



# Non-Compacted Cardiomyopathy: Is there a Need of a New Cardiomyopathy?

Francesco Bianco<sup>1,2\*</sup>, Piergiusto Vitulli<sup>1</sup>, Valentina Bucciarelli<sup>1</sup>, Alvin Chandra<sup>1,2</sup>, Masatoshi Minamisawa<sup>2,3</sup> and Sabina Gallina<sup>1</sup>

<sup>1</sup>Institute of Cardiology, Chieti, Italy

<sup>2</sup>Brigham and Women's Hospital, Boston, USA

<sup>3</sup>Department of Cardiovascular Medicine, Matsumoto, Japan

\*Corresponding author: Francesco Bianco, Institute of Cardiology, Chieti, Italy

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## Abstract

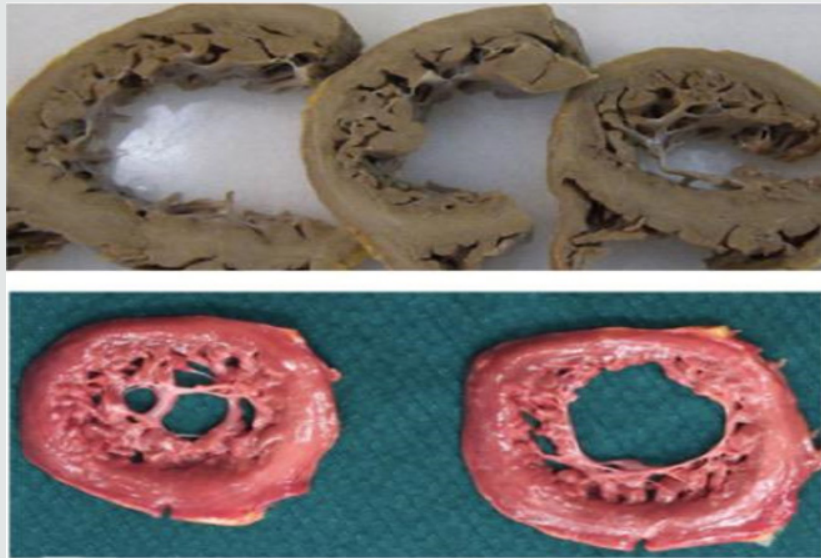
Left ventricular non-compaction (LVNC) is a myocardial disorder, classically defined as a double-layered myocardium, consisting of a thick, spongy/hypertrabeculated, non-compacted endocardial segment and a thin, compacted, epicardial portion. The American Heart Association (AHA) classifies LVNC as a distinct primary genetic cardiomyopathy, while the European Association of Cardiology (ESC) as an unclassified cardiomyopathy. Despite the magnitude of the entire literature yield on this topic, to date the pathogenesis, prognosis, and treatment are still unclear. Prevalence and mortality can range respectively from 0.05% to 0.26% and 5% to 47%, but they are affected by the imaging criteria adopted for the diagnosis. In fact, LVNC has been for years incidentally discovered during autopsy of unexplained sudden cardiac deaths. Conversely, with the advent of increasingly sophisticated cardiac imaging techniques, the presence of hypertrabeculated myocardium has become very common. Both echocardiographic and magnetic resonance criteria have been proven to overestimate the diagnosis, which shares a peculiar phenotype with other pathologies. It is known that a hypertrabeculated left ventricle leads to a symptomatic triad consisting of heart failure, arrhythmias and thromboembolisms. Therefore, it is current opinion of the authors that a “non-compaction cardiomyopathy” (NC-CMP) seems to be the most comprehensive definition of a disease that, similarly to the other cardiomyopathies, and regardless of its etiology, beyond a peculiar phenotype shares a distinct symptomatology and deserves to be listed as an entity between cardiomyopathies.

**Keywords:** Left Ventricle Non-Compaction; Non-Compacted Cardiomyopathy; Cardiomyopathies; Heart Failure; Sudden Cardiac Death

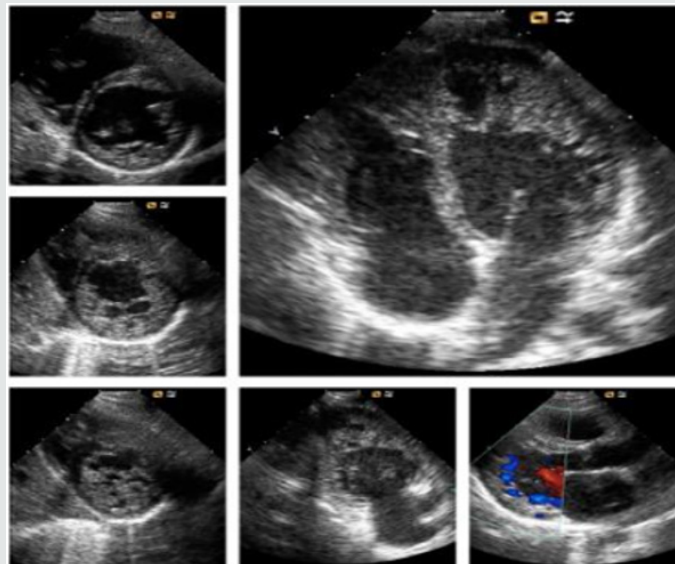
## Introduction

Left ventricular non-compaction (LVNC) is a myocardial disorder, classically defined as a double-layered myocardium, consisting of a thick and spongy or hypertrabeculated endocardial segment, defined as non-compacted, and a thin and compacted portion, laying epicardially [1]. The above-mentioned hypertrabeculations (HXTs) characteristically involve the left ventricle (LV), especially the apex, the lateral, infero-lateral and inferior wall [1,2], and less frequently the right ventricle [3]. Since its first reports, LVNC has always been considered a controversial pathology

(Figures 1 & 2). In fact Grant and colleagues, for long accredited as discoverers in 1926, presented a case of persistent sinusoids instead of LVNC [1]. In addition, a lack of uniqueness among the World Health Organization [4], the European Society of Cardiology [5], and the American Heart Association [6] for its classification, and the presence of trabeculae as a terminal phenotype of LV hemodynamic overload or other myocardial affections, has led several authors to debate on the real existence of a true form of uncomplicated primitive non-compacted cardiomyopathy [7,8].



**Figure 1:** Two different anatomic-pathological macroscopic sections of the left ventricle, presenting a non-compacted myocardium. Modified from Lorca et al. *Int J Cardiol* 2016.



**Figure 2:** Echocardiographic features of a young adult of 16-years old, admitted in emergency room with acute signs and symptoms of acute heart failure.

## Morpho Pathogenesis

The primitive hypothesis concerning LVNC is that the presence of HTXs is due to a failure in myocardial morphogenesis, in which the immature, non-compacted fetal myocardium normally undergoes a physiological compaction process during ontogenesis [1]. LVNC may occur isolated, in familial forms or associated with several congenital, genetic, neuromuscular and chromosomal conditions [9]. Mutations in the sarcomere gene, particular in MYH7, are the most common and non-sarcomere gene mutations (such as TAZ and NOTCH1) have also reported [10-12]. Some LVNC individuals have been detected by tracking asymptomatic relatives of affected patients [9], and therefore, a close correlation between genotype and phenotype has been recently underlined by 2 recent studies

using NEXT-generation sequencing [13,14]. All these pathogenic variants were independent risk factors for cardiovascular events [13]. In addition, mutations in hyperpolarization-activated cyclic nucleotide channel 4 (HCN4) have also been reported in families with sinus node dysfunction and LVNC [15,16].

## Epidemiology

Since only few studies focused on LVNC incidence, both prevalence and mortality are challenging to assess [1]. Among adults, it can be diagnosed in 0.05% - 0.26% of the cases, and approximately 0.14% of pediatric patient, with an overall mortality ranging from 5% to 47% in both populations [1]. Unfortunately, all the reports are affected by the diagnostic criteria adopted, imaging or autopsies, overestimating or underestimating the real prevalence

[1,17]. In addition, and similarly with others cardiomyopathies, LVNC can be a subtle disease [17]; if not promptly diagnosed, patients may be asymptomatic for a long time and the onset may range from the early life to the adulthood [8].

## Diagnosis

The advent of increasingly sophisticated cardiac imaging techniques set the spotlight on HXTs as a very common finding, instead of the rare disease that was previously considered [2,18,19]. Accordingly, Jenni, Chin and Stollberg defined different echocardiographic criteria, while Petersen, Jacquier, Captur and Stacey defined some cardiovascular magnetic resonance (CMR) criteria. Unfortunately, they both showed very poor specificity [7,8], even if CMR overcame the ultrasound-related limits in morphologic assessment, and demonstrated a high correlation between late gadolinium enhancement myocardial fibrosis and clinical severity of the disease [20]. Nevertheless, there still a lack of an imaging-driven diagnostic gold standard [1,9].

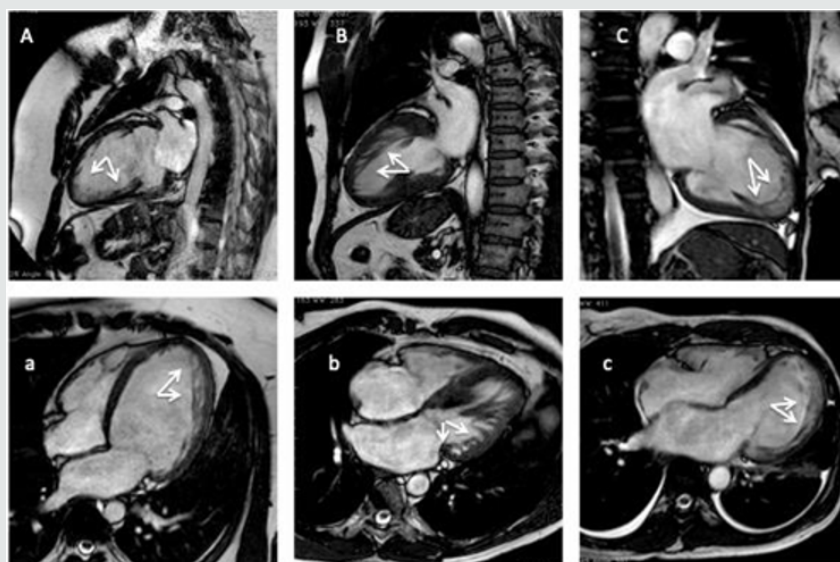
## Clinical Aspects and Treatment

Clinical findings are variable, including several grades of diastolic and systolic dysfunction, heart failure (HF), thromboembolic events, and malignant arrhythmias. However, the most severe outcome is the sudden cardiac death. Atrial fibrillation, right/left bundle branch block, and repolarization abnormalities may be the only electrocardiographic features present at the moment of the diagnosis [2,8]. There is no specific therapy and LVNC management

depends on the clinical manifestations; anticoagulation is indicated only if atrial fibrillation, heart failure, previous embolism, or intracardiac thrombus formation are present [1,21].

## Discussion

LVNC has always been a controversial disease, with some unresolved issues. First of all, there is a heterogeneous genetic background and a wide spectrum of associated conditions that may occur contextually with HTXs. Secondly, LVNC real prevalence is still unknown. Certainly, the lack of any echocardiographic or CMR diagnostic gold standard, with frequent overestimation/underestimation, does not help to clarify all the uncertainties. In addition, there are a wide variety of overlapping conditions that may occur with secondary myocardial HXTs, for example, a dilated cardiomyopathy or the end-stage hypertrophic cardiomyopathy (Figure 3). On the other hand, it is common experience that not all the above-mentioned cardiomyopathies and conditions can present an end-stage non-compacted phenotype and generalizing this aspect would be very simplistic. In addition, Lorca and colleagues recently reiterated that non-compacted forms of cardiomyopathy do exist, especially during early stages of life, and they can be demonstrated in some forms of unexplained sudden deaths. Furthermore, a multicenter longitudinal prospective study [7], despite its conclusions, and if carefully read between the lines, suggests that a significant proportion of asymptomatic patients meets all currently used imaging diagnostic criteria for LVNC.



**Figure 3:** Cardiac magnetic resonance imaging (CMR) exams of patients matching the currently imaging criteria for CMR (A, B, C, 2-chambers view; a, b, c, 4chambers view). (A, a) A 23-years-old male patients with a dilated cardiomyopathy. (B, b) a 38-years old woman with an end-stage hypertrophic cardiomyopathy. (C, c) a 45-years old woman admitted in emergency room for acute heart failure, and history of silent cerebral infarcts.

However, they demonstrated that outcomes are increased by symptoms and clinical conditions when associated with a non-compacted phenotype. Indeed, a recently published multicenter register provided an accurate estimation of genetic-phenotype association, and clinical and events of LVNC patients, concluding

that the clinical course of symptomatic LVNC patient with a genotype-phenotype matching can be severe [13,14]. Given all these premises, it is reasonable considering the existence of a primitive non-compacted disease, congenital, and a mild form, with a late-onset, and/or acquired conditions. HF, thromboembolic

events, and malignant arrhythmias seem to constitute the clinical triad for LVNC patients, and sudden cardiac death the most severe outcome. There is a tight genotype-phenotype correlation, with a wide spectrum of genes and mutation involved, as well as hypertrophic cardiomyopathy, for example, and the current imaging-derived diagnostic criteria probably need to be revised; perhaps it should be worth to combine some imaging and clinical criteria. At last, multicentric registries should be considered to help the real prevalence assessment of non-compacted forms of cardiomyopathies.

## Conclusion

It is current opinion of the authors that a “non-compacted cardiomyopathy” (NC-CMP) seems to be the most comprehensive definition of a disease that, similarly to the other cardiomyopathies, and regardless of its etiology, beyond a peculiar phenotype shares a distinct symptomatology and deserves to be listed as an entity between cardiomyopathies.

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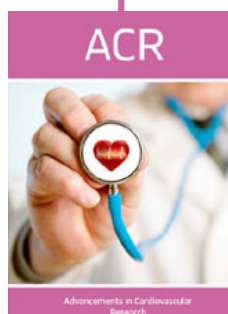
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