Med.* 1964; 271: 68-72.
16. Attenhofer Jost CH, Connolly HM, O'Leary PW, Warnes CA, Tajik AJ, Seward JB. Left heart lesions in patients with Ebstein anomaly. *Mayo Clin Proc.* 2005; 80 (3): 361-8.
17. Friedberg MK, Ursell PC, Silverman NH. Isomerism of the left atrial appendage associated with ventricular noncompaction. *Am J Cardiol.* 2005; 96 (7): 985-90.
18. Lilje C, Razek V, Joyce JJ, Rau T, Finckh BF, Weiss F, et al. Complications of non-compaction of the left ventricular myocardium in a paediatric population: a prospective study. *Eur Heart J.* 2006; 27 (15): 1855-60.
19. Zaragoza MV, Arbustini E, Narula J. Noncompaction of the left ventricle: primary cardiomyopathy with an elusive genetic etiology. *Curr Opin Pediatr.* 2007; 19 (6): 619-27.
20. Ichida F, Tsubata S, Bowles KR, Haneda N, Uese K, Miyawaki T, et al. Novel gene mutations in patients with left ventricular noncompaction or Barth syndrome. *Circulation.* 2001; 103 (9): 1256-63.
21. Xing Y, Ichida F, Matsuoka T, Isobe T, Ikemoto Y, Higaki T, et al. Genetic analysis in patients with left ventricular noncompaction and evidence for genetic heterogeneity. *Mol Genet Metab.* 2006; 88 (1): 71-7.
22. Vatta M, Mohapatra B, Jimenez S, Sanchez X, Faulkner G, Perles Z, et al. Mutations in cyphe/ZASP in patients with dilated cardiomyopathy and left ventricular non-compaction. *J Am Coll Cardiol.* 2003; 42 (11): 2014-27.
23. Sasse-Klaassen S, Probst S, Gerull B, Oechslin E, Nürnberg P, Heuser A, et al. Novel gene locus for autosomal dominant left ventricular noncompaction maps to chromosome 11p15. *Circulation.* 2004; 109 (22): 2720-3.
24. Monserrat L, Hermida-Prieto M, Fernandez X, Rodríguez I, Dumont C, Cazón L, et al. Mutation in the alpha-cardiac actin gene associated with apical hypertrophic cardiomyopathy, left ventricular non-compaction, and septal defects. *Eur Heart J.* 2007; 28 (16): 1953-61.
25. Conces DJ Jr, Ryan T, Tarver RD. Noncompaction of ventricular myocardium: CT appearance. *Am J Roentgenol.* 1991; 156 (4): 717-8.

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26. Ichida F, Hanamichi Y, Miyawaki T, Ono Y, Kamiya T, Akagi T, et al. Clinical features of isolated noncompaction of the ventricular myocardium: long-term clinical course, hemodynamic properties, and genetic background. *J Am Coll Cardiol*. 1999; 34 (1): 233-40.
27. Hook S, Ratliff NB, Rosenkranz E, Sterba R. Isolated noncompaction of the ventricular myocardium. *Pediatr Cardiol*. 1996; 17 (1): 43-5.
28. Pignatelli RH, McMahon CJ, Dreyer WJ, Denfield SW, Price J, Belmont JW, et al. Clinical characterization of left ventricular noncompaction in children: a relatively common form of cardiomyopathy. *Circulation*. 2003; 108 (21): 2672-8.
29. Salerno JC, Chun TU, Rutledge JC. Sinus bradycardia, Wolff Parkinson White, and left ventricular noncompaction: an embryologic connection? *Pediatr Cardiol*. 2008; 29 (3): 679-82.
30. Jenni R, Oechslin E, Schneider J, Attenhofer Jost C, Kaufmann PA. Echocardiographic and pathoanatomical characteristics of isolated left ventricular non-compaction: a step towards classification as a distinct cardiomyopathy. *Heart*. 2001; 86 (6): 666-71.
31. Frischknecht BS, Jost CH, Oechslin EN, Seifert B, Hoigné P, Roos M, et al. Validation of noncompaction criteria in dilated cardiomyopathy, and valvular and hypertensive heart disease. *J Am Soc Echocardiogr*. 2005; 18 (8): 865-72.
32. Stollberger C, Finsterer J, Blazek G. Left ventricular hypertrabeculation/noncompaction and association with additional cardiac abnormalities and neuromuscular disorders. *Am J Cardiol*. 2002; 90 (8): 899-902.
33. Rigopoulos A, Rizos IK, Aggeli C, Kloufetos P, Papacharalampous X, Stefanadis C, et al. Isolated left ventricular noncompaction: an unclassified cardiomyopathy with severe prognosis in adults. *Cardiology*. 2002; 98 (1-2): 25-32.
34. Daimon Y, Watanabe S, Takeda S, Higikata Y, Komuro I. Two-layered appearance of noncompaction of the ventricular myocardium on magnetic resonance imaging. *Circ J*. 2002; 66 (6): 619-21.
35. Petersen SE, Selvanayagam JB, Wiesmann F, Robson MD, Francis JM, Andersen RH, et al. Left ventricular non-compaction: insights from cardiovascular magnetic resonance imaging. *J Am Coll Cardiol*. 2005; 46 (1): 101-5.
36. Kohli SK, Pantazis AA, Shah JS, Adeyemi B, Jackson G, McKenna WJ, et al. Diagnosis of left-ventricular noncompaction in patients with left-ventricular systolic dysfunction: time for a reappraisal of diagnostic criteria? *Eur Heart J*. 2008; 29 (1): 89-95.
37. Stollberger C, Finsterer J. Pitfalls in the diagnosis of left ventricular hypertrabeculation/non-compaction. *Postgrad Med J*. 2006; 82 (972): 679-83.
38. Alhabshan F, Smallhorn JF, Golding F, Musewe N, Freedom RM, Yoo SJ. Extent of myocardial non-compaction: comparison between MRI and echocardiographic evaluation. *Pediatr Radiol*. 2005; 35 (11): 1147-51.
39. Bocchi EA, Braga FGM, Ferreira SMA, Rohde LEP, Oliveira WA, Almeida DR, et al/Sociedade Brasileira de Cardiologia. III Diretriz brasileira de insuficiência cardíaca crônica. *Arq Bras Cardiol*. 2009; 93 (1 supl.1): 1-71.
40. Toyono M, Kondo C, Nakajima Y, Nakazawa M, Momma K, Kusakabe K. Effects of carvedilol on left ventricular function, mass, and scintigraphic findings in isolated left ventricular non-compaction. *Heart*. 2001; 86 (1): E4.
41. Sengupta PP, Mohan JC, Mehta V, Jain V, Arora R, Pandian NG, et al. Comparison of echocardiographic features of noncompaction of the left ventricle in adults versus idiopathic dilated cardiomyopathy in adults. *Am J Cardiol*. 2004; 94 (3): 389-91.