Non-compacted myocardium: Should it not be considered a disease? Critical thinking on 140 patients with non-compacted myocardium evaluated by cardiovascular magnetic resonance

Miocardio no compacto ¿Puede no ser una enfermedad? Razonamiento crítico sobre 140 miocardios no compactos evaluados con resonancia magnética cardiovascular

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ABSTRACT

A physical alteration is considered a disease when it meets the criteria defined by the WHO. Non-compacted myocardium (NCM) is a non-well defined ventricular hypertrabeculation which is still under discussion whether it is a cardiomyopathy itself or just a change from normality. We analyzed 161 studies in 140 patients with NCM and their relationships with other pathologies. Later, we exposed them to the "disease" criteria defined by the WHO. After a critical analysis, we consider that NCM should not be considered a cardiomyopathy itself, but rather a myocardial adaptation to adverse conditions.

Key words: Magnetic Resonance – Cardiomyopathies - Left Ventricular Non-Compaction

RESUMEN

Para que una alteración física sea considerada una enfermedad, debe cumplir con los criterios definidos por la OMS. El miocardio no compacto (MNC) es una hipertrabeculación ventricular no bien definida, de la que se duda si es una miocardiopatía en sí misma, o solo una variación de la normalidad. Nosotros analizamos 161 estudios realizados a 140 pacientes con MNC y sus relaciones con otras patologías, exponiéndolos a los criterios de "enfermedad" definidos por la OMS. Tras un análisis crítico, consideramos que no debería ser considerada una miocardiopatía en sí misma, sino una adaptación miocárdica ante condiciones adversas.

Palabras claves: Resonancia Magnética – Cardiomiopatías - Miocardio no compacto

INTRODUCTION

A “healthy heart” means good prognosis. A “sick” heart, however, involves worse prognosis for any subject. Therefore, it is essential to distinguish between healthy individuals and sick patients.

Left ventricular non-compaction is an increasingly common diagnosis. It has always been considered a disease. Improved non-invasive imaging techniques, such as echocardiography, computed tomography, and particularly, cardiac magnetic resonance (CMR), have helped to increase diagnosis. (1) Nevertheless, it is still under discussion whether non-compacted myocardium (NCM) is a disease itself or a histological change in a normal myocardium resulting from a physiological adaptation.

For the World Health Organization (WHO), a disease is “any physiological disorder or impairment in one or several parts of the body, for generally known reasons, associated with certain signs and symptoms and with a quite predictable progress.” To confirm whether a NCM meets these criteria and can be considered a disease, we have performed an observational analysis of 161 CMR studies in 140 patients diagnosed with NCM. Data from the study population were compared against a group of health subjects (control group) to determine if they were “pathologically different” when applying the concept of disease as defined by the WHO.

METHODS

From July 2007 to January 2022, 161 CMR studies were conducted in 140 patients diagnosed with NCM. Patients were referred to our site for a CMR study due to several conditions (Figure 1). The criteria used to diagnose NCM was identification of two myocardial layers: a non-compact (NC) trabecular layer and a compact (C) layer, both located on some segment of the ventricular walls with a > 2.3 ra-
tio between them based on Petersen’s criterion (2) (Figure 2-A). To analyze NCM location, the 17 ventricular segments rating proposed by Cerqueira et al. was used, (3) where the apical segment was considered one with no segmentation. The group of patients diagnosed with NCM was compared to a group of 14 normal subjects or control group (control). The subjects from the control group had a CMR for several non-cardiovascular reasons; they had no history of arterial hypertension, coronary artery disease, or valvular heart disease at the time of the study. In addition, lack of a left atrial area larger than 22 cm² was used as a safety variable to define normal values. Due to its sensitivity, this variable was used to identify any type of left ventricular diastolic dysfunction. (4)

**Resonance study:** Resonance imaging was performed using 3T (Philips Innova scanner) equipment. To assess the motility and the ventricular function, steady-state free precession (SSFP) cine sequences in long axis planes, four chambers and multiple short axis planes were used, covering the entire ventricle, from the base to the top, as previously published. (5) In segments showing hypertrabeculation, thickness of trabeculated and non-trabeculated myocardial layers was analyzed in diastole. NCM was considered when the ratio exceeded 2.3 (Figure 2-A). For contrast images, 0.2 mmol/kg gadopentetate dimeglumine (Viewgam, Bacom) were injected intravenously. T1 mapping required a single-apnea modified look-locker inverted sequence, with three short-axis basal and midventricular planes before and after the contrast agent administration. Late images were obtained 10 to 20 minutes after the contrast injection, according to parameters published beforehand. (6)

**Statistical analysis**
Data were analyzed using IBM SPSS statistics V25 (IBM). Binomial variables are expressed as percentages, and continuous variables as means ± SD. Normally distributed continuous variables comparison used a T test for different samples, or otherwise a Mann-Whitney’s U test. The chi-square test was used to analyze categorical variables, with a significant difference if p ≤0.05.

**RESULTS**

**Baseline characteristics:** In the study group (n=140), 51.4% (n=72) were men. The average age was 31.37 ± 20.01 (range 1-89 years), and the median was 30 years. The control group was on average 39.9 ± 3.45 years old, with no significant differences as compared to the NCM group. The age of patients was normally distributed. Most patients, 62.42%, were aged 26 to 65 years. The left ventricular ejection fraction (LVEF) in patients with NCM was globally preserved (56.66 ± 19.41), with a variable grade of severity (Table 1, Figure 3).

**NCM distribution and scope:** It was observed that 59.6% of segments corresponded to left ventricular anterolateral and apical planes. Ventricular segments with less NCM involvement were basal segments in both ventricles and the interventricular septum (7.14 % and 12.9% of patients, respectively) (Figure 4). The global average of wall thickness in the NC portion was 13.91 ± 4.1 mm vs. 5.14 ± 1.80 mm on the C, with a NC/C ratio of 2.87 ± 0.92.

**Comparison of NCM and normal heart patients versus the control group**
Thirty-eight subjects, 27.1% of the total number of patients diagnosed with NCM, did not show any other pathological disorder in the heart, except for the NCM finding, and they were considered to have normal hearts with hypertrabeculation in the CMR study. In 91.7% of these patients, the reason for a CMR was cardiac arrhythmia (67%) or suspected cardiomyopathy (24.5%). (Figure 1) Upon a “global” comparison of the control group versus NCM patients, the latter showed larger volumes and a lower LVEF, although observed values remained within normal ranges (Table 1). No difference in the NCM scope was observed between all

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**Fig. 1.** Reasons for the CMR study (n=156)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number</th>
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<tr>
<td>Cardiomyopathies</td>
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<tr>
<td>Other diagnoses</td>
<td>5</td>
</tr>
<tr>
<td>SD</td>
<td>2</td>
</tr>
<tr>
<td>Congenital</td>
<td>17</td>
</tr>
<tr>
<td>NCM</td>
<td>52</td>
</tr>
<tr>
<td>Arrythmias</td>
<td>8</td>
</tr>
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</table>

Different NCM-associated conditions in our patient population.
NCM: non-compacted myocardium; SD: sudden death
the patients and the group with NCM and a normal heart. The only significant functional difference observed between the group of patients with NCM plus “a heart with normal characteristics” and the control group was that the former had a better LVEF: 66.86 ± 9.67% vs. 62.43 ± 5.39%, p <0.001 (Table 1).

**FIG. 2. CMR diagnostic sequences**

A: Midventricular cine images with SSFP sequence in short axis showing ventricular trabeculation upon both myocardial layers measurement, leading to NCM criteria (4.7/1.35=3.48) B: Recovery double-inversion sequence, with late gadolinium enhancement, showing linear intramyocardial hyperintensity in the lateral pericardium and the interventricular septum. C: Myocardial mapping sequence, with a 1440-ms T1 increase in the septum in a patient with recurrent myocarditis. D: Patient with dilated cardiomyopathy and severely impaired ventricular function. The image on the left shows diastole, and the one on the right shows systole. During systole, there is better myocardial motility in segments with a NCM on the side (arrows) as compared to septal segments “lacking a NCM”.

**FIG. 3. Various left ventricular ejection fractions in the NCM**

Ejection fractions observed in patients with NCM. EF = ejection fraction

**DISCUSSION**

The NCM diagnostic criteria were developed based on the relationship between the trabeculated and non-trabeculated myocardium in a population of normal subjects, rather than on the clinical signs and symptoms of patients where these “anomalies” were ob-
served. It could be said that first something was found in the ventricle and then it began to be associated with multiple clinical findings.

This is one of the first papers studying NCM occurrence “in the real world,” regardless of the background condition leading to the study, thus avoiding “an inclusion bias” in patients.

According to the WHO, a disease is “any physiological disorder or impairment in one or several parts of the body, for generally known reasons, associated with certain signs and symptoms and with a quite predictable progress.” We have broken down this definition to see whether the NCM should be considered a disease or not.

1. It is “any physiological disorder or impairment in one or several parts of the body.” Considering this first part of the WHO’s definition of disease, the presence of trabeculae in the ventricles is normal. In the study population, 27% of subjects had a NCM with a normal heart. The high percentage of healthy individuals with a NCM would support this as a major or minor finding within normal ranges. It is interesting to note that patients with a NCM and a normal heart had a higher LVEF than the patients in the control group.

### Table 1. Comparative biometric data across the study groups

<table>
<thead>
<tr>
<th></th>
<th>Total NCM patients (n=140)</th>
<th>Control group (n=14)</th>
<th>p</th>
<th>NCM with a normal heart (n=38)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>31.37±20.01</td>
<td>39.92±12.46</td>
<td>0.011</td>
<td>39.9±4.35</td>
<td>0.02</td>
</tr>
<tr>
<td>Male sex</td>
<td>72/68</td>
<td>10/4</td>
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<td></td>
<td></td>
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<tr>
<td>EDV (ml)</td>
<td>164.42±86.03</td>
<td>138.50±22.07</td>
<td>0.017</td>
<td>132.50±51.55</td>
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<tr>
<td>ESV (ml)</td>
<td>81.03±82.17</td>
<td>52.43±13.17</td>
<td>0.01</td>
<td>47.0±24.43</td>
<td>0.001</td>
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<tr>
<td>SV (ml)</td>
<td>83.39±37.57</td>
<td>86.07±11.72</td>
<td>0.01</td>
<td>85.47±32.41</td>
<td>0.54</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>56.66±19.41</td>
<td>62.43±5.39</td>
<td>0.001</td>
<td>66.86±9.67</td>
<td>0.001</td>
</tr>
<tr>
<td>Trabecular myo. (mm)</td>
<td>14.44±4.16</td>
<td>-</td>
<td>-</td>
<td>13.74±3.78</td>
<td>0.71</td>
</tr>
<tr>
<td>Comp. myo. (mm)</td>
<td>5.21±1.92</td>
<td>-</td>
<td>-</td>
<td>4.94±1.31</td>
<td>0.27</td>
</tr>
<tr>
<td>C/NC ratio</td>
<td>2.95±0.91</td>
<td>-</td>
<td>-</td>
<td>2.82±0.92</td>
<td>0.63</td>
</tr>
<tr>
<td>T1 mapping (ms)</td>
<td>1302±62.41</td>
<td>1236±29</td>
<td>0.006</td>
<td>1280.00±8.49</td>
<td>0.05</td>
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<tr>
<td>T2 mapping (ms)</td>
<td>42.45±6.46</td>
<td>43.53±2.07</td>
<td>0.107</td>
<td>43.00±1.41</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Comp. myo.: compacted myocardium, EDV: left ventricular end-diastolic volume, ESV: left ventricular end-systolic volume, LVEF: left ventricular ejection fraction, SV: systolic volume, Trabecular myo.: trabeculated myocardium. NCM: non-compacted myocardium, nonC/NC: compacted/non-compacted

(*) = Significance between the entire NCM group vs. the control group. (†) = Significance between the control group vs. the group with a NCM and a normal heart.

**Fig. 4.** NCM ventricular location. Number of compromised segments.
group with no NCM (Table 1). These “improved normality” concepts coincide with the findings by Moore et al., who study ventricular function by fractal analysis, and state that the trabeculae are not deleterious to ventricular function, but all the opposite, since they "help" adequate ventricular contraction and relaxation in normal hearts. (7) The myocardial mapping performed by the CMR also failed to show any differences between these groups of patients, despite the high sensitivity of this method to identify myocardial anomalies (Figure 2-C, Table 1).

Therefore, a normal myocardium under stress conditions may develop hypertrabeculations. This has been observed in high-performance athletes: trained subjects show significantly higher trabeculations than untrained individuals (18.3% vs. 7.0%), as published by Fermia and Gati. (8,9)

2. The second part of the WHO’s definition of disease claims “… for generally known reasons...”. While there are several theories on NCM development in humans, such as arrest of the ventricular compaction mechanism, or genetic disorders leading to intercalated discs disjunction and a non-compacted myocardium, we lack a single and certainly documented theory applicable to all NCM subjects. Theories are both varied and associated with many conditions, including hypertrabeculation. The coincidence in most people with NCM is that the myocardium where trabeculae develop is under greater stress, either due to pathological or physiological conditions, as observed in ischemic areas, myocardial edema, or high-performance athletes.

3. The “genetic origin...” While the American Heart Association includes NCM as a genetic cardiomyopathy, the European Society of Cardiology considers it as a non-classified cardiomyopathy. NCM diagnosis in newborns with heart failure has led to consideration of a genetic role in these findings. Rare or familial (10) NCM occurrence continues to be under study. Most familial cases identified to date are associated with genetic mutations that are also the cause of other cardiomyopathies and very closely related, such as mucopolysaccharidosis, birth defects, (11,12) hypertrophic cardiomyopathy, or heart failure in the newborn. (13) In our population, NCM was associated with multiple and various well-defined conditions (Figure 1).

NCM is typically considered to be the result of a disruption in normal myocardial development occurring between week 5 and 8 of embryogenesis. (14) If we assume that NCM is the phenotypical expression of a genetic disorder, we should explain why some NCM vary over time and have such erratic behavior; increasing or decreasing in scope and with no definitive behavior, as is usually the case with conditions “marked” by genes. Genetic overlapping with other conditions is a rule for NCM, to such an extent that Arbustini et al. have proposed seven subtypes of genetic disorders for NCM. (15)

The hypothesis of a non-genetic origin... Development of a NCM in adults (acquired NCM), as observed in high-performance athletes (9) or in pregnancy, and occurring in more than 25% of patients, (16) would be opposed to these genetic theories. In the case of acquired NCM, development of a NCM should be a ventricular “remodeling” secondary to increased loading conditions or myocardial ischemia. The need to search for oxygen in the ventricular cavity would trigger endocardial trabeculae in some patients, thus increasing the contact surface with ventricular blood, as in the embryonal stage of development. (17) This might be called an “adaptive myocardium” due to adaption to different loading or ischemic conditions resulting in trabeculae (18) (Figure 5). Likewise, if the NCM trigger stops, trabeculae reversal in different pathological stages has been observed, as described by Philip and Fang (19) in a patient with heart failure under cardiac resynchronization therapy, or in pregnant women, where the NCM appeared or disappeared as a result of pregnancy. (16).

4. The third part of the definition refers to occurrence of “certain signs and symptoms...” NCM has been associated with cardiac arrhythmias, stroke, and heart failure, showing signs and symptoms that are common in these conditions. Out of 140 patients in our population, only 21% showed a LVEF lower than 55%; most patients with NCM (79%) had no impaired left ventricular function (Table 1). When comparing patients with a normal LVEF versus patients with a reduced LVEF, no differences were observed relative to the NCM scope or the compacted/non-compacted myocardium ratio (Table 2). Consequently, the NCM scope cannot be directly associated with ventricular dysfunction. It is interesting to note a few doubts regarding patients with impaired left

<table>
<thead>
<tr>
<th>Variables</th>
<th>LVEF ≥55% (n=51)</th>
<th>LVEF &lt;55% (n=30)</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Non-compact (mm)</td>
<td>1419±4.14</td>
<td>15.04±4.23</td>
<td>0.52</td>
</tr>
<tr>
<td>Compacted (mm)</td>
<td>5.24±2.09</td>
<td>5.23±1.62</td>
<td>0.56</td>
</tr>
<tr>
<td>Compacted/Non-compact</td>
<td>2.90±0.92</td>
<td>3.04±0.91</td>
<td>0.70</td>
</tr>
<tr>
<td>T1 mapping (ms)</td>
<td>1303±45.66</td>
<td>1301±77.78</td>
<td>0.11</td>
</tr>
<tr>
<td>T2 mapping (ms)</td>
<td>43.33±2.94</td>
<td>41.40±9.52</td>
<td>0.19</td>
</tr>
</tbody>
</table>

ventricular function and NCM. We have observed that the most important motility impairments in the regional wall of the left ventricle occur in regions “with no NCM”, as evidenced by patients with heart failure and severe akinesia in septal or basal regions of the left ventricle, when the NCM involved the anterolateral and apical walls (Figure 2-C). This would be opposed to saying that NCM is the primary cause of ventricular dysfunction in these patients.

5. Finally, there is the concept of disease “... and with a quite predictable progress.” NCM has been associated with different kinds of progress, such as hypertrophic cardiomyopathy, ischemic heart disease, heart failure with a reduced LVEF, arrhythmias, peripheral embolism, and even sudden death. This wide range of conditions itself may progress in different ways; therefore, when associating NCM with them, we need to assume that prognosis is highly variable and unpredictable. Upon analysis of patients with NCM and impaired ventricular function, occurrence of NMC itself was not associated with worse prognosis, as shown by Ivanov et al. (20) Even in patients with confirmed dilated cardiomyopathy diagnosis, NCM did not prove to be an independent indicator of bad prognosis, unlike LVEF and myocardial fibrosis. (21,22) In addition, if NCM is only a finding in a patient with normal ventricular function, survival is the same as in the general population, as recently published by Vaidya et al. (23)

Based on the WHO definition, NCM would fail to meet the criteria to be considered a disease, as it lacks a well-known cause, it has no specific signs or symptoms, and progress is unpredictable. Progress seems to depend on other background conditions in patients.

Clinical implications of findings
It is essential to determine whether NCM is a disease or not. This would be of help for normal patients and prevent their disease due to wrong diagnosis. However, NCM association with several diseases or conditions stressful for the myocardium is well known (Figure 5); its occurrence should be considered a “red flag” to investigate its cause. Also, development of NCM in athletes and pregnant women shows that the presence of these trabeculations might contribute to a better ventricular performance under stress in normal subjects.

Prospects
For all the above, NCM should not be considered a cardiomyopathy, but an “adaptive myocardium” under various stress conditions. It has shown to have good rather than bad prognosis. NCM has improved ventricular function both segmentally and globally, which opens the way to future genetic studies, where isolation of the gene causing NCM might be considered a therapy for patients with impaired ventricular function.

CONCLUSIONS
Our results and thoughts warrant strong reconsideration of the notion of NCM as a disease: it is rather an adaptive myocardial response to physiological or pathological stress conditions. NCM diagnosis needs to be considered as a finding to study other conditions or functional changes involved.
Conflicts of interest
None declared.
(See authors’ conflicts of interest forms on the website/Supplementary material).

REFERENCES