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EDITORIAL COMMENT

Left Ventricular Noncompaction

A Genetic Cardiomyopathy Looking for Diagnostic Criteria*

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Left ventricular noncompaction (LVNC) is a relatively rare cardiomyopathy characterized by prominent ventricular trabeculations and deep intertrabecular recesses on the luminal surface of the left ventricle (1). LVNC can be asymptomatic or can manifest as depressed systolic function, and is sometimes accompanied by thromboembolism, malignant arrhythmias, and heart failure (2,3). The American Heart Association considers LVNC to be a distinct primary genetic cardiomyopathy caused by the arrest of the normal compaction process of the developing myocardium (4). In contrast, the European Society of Cardiology (ESC) refers to LVNC as an "unclassified cardiomyopathy" because LVNC can appear as a morphological trait of diverse cardiomyopathies (5). Support for a genetic cause of LVNC has been obtained through the identification of mutations in the genes that encode the sarcomeric (6), cytoskeletal (7), and nuclear membrane proteins (8). Recently, the hypothesis of a developmental basis for LVNC (3) received strong support from the identification in families with LVNC of deleterious mutations in MIB1, a NOTCH signaling pathway regulator (9).

Since the initial description of LVNC almost 25 years ago, the cardiac imaging landscape has changed substantially (10). Advances in imaging diagnostic technologies have led to better delineation of the morphological appearance of the myocardium and reformulation of LVNC imaging diagnostic criteria (**Table 1**) (1,11–16). Research over the last decade has also shown poor agreement among the proposed diagnostic criteria (17). Moreover, with the increasing use of cardiac magnetic resonance imaging (CMRI) in clinical practice, a high number of apparently healthy individuals have been found to have prominent LV trabeculations; these individuals fulfill the proposed LVNC criteria. This poses the question of whether these apparently healthy individuals have a preclinical cardiomyopathy or merely have a normal variation without the clinical consequences.

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In this issue of the *Journal*, Zemrak et al. (18) conducted a study of more than 2,700 individuals included in MESA (Multi-Ethnic Study of Atherosclerosis) (18). These investigators determined the number of healthy individuals included in this long-term follow-up study who fulfilled 1 of the proposed LVNC criteria (the criteria used in Petersen et al. [13]) and examined whether these patients had deterioration of their LV volumes and LV ejection fraction (LVEF) compared with values measured at the beginning of the study, almost 10 years before. The investigators also examined the impact of hypertrabeculation on the participants' clinical courses during this period. They found that 25% of participants exhibited at least 1 cardiac segment with a noncompacted to compacted (NC/C) ratio >2.3, and that 8% of participants displayed 2 or more affected segments (18). Although LV volumes increased and LVEF decreased in the 9.5 years between the 2 examinations, there were no differences across the maximal NC/C ratio quintiles, and patients with greater trabeculations showed even smaller LV end-diastolic volume changes. Remarkably (and contrary to previous reports), there were no racial variations in the maximal NC/C ratio. Finally, adverse clinical events were scarce in the studied cohort,

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TABLE 1 Proposed Left Ventricular Noncompaction Diagnostic Criteria

Criterion	Chin (1)	Jenni et al. (11)	Stöllberger et al. (12)	Petersen et al. (13)	Jacquier et al. (14)	Captur et al. (15)	Melendez-Ramirez et al. (16)
Imaging technique	Echocardiography	Echocardiography	Echocardiography	CMRI	CMRI	CMRI	MDCT
Number of LVNC patients	8	7	–	7	16	30	10
Criteria	Excessive prominent trabeculations with deep intertrabecular recesses. Progressive decrease of the epicardial to the trabecular trough distance/TWT ratio and progressive increase of TWT from mitral valve to apex.	Maximal NC/C wall thickness ratio. Intertrabecular spaces filled by direct blood flow. Absence of cardiac anomalies.	>3 prominent trabeculae visible in 1 image plane at end-diastole that moves synchronously with the compacted myocardium. Two-layered myocardium visible at end-systole.	Maximal NC/C wall thickness ratio (true apex excluded).	Trabecular mass: total LV mass - compacted myocardial mass (including papillary muscles).	Maximal apical fractal dimension.	Maximal NC/C wall thickness ratio in 16 segments (true apex excluded).
Phase cardiac cycle	End-diastole	End-systole	End-diastole and end-systole	Diastole	End-diastole	End-diastole	End-diastole
Views	Long-axis and 4-chamber	Short-axis	Short-axis	Long-axis	Short-axis	Short-axis	Short-axis
NC/C ratio or other	–	NC/C >2	–	NC/C >2.3	Trabecular mass >20% of total LV mass	Fractal dimension >1.30	NC/C >2.2 in ≥2 segments
Sensitivity	–	–	–	86%	94%	100%	100%
Specificity	–	–	–	99%	94%	100%	95%

C = compacted; CMRI = cardiac magnetic resonance imaging; LV = left ventricle; MDCT = multidetector computed tomography; NC = noncompacted; TWT = total wall thickness.

despite the apparently high proportion of participants with a potential unmasked cardiomyopathy.

The investigators should be congratulated for this work, although some limitations of the study should be considered. The first limitation refers to the LVNC criteria used. Although frequently used in clinical practice, the criteria used by Petersen et al. (13) were derived from a small group of LVNC patients (just 7 individuals) and are the only criteria that used long-axis views to measure noncompacted cardiac tissue (**Table 1**). Most diagnostic criteria require short-axis views to measure the NC/C ratio because it is easier to exclude papillary muscles. In long-axis views, portions of the papillary muscles are imaged and could be considered as potential trabeculations. Of note, an elegant CMRI study, in which the maximal short-axis NC/C ratio was measured in 120 healthy volunteers, found that only 1 volunteer exhibited a NC/C ratio >2.3 (19). Other acknowledged limitations of the Zemrak et al. (18), report were that only 2,754 of the initial 5,004 participants (55%) of the MESA study were included in the subanalysis, and that, for technical reasons, trabeculations were not measured in the initial CMRI studies. This implies that survivor bias could have influenced the results and that trabeculations did not change over time. Nevertheless, this report will have immediate consequences in clinical practice, because due to their simplicity and high intraobserver and interobserver agreement, the criteria used by Petersen et al. (13) are the most frequently used LVNC criteria in CMRI examinations. The data from this study support cessation of follow-up in healthy individuals lacking a family history of cardiomyopathies, but in whom hypertrabeculation has been found, and pose important challenges for current LVNC diagnostic criteria.

Zemrak et al. (18) also suggest that despite their findings, the LVNC criteria used by Petersen et al. (13) should still be used according to pre-test disease probability. Although we agree with the investigators that pre-test probability is crucial to interpreting all available criteria (and any other medical test), in our opinion, the previously mentioned limitations and the high number of healthy volunteers who fulfilled the criteria used by Petersen et al. (13), make abandoning them, in favor of demonstrably superior criteria, reasonable (14,15).

A sophisticated mathematical technique (fractal analysis) was recently used to study complex trabeculation patterns in LVNC and other cardiomyopathies (15). The results for diagnosis of LVNC and other entities, such as hypertrophic cardiomyopathy sarcomere gene mutation carriers without LV hypertrophy, are impressive (20). Further studies will tell

us if fractal dimension may become the holy grail of LVNC diagnosis.

We consider that a definitive LVNC diagnosis should be established only in those patients who 1) fulfill a quantitative short-axis diagnostic criterion (Jenni criteria for echocardiography and Jacquier criteria for CMRI); and 2) also exhibit 1 of the following features: LVNC diagnosed in another family member; regional wall motion abnormalities; LVNC-related complications (arrhythmia, heart failure, or thromboembolism); and being a carrier of a pathogenic mutation in a gene previously associated with LVNC in various families. With regard to the latter, identification of novel disease-causing mutations using next-generation sequencing techniques and validation of these mutations in experimental disease models will contribute to the LVNC diagnosis.

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