Noncompaction Cardiomyopathy – is it a New "Prolapse"? An Early Stigma of Cardiomyopathy

Miocárdio não Compactado – um Novo "Prolapso"? Um Estigma Precoce de uma Cardiomiopatia

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An analysis of publications on non-compaction cardiomyopathy (NCC) reveals skepticism regarding its etiology, which is considered by some to be an epiphenomenon of other cardiomyopathies.[1] A diagnostic method is validated based on a gold standard method, be it biopsy, genetic analysis, enzyme measurement, autopsy study, or even another imaging method. However, healthy individuals with a pathological morphological feature (for example, left ventricular (LV) hypertrabeculation, as described in athletes, pregnant women, and black individuals) are more difficult to analyze.[2] Unfortunately, the actual pathophysiology of NCC is not understood. Currently, there are two hypotheses: The first—and the most widespread—postulates that an intrauterine arrest occurs in the embryonic process of myocardial compaction,[3] while the other postulates dysregulation in the embryonic signaling between the endocardial layer of the epicardium, which stimulates compaction of the cardiomyocytes and their hypertrabeculation.[4] Recently, Tavares de Melo et al. demonstrated that compared with healthy controls, NCC patients showed a lower myocardial glucose uptake independent of the LV ejection fraction.[5] Based on this, primary mitochondrial dysfunction may be at the heart of NCC pathophysiology. Mitochondrial changes are common to all myocardial dysfunctions; however, under metabolic stress, NCC behaves antagonistically (reduced glucose uptake).

Transthoracic echocardiogram is a first-line diagnostic tool used for the most diverse cardiomyopathies, including NCC.

Keywords

Diagnosis; Noncompaction cardiomyopathy; Echocardiogram.

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The first echocardiographic description of NCC was reported in 1984[6] and the first diagnostic echocardiographic criterion was established in 1990.[7] There are three diagnostic criteria implemented in clinical practice:

1. Criterion by Chin et al. (California)[7]: an X/Y ratio less than or equal to 0.5, wherein X is the distance from the epicardial surface to the trabecular recess and Y is the distance from the epicardial surface to the peak of the trabeculations. This criterion is used for LV apical trabeculae in the short-axis and apical parasternal sections at the end of diastole.

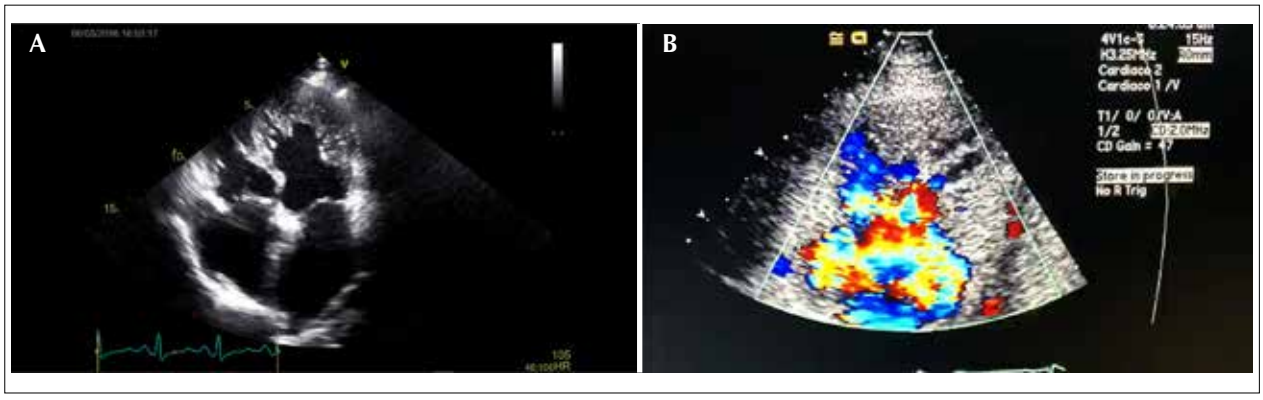
2. Criteria by Jenni et al. (Zurich)[8]: absence of coexisting cardiac changes; thickening of the LV myocardial wall with two layers filled with blood coming from the ventricular cavity: one layer is the thin and compacted epicardium (C), while the other is the thick and non-compacted endocardium (NC). At the end of the systole, the NC/C ratio is greater than 2 in the short axis. The trabeculae are usually located on the apical, mid-lateral, and mid-inferior LV walls.

3. Criteria by Stöllberger et al. (Vienna)[9]: presence of four or more trabeculae in the LV wall, with apically located papillary muscles, visible in a single image plane. Trabeculae have the same echogenicity as the myocardium and show synchronous movement with ventricular contraction. Intratrabecular spaces are filled with blood from the ventricular cavity, which is visualized on color Doppler. The image is acquired in the apical section with four chambers. Different sections should be recorded to enhance image definition and to identify LV false tendons and anomalous strands.

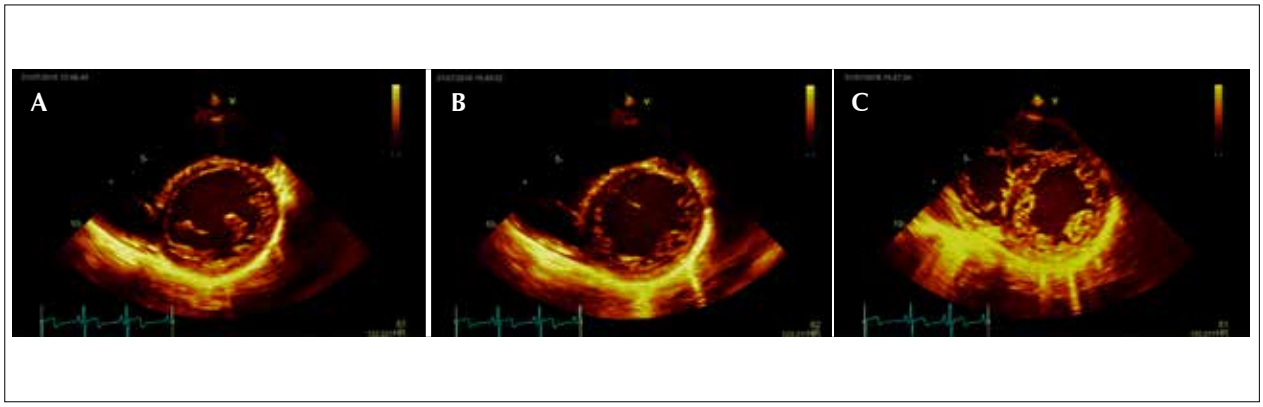
It was observed that although these three criteria had some similarities, when applied to NCC patients, only 29.9% of those previously diagnosed with NCC met all three. Moreover, 8% of the healthy individuals met one or more criteria.[10] Excessive bilateral anxiety is shared between the echocardiographer and the requesting physician when faced with LV hypertrabeculation. Importantly, before establishing the diagnosis, the attending physician should be aware of the technical challenges associated with LV hypertrabeculation. One of these—the most trivial, albeit extremely relevant—is

the calculation of the LV ejection fraction using the modified Simpson's rule (biplane method of disks) (Videos 1A and 1B). Video 1A clearly shows the difficulty in locating the endocardial border (boundary between the non-compacted and compacted layers), a peremptory finding for tracing the endocardial border and thereby, calculating the ejection fraction. Furthermore, the color Doppler velocity should be adjusted between 30 and 40 cm/s to visualize the blood flow between the trabeculae. LV hypertrabeculation must be carefully analyzed while measuring the NC/C ratio to avoid mistakes resulting from the presence of mitral valve chordae, which can be mistaken for trabeculae, or even when acquiring oblique LV sections. In NCC patients, papillary muscle dysmorphisms are often noted as fragmentation, accessory papillary muscle, or apical displacement. Other common findings, which are outside the diagnostic scope but can help in diagnosing other findings, are associations with Ebstein's anomaly, atrial septal defect, false tendons, and mitral valve prolapse. This may be derived from the subvalvular involvement of the papillary muscles, which leads to dysfunction in the mitral valve dynamics. When quantifying the NC/C ratio for diagnostic measurements, perpendicular alignment must be performed in the short axis of the LV, because oblique acquisitions may overestimate this relationship. Conversely, according to another theory, LV hypertrabeculation may work as a substrate for the formation of an intracavitary thrombus, even in sinus rhythm.[11] To test this hypothesis, oblique echocardiographic sections must be performed in the short-axis and apical sections. Two major myths remain: The first is that compacted region thinning is observed during NCC diagnosis, while the second, and the most difficult, is that the LV ejection fraction must be reduced to establish the diagnosis (Videos 2A to 2C show a patient with preserved ejection fraction viewed in the short, middle, and apical axes, respectively). The Petersen criterion, the main diagnostic criterion widely used in cardiac magnetic resonance imaging, establishes an NC/C ratio of greater than 2.3 as the criterion for NCC, based on a sample of seven patients (71% of whom had preserved LV ejection fraction).[12]

To analyze myocardial strain using the speckle-tracking method, the endocardial border must be visualized (Video 3). However, this is challenging in NCC patients, in whom the compacted layer is difficult to distinguish from the non-compacted layer. We must critically assess studies reporting a peculiar longitudinal strain pattern of the LV in NCC that exposes lower values in the apical portions, in contrast to dilated cardiomyopathy, in which the three regions (basal, middle, and apical) are reduced.[13] Considering the highly variable phenotypic and genetic range in NCC patients, achieving a single longitudinal LV deformation pattern is



Video 1 – *A) 4-chamber apical video in a patient with non-compacted layer, demonstrating the technical difficulty in delimiting the compacted and non-compacted layer for Simpson's calculation. B) video zoomed in in the 4-chamber apical portion with color Doppler, showing the flow between the trabeculae.*



Video 2 – *Show a patient with preserved ejection fraction viewed in the short, middle, and apical axes, respectively.*

unlikely; in practice, different patterns are observed (Figure 1). The speckle-tracking method shows a key limitation in the hypertrabeculated apical region. The helicoidal arrangement of the epicardial and endocardial myocardial fibers enables ventricular systolic twisting. With respect to the LV apex, the apical portion presents a resultant counterclockwise rotation and the base presents a clockwise rotation. Curiously, van Dalen et al. proposed a new criterion based on LV twist analysis because 88% of the NCC patients showed a loss of twist, with the rotation at the basal and apical levels predominantly in the same direction.[14] However, in daily practice, a lower frequency and standard variables are noted (Figure 2); this closely resembles the study by Peter et al., which detected this pattern in 53.3% NCC patients.[15] This evaluation is still restricted to the research field, because imaging devices rarely include this tool. Furthermore, the clinical application and prognostic utility of this finding is unknown, although it may be useful for differentiating excess trabeculae from NCC.

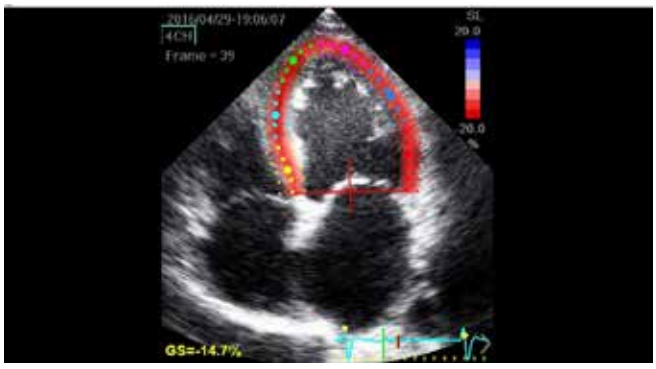
Myocardial hypertrabeculation requires clinical contextualization. A Danish study has shown that children are more likely to have a mutation; conversely, mutations are sporadic in adults. The presence of a mutation in children entails a worse prognosis; among adults, its presence is not a prognostic factor. Lastly, reduced ejection fraction has a negative impact only on NCC patients with some mutation; compared with cases of preserved ejection fraction, there is no impact on survival in sporadic cases with reduced ejection fraction.[16] Thus, children or patients with reduced LV ejection fraction should be judiciously tested for mutations through genetic counseling, because these mutations are mostly autosomal dominant. Randomly performing genetic testing is expensive and may identify variants of undetermined meaning, generating great emotional impact without clinical benefit. In contrast to other cardiomyopathies that are diagnosed when an established phenotype (hypertrophic cardiomyopathy, dilated cardiomyopathy, and arrhythmogenic dysplasia) is found, NCC allows follow-up at preclinical early stages and screening of family members. Considering the lack of knowledge of its pathophysiology and of a gold standard exam for its diagnosis, clinicians face difficulty in putting the puzzle together and establishing a watchful waiting strategy or medical intervention.

Author contributions

Image acquisition and editing and manuscript writing: Melo MDT; Revision: Salemi VMC.

Conflict of interest

The authors have declared that they have no conflict of interest.



Video 3 – *Four-chamber view of the left ventricle, showing the ideal width of the region of interest for analysis of myocardial strain in the compacted layer in a ventricle with hypertrabeculation, avoiding the trabeculae.*

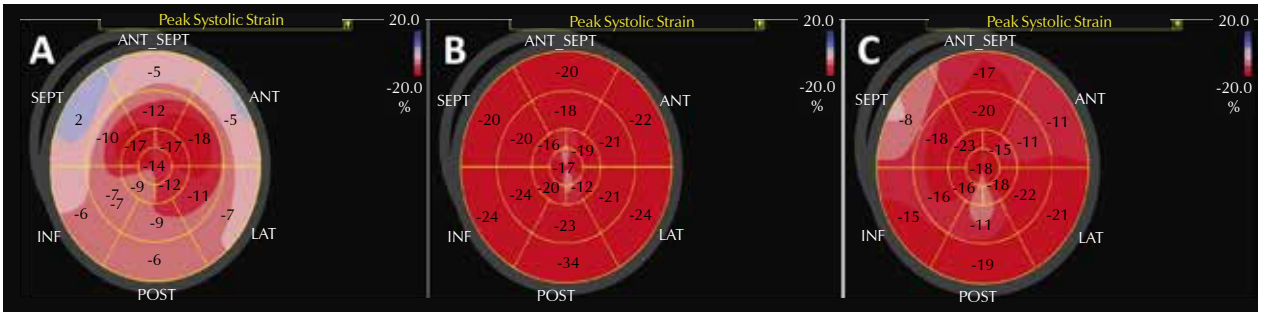


Figure 1 – *Different patterns of LV longitudinal deformation in the bullseye plot for NCC patients. A: pattern typically described in amyloidosis, sparing the apex; B: pattern with reduction of apical values only; and C: without a specific pattern (most common). LV: left ventricle; NCC: non-compacted cardiomyopathy.*

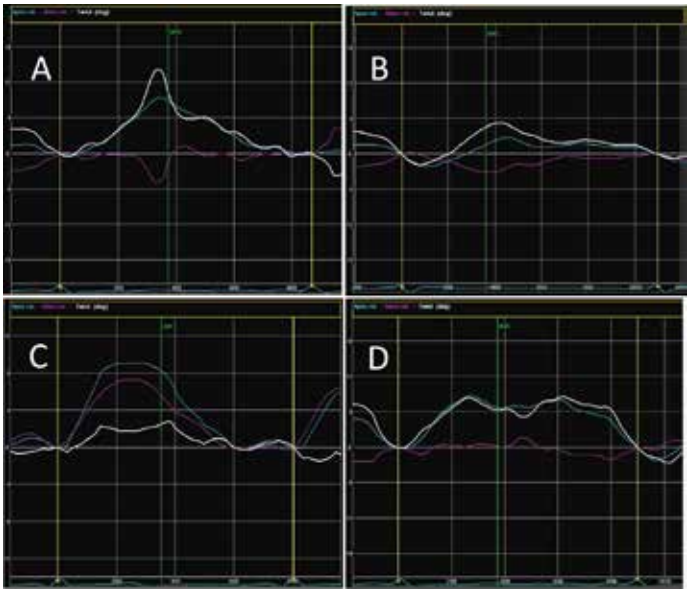


Figure 2 – *NCC patients with different twist patterns. A: preserved; B: reduced twist at the apical and base levels; C: patterns described in NCC with loss of twist (rigid body rotation); and D: loss of twist only at the base of the LV. NCC: non-compacted cardiomyopathy; LV: left ventricle.*

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