

## Uncompacted Myocardium: A Disease or a Phenotype?

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### Introduction

Non-compacted myocardium (NCM) remains controversial between those who consider it a genetic cardiomyopathy<sup>1</sup> and those who believe that excessive trabeculation is a characteristic morphological condition shared by distinct pathological processes and, therefore, not a single disease.<sup>2</sup>

The hallmark of this phenotype is the presence of prominent trabeculae in the left ventricle (LV) and deep intertrabecular recesses, continuous with the LV cavity and separated from the epicardial coronary arteries.<sup>3,4</sup> Such abnormalities are identified through imaging exams and may affect the LV, the right ventricle (RV), or both, and do not by themselves define cardiomyopathy.<sup>3</sup>

The prevalence of this phenotype varies greatly according to the imaging criteria applied, ranging from 0.56% in cohorts that used Jenni's echocardiographic criteria to 20% in cohorts that applied Petersen's magnetic resonance criteria.<sup>3</sup>

In this review article, we will bring the most current evidence on excessive LV trabeculation and its association with cardiomyopathies.

### Definition

Several criteria based on imaging methods have been proposed to define excessive LV trabeculation (Table 1 and Figure 1). The most typical location of trabeculations is in the mid-lateral, apical, and mid-inferior segments of the LV and is presumed to be in the absence of pre-existing cardiac abnormalities.<sup>3</sup>

Sensitivity and specificity vary according to the imaging method adopted to define excessive LV trabeculation.<sup>5</sup> Some criteria were developed based on the echocardiogram, but cardiac magnetic resonance imaging seems to have greater resolution and better differentiation between muscle and blood, allowing more precise identification of LV trabeculations.<sup>3</sup>

As we have different criteria with very variable accuracies, such definitions can be very simplistic and limited, and there are still important gaps in recognizing this phenotype.

### Keywords

Miocardopatias; Miocárdio não Compactado

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### Pathophysiology

Initially, it was thought that excessive trabeculations originated from the embryological arrest of normal endomyocardial morphogenesis, but this theory is currently being questioned.<sup>13</sup>

During normal embryogenesis, at the beginning of pregnancy, the ratio between trabecular and non-trabeculated myocardium is high, and as pregnancy progresses, this ratio decreases.<sup>3</sup> Previously, this ratio was thought to decrease throughout pregnancy due to compaction of the trabecular myocardium.<sup>13</sup> However, what is currently known is that the trabecular and non-trabecular myocardium grow independently. In early pregnancy, the growth rate of the trabecular myocardium is higher than that of the non-trabecular myocardium. As the pregnancy progresses, this relationship is reversed (Figure 2).<sup>3,14</sup>

For several reasons, the ratio between trabecular and non-trabecular myocardium may remain high in late pregnancy. However, the more appropriate term for this phenomenon would be excessive trabeculation rather than non-compaction of the myocardium.<sup>3</sup>

Several factors have already been identified in the pathophysiology of this phenotype. The first is genetics, which has been increasingly studied in these patients. The pathogenic variants responsible for this phenotype belong to a wide range of proteins involved in the sarcomere, cytoskeleton, mitochondria, desmosome, storage, and ion channels, which are implicated in various heart diseases.<sup>15</sup> In about one-third of cases, a related pathogenic variant is identified, with the majority being autosomal dominant.<sup>3</sup> The most commonly related genes are MYH7, MYBPC3, ACTC1, and TTN, and the most specific ones seem to be MYH7, ACTN2, and PRDM16.<sup>3</sup> Variants in the LMNA and RBM20 genes are associated with an increased risk of sudden arrhythmic death.<sup>16</sup>

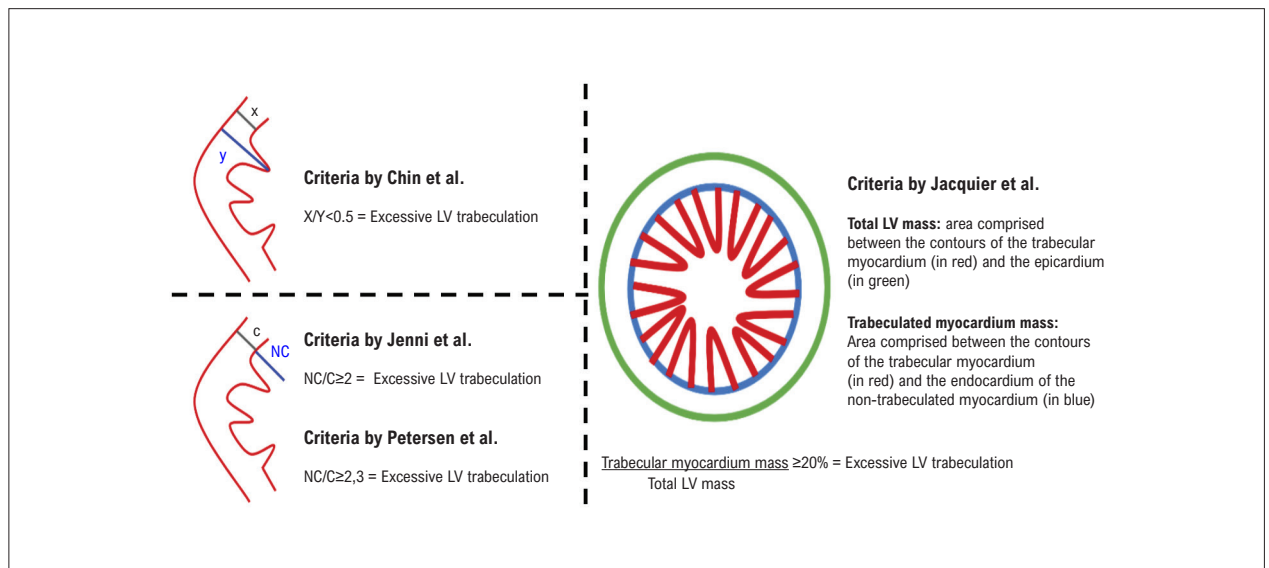
However, the genetic test only helps if we find any evidence of cardiomyopathy, keeping in mind that this phenotype can be a variant of normality.<sup>3,15</sup> It was demonstrated that 52% of the cases of cardiomyopathy associated with excessive LV trabeculation were sporadic, 32% with factors associated with genetics, and 16% had affected family members even with a negative genetic test. However, they did not always present the same phenotype as the proband (e.g., some had dilated, hypertrophic or sudden death phenotypes).<sup>17</sup>

Another factor related to excessive LV trabeculation is neuromuscular diseases, as we found this phenotype in diseases such as Barth syndrome, mitochondrial disorders, myotonic dystrophy, nuclear envelopathies, and Becker and Duchenne dystrophies.<sup>3</sup> Of patients with excessive trabeculation according to the echocardiographic criteria of Stöllberg, 80%

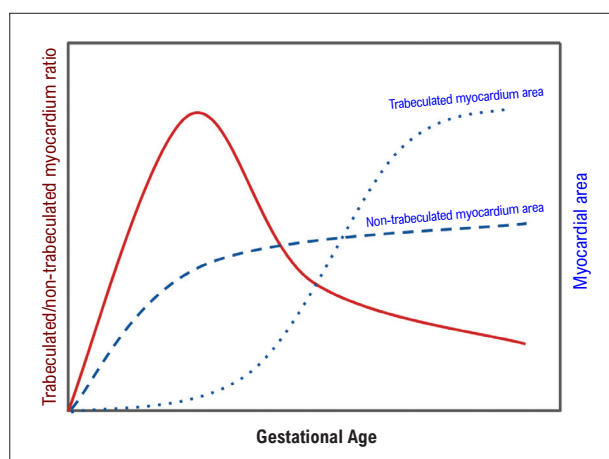
**Table 1 – Different definitions of excessive left ventricular trabeculation<sup>6-12</sup>**

Echocardiogram			
Criterion	Description	Method	Accuracy
Chin et al.	Distance (X) from the deepest trabecular recess to the epicardial surface Distance (Y) from the highest trabeculation to the epicardial surface $X/Y < 0.5$ = excessive trabeculation	Telediastole, parasternal long-axis, or apical 4-chamber windows	S=79-100%
Stollberg et al.	Ratio of non-compacted (NC) to compacted (C) myocardium $\geq 2$ at end-diastole >3 trabeculations in the LV wall distal to the papillary muscles Perfusion of the intertrabecular recesses through the ventricular cavity Trabeculations must have the same echogenicity as the myocardium while moving in sync with ventricular contractions	Telediastole, 4-chamber apical windows	S= 79-80% E= 79-93%
Jenni et al.	Ratio NC/C $\geq 2$ Absence of coexisting cardiac abnormalities Numerous prominent trabeculations and deep intertrabecular recesses Intertrabecular spaces filled by direct blood flow from the ventricular cavity	Telesystole, short axis parasternal window	Little sensitive
Cardiac magnetic resonance imaging			
Criterion	Description	Method	Accuracy
Petersen et al.	NC/C > 2.3 in diastole	Telediastole, long apical axis (4 chambers, 3 chambers, and 2 chambers)	S=86% E=99%
Jacquier et al.	Total trabecular mass compared to total LV mass NC ventricular mass > 20% of total LV mass	Telediastole, short-axis cine imaging	S=93.7% E=93.7%
Grothoff et al.	Total NC mass index of 15 g/m <sup>2</sup> of the overall LV mass VC mass > 25% of global LV mass	Telediastole, short-axis cine imaging	High S and E
Stacey et al.	NC/C > 2 at the end of systole	Telesystole, short-axis statistical images	-
Captur et al.	Fractal analysis used to quantify CN surge along the cardiac apex Maximum apical fractal dimension $\geq 1.392$	Telediastole, short-axis cine imaging	-

C: compacted or trabeculated myocardium; E: specificity; NC: non-compacted or non-trabeculated myocardium; S: sensitivity; LV: left ventricle.



**Figure 1 – Schematic drawing of the main diagnostic imaging criteria that define excessive left ventricular trabeculation. C: compacted or trabeculated myocardium; NC: non-compacted or non-trabeculated myocardium; LV: left ventricle**



**Figure 2** – Different growth rate ratios between trabecular and non-trabecular myocardium during pregnancy. Image adapted from Ishiwata et al.<sup>14</sup>

had some neuromuscular disease.<sup>18</sup> Furthermore, 20 to 30% of patients with Becker or Duchenne muscular dystrophies have cardiomyopathy with excessive LV trabeculation.<sup>19</sup>

Several factors that are related to increased ventricular preload can lead to the hypertrabeculation phenotype, such as pregnancy (more common in black women and tends to resolve after 12 weeks of delivery), frequent and intense physical exercise, and hemoglobinopathies.<sup>3</sup>

Some case series have described the relationship between the phenotype and polycystic kidney disease.<sup>20–22</sup> It is still unknown how to explain this relationship with certainty, but it is admitted that there is a genetic background in common for both entities or that hypervolemia caused by chronic kidney disease leads to increased preload, contributing to excessive LV trabeculation.<sup>3</sup>

Chemotherapy-related cardiotoxicity has also been associated with this phenotype.<sup>23</sup> It is not known with certainty what is the cause or consequence, but some studies demonstrate the association of cardiomyopathy associated with excessive LV trabeculation in response to chemotherapy, being related to the gene TTN in some cases.<sup>24</sup>

Therefore, based on what we know today, we can conclude that the LV excessive trabeculation phenotype already begins to develop in intrauterine life, has a multifactorial etiology with a relevant genetic component, and does not always culminate in cardiomyopathy.

### Clinical condition

Data on the prevalence of clinical findings, natural history, and prognosis of cardiomyopathy associated with excessive LV trabeculation or “non-compact cardiomyopathy” (NCM) are full of biases because, as we will see later, diagnostic methods are still very divergent, and even today we do not have a gold-standard method.<sup>15</sup>

Classically, NCM is represented by the triad of heart failure, arrhythmias, and thromboembolic events.<sup>25</sup> A meta-analysis showed that heart failure is present in

43% of cases<sup>26</sup> and may occur due to systolic or diastolic dysfunction even with a pattern of restriction.<sup>27</sup> In the same meta-analysis, 20% of patients had sustained or non-sustained ventricular arrhythmias, mostly monomorphic, and 9% had thromboembolic events.<sup>26</sup> Trabeculations are involved in developing the His-Purkinje system; therefore, any change in this system can cause conduction disorders and arrhythmias.<sup>5</sup>

### Diagnosis

On the electrocardiogram (ECG), several findings were described in NCM, such as delay in intraventricular conduction (31%), bundle branch blocks (19%), voltage criteria for LV hypertrophy (38%), and changes in repolarization (72%), including ST segment changes (61%), T wave inversion (41%) and QTc prolongation (52%). There is no specific ECG pattern for NCM; the ECG is normal in 13% of cases.<sup>28</sup> In addition to ventricular arrhythmias, we can find supraventricular arrhythmias, such as atrial fibrillation, in 17% of cases.<sup>25</sup> Ventricular tachycardia and Wolf’s syndrome -Parkinson-White (WPW) seem more frequent in children with NCM, whereas other ventricular arrhythmias and atrial fibrillation are more common in adults.<sup>29</sup> The etiology of the WPW syndrome remains controversial, but some authors suggest a developmental disorder of the *annulus fibrosus*.<sup>30</sup>

Despite more than 30 years since the first description of NCM occurred in 1990, we still do not have a gold-standard method for diagnosing this entity. Developments in imaging technology and increased access to cardiac magnetic resonance imaging (CMR) have improved the visualization of trabeculae and previously overlooked endocardial details.<sup>5</sup> The consistent finding across multiple cohorts is that CMR methods generate a 12-fold higher prevalence of NCM than echocardiography. On the other hand, this improved detection resulted in the “overdiagnosis” of MNC, as many patients with excessive LV trabeculation without associated heart disease were labeled as NCM.<sup>31</sup> Thus, the real prevalence of NCM is impossible to calculate.<sup>5</sup> On cardiac magnetic resonance imaging, several patterns of delayed enhancement have already been described, ischemic (subendocardial or transmural) or not. The most common non-ischemic pattern is in the middle septum and right ventricular insertion points. It is noteworthy that delayed enhancement can affect both areas of trabecular and non-trabeculated myocardium and may even predominate in areas far from sites with greater trabeculation.<sup>32,33</sup>

There are several diagnostic criteria for excessive LV trabeculation, as shown in Table 1, with different sensitivities and specificities. Computed tomography, not represented in Table 1, can also be used to diagnose excessive LV trabeculation. However, it does not evaluate myocardial fibrosis like magnetic resonance imaging, which is an important prognostic factor, in addition to adding significant exposure to radiation to the patient. Thus, it is rarely used in clinical practice.<sup>34</sup> Mendelez-Ramirez et al. described the only tomographic criteria as excessive trabeculation, the ratio between non-trabeculated myocardium (NC) and trabecular myocardium (C) greater than 2.2 in 2 or more segments.<sup>35</sup>

The role of endomyocardial biopsy (EMB) in diagnosing NCM is much questioned. However, the findings are very nonspecific<sup>36</sup> and there are no significant differences in the area of trabecular myocardium between patients with NCM and those with secondary causes of excessive LV trabeculation.<sup>37</sup> The role of EMB resides mainly in neuromuscular diseases associated with this phenotype since it can bring about more specific changes in these diseases, such as mitochondrial diseases.<sup>38</sup> Therefore, EMB must be individualized and indicated for the minority of cases.

However, in the absence of a gold-standard method, in order to arrive at a more accurate diagnosis of NCM, we must add various information, such as a detailed anamnesis, family history, and physical examination, in addition to the integration of several complementary tests, such as ECG, echocardiogram, CMR and, if there is suspicion of cardiomyopathy associated with excessive LV trabeculation, we must proceed with additional tests, such as genetic testing, 24-hour Holter monitoring, exercise testing, in addition to work-up aimed at ruling out differential diagnoses. (Figure 3)

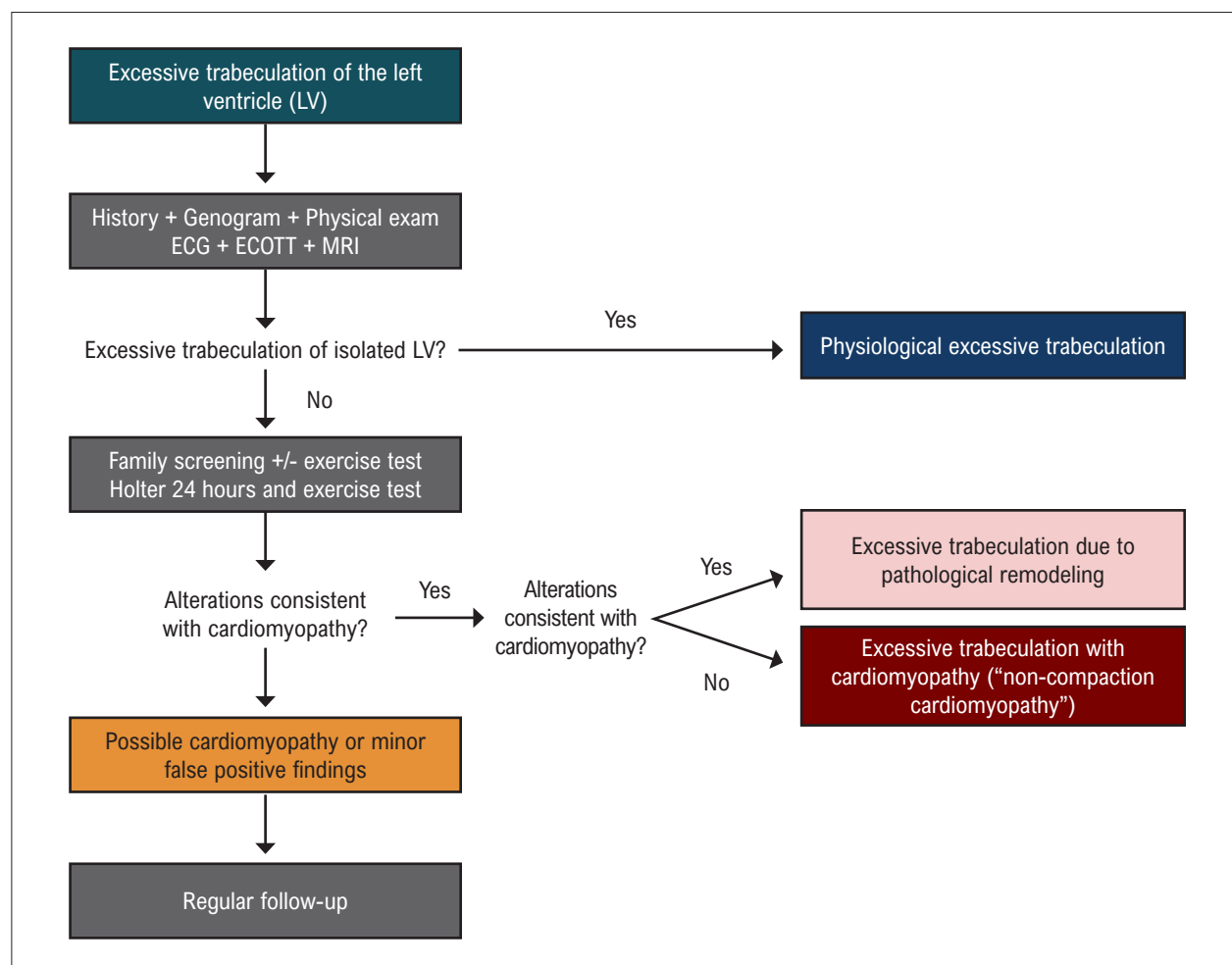
Genetic testing can help in cases where we cannot conclusively exclude the presence of associated

cardiomyopathy and where there is still a suspicion that excessive LV trabeculation is not physiological.<sup>5</sup> Besides helping with diagnostic confirmation, different sarcomeric mutations can cause different phenotypes among family members, influencing potential therapies and genetic counseling.<sup>25,39</sup>

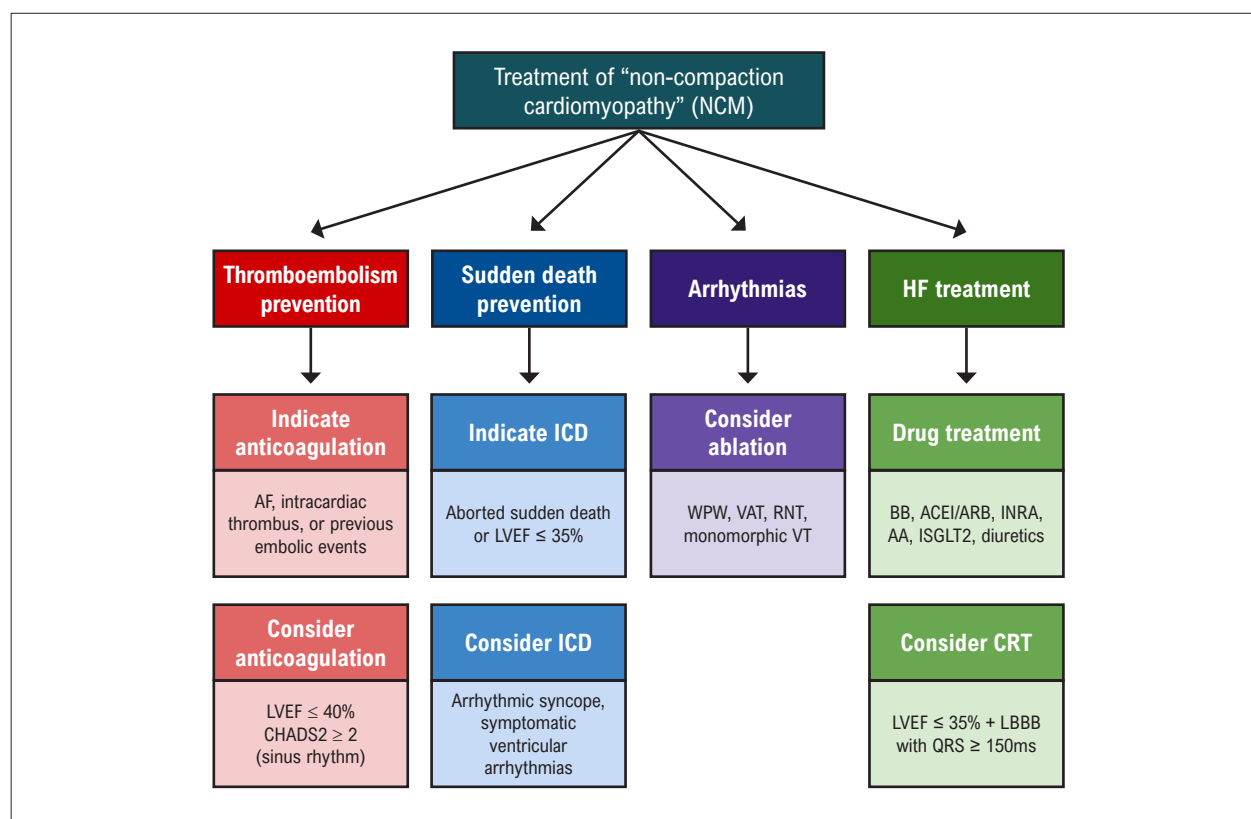
### Treatment

There is a paucity of scientific evidence regarding the specific treatment of NCM, which is mainly aimed at preventing the main complications of the disease (Figure 4).

The first discussion is about anticoagulation since we already know that thromboembolic events are one of the concerns in these patients. In addition to arrhythmias such as atrial fibrillation, the numerous intertrabecular recesses are thought to contribute to the formation of intracardiac thrombi.<sup>40</sup> However, in a cohort of over 10,000 Danish citizens, trabecular mass was not significantly related to the incidence of stroke.<sup>41</sup> The most established recommendations for anticoagulation in these patients are the presence of intracardiac thrombus, atrial fibrillation, or previous



**Figure 3** – Proposed diagnostic algorithm for excessive left ventricular trabeculation. Image adapted from D'Silva e Jensen.<sup>15</sup>



**Figure 4** – Proposed treatment for non-compaction cardiomyopathy. AA: aldosterone antagonist; BB: beta-blocker; LBBB: left bundle branch block; AF: atrial fibrillation; LVEF: left ventricular ejection fraction; ACEI/ARB: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; INRA: neprilysin and angiotensin-neprilysin receptor inhibitor; HF: heart failure; ICD: implantable cardioverter-defibrillator; ISGLT2: sodium-glucose cotransporter-2 inhibitor; WPW: Wolff-Parkinson-White syndrome; VAT: reentrant atrioventricular tachycardia; RNT: nodal reentry tachycardia; VT: ventricular tachycardia.

thromboembolic events.<sup>5,27,34</sup> However, other indications, such as ventricular dysfunction guided by the CHADS2 score (in sinus rhythm), are more debatable. Some authors advocate anticoagulation when the left ventricular ejection fraction (LVEF) is below 40%,<sup>4</sup> but such patients have the same risk of stroke as those without excessive trabeculation.<sup>42</sup> The WARCEF clinical trial included 2305 patients with other cardiomyopathies with LVEF ≤ 35% and sinus rhythm randomized to warfarin versus ASA 325mg daily. There was no difference in the primary composite endpoint of ischemic stroke, hemorrhagic stroke, and death from any cause. Although warfarin was associated with lower rates of ischemic stroke, at the expense of more major bleeding.<sup>43</sup> Other authors also recommend anticoagulation in these patients if CHADS2 score ≥ 2 in the presence of sinus rhythm, but based on a small retrospective study, which did not evaluate bleeding and long-term events.<sup>44</sup> Regarding the choice of anticoagulant, the initial studies were with warfarin, but there is already evidence to use direct oral anticoagulants (DOACs) in the indication for AF, as well as for intracardiac thrombus.<sup>27</sup>

Another important point is the indication of an implantable cardioverter-defibrillator (ICD). In the current ESC guidelines for heart failure (HF) treatment, there is no specific indication for NCM.<sup>45</sup> Following the same general indications for HF, the ICD is recommended as secondary prophylaxis after an aborted sudden death and primary prophylaxis in

LVEF ≤ 35% of cases.<sup>45</sup> Some cohorts observed higher risks of sudden death in some subgroups of patients with NCM, such as syncope of arrhythmic origin and symptomatic and/or refractory ventricular arrhythmias to ablation, suggesting the ICD implant.<sup>3,36,46,47</sup>

The drug treatment of HF should follow the recommendations of current guidelines, with medications that act in the natural history of HF and those that are symptomatic.<sup>45</sup> The device implantation should be considered in patients with NCM and advanced HF who meet the general criteria for resynchronization therapy (CRT).<sup>45</sup> It was also observed that patients with more extensive areas of non-trabeculated myocardium had better responses to CRT, with greater chances of reverse remodeling.<sup>48</sup> Heart transplantation should be considered for patients refractory to drug therapy for HF.<sup>5</sup> An analysis of the United Network of Organ Sharing (UNOS) database compared patients who underwent heart transplantation between 2000-2013 for NCM and for idiopathic dilated cardiomyopathy.<sup>49</sup> Survival rates between groups were similar, but the incidence of surgical wound infection was higher in the NCM group, probably due to a greater need for ventricular assist devices in the peritransplantation period.<sup>49</sup>

Ablation is another important discussion in patients with NCM, as they have more frequent arrhythmias and conduction

disorders. Thus, radiofrequency ablation may benefit patients with WPW syndrome, atrioventricular reentrant tachycardia, nodal reentry tachycardia, and monomorphic ventricular tachycardia.<sup>5,46,50,51</sup> However, the procedure may also be necessary on the epicardial surface and the standard endocardial approach, as areas of arrhythmias were found in the fibrotic myocardial tissue present in trabecular and non-trabecular myocardium.<sup>5</sup>

In line with ESC recommendations for participation in competitive sports, athletes with excessive trabeculations revealed on any imaging method, without

impaired LV systolic function, ventricular arrhythmias, or thromboembolic events, are unrestricted in competitive sports. Athletes diagnosed with NCM are stratified according to LV systolic function. Those with normal LV function can participate in all competitive sports (except for those in which syncope can cause death or serious injury) if they are asymptomatic, have no history of unexplained syncope, and have no ventricular arrhythmia on Holter and exercise testing. Athletes with compromised LV systolic function and/or ventricular arrhythmia should be advised to refrain from participating in competitive sports and to remain under regular clinical follow-up.<sup>52</sup>

### Prognosis

Asymptomatic and healthy patients with excessive trabeculation have a good prognosis. A 9.5-year study showed no differences in LV volume, systolic function, HF, stroke, and cardiovascular outcomes between hypertrabeculated patients versus those with normal trabeculation.<sup>53</sup> Therefore, excessive trabeculation with normal LVEF and without fibrosis does not have a worse prognosis.<sup>32</sup> Worse results were seen in the presence of delayed enhancement on CMR and reduced LVEF.<sup>32,42</sup>

The risk of major cardiovascular events also appears to be greater in patients with LV systolic dysfunction associated with

some pathogenic variant associated with NCM, compared to those with sporadic forms of the disease and also with ventricular dysfunction, suggesting that genetics also play a key role in the prognosis.<sup>54</sup>

Other factors associated with a worse prognosis are: atrial fibrillation, left atrial diameter greater than 40mm, advanced age, and neuromuscular diseases.<sup>5</sup>

Mortality varies in the literature; however, a retrospective study estimated mortality of NCM at 5.8% per year, but most patients had ventricular dysfunction and/or atrial fibrillation.<sup>55</sup>

### Author Contributions

Conception and design of the research; Acquisition of data; Analysis and interpretation of the data; Statistical analysis; Obtaining financing; Writing of the manuscript; Critical revision of the manuscript for important intellectual content: Correia VM, Madrini Junior V, Ramires JFA.

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This study is not associated with any thesis or dissertation work.

### Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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