

**EDITORIAL**

# Left Ventricular Noncompaction Cardiomyopathy: New Clues in a Not So New Disease?

John L. Jefferies , MD, MPH

"I've learned that I still have a lot to learn"  
—Maya Angelou

**L**eft ventricular noncompaction cardiomyopathy (LVNC) remains a largely underinvestigated and poorly understood diagnosis. The number of peer-reviewed articles published on LVNC has grown dramatically over the past decade. Clinicians and scientists around the globe have advanced our understanding of the genetics, diagnostics, therapeutics, and outcomes for adult and pediatric patients with LVNC. Yet, there continues to be disagreement about diagnostic criteria, management, and classification of this complex phenotype.<sup>1–6</sup>

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**See Article by Vaidya et al.**

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In this issue of the *Journal of the American Heart Association (JAHA)*, Vaidya and colleagues present data on identifiable clinical and imaging criteria that may predict mortality in adults with LVNC.<sup>7</sup> The current report consists of 339 patients (median age, 47.4 years) with confirmed LVNC, as diagnosed by either echocardiography or cardiac magnetic resonance imaging (CMR). The median follow-up was 6.3 years, during which time 69 patients died. On multivariable Cox regression analysis, the authors found that age, left ventricular ejection fraction (LVEF) <50%, and non-compaction extending from the apex to the mid or

basal segments were associated with all-cause mortality. Not surprisingly, patients with a formal diagnosis of LVNC had reduced overall survival compared with the expected survival of an age- and sex-matched US population. In addition, those patients with noncompaction isolated to the apex of the left ventricle (LV) and those with an LVEF >50% had similar survival to the general population. Overall, this is an important addition to the existing literature and helps provide a partial framework for the management of these patients.

LVNC remains a heterogeneous disease with multiple possible concomitant phenotypes. We have described these previously and characterized the possible findings into 9 distinct subtypes.<sup>8</sup> Briefly, these subtypes are as follows: (1) the isolated or benign form of LVNC, (2) the arrhythmogenic form of LVNC, (3) the dilated form of LVNC, (4) the hypertrophic form of LVNC, (5) the “mixed” form of LVNC, (6) the restrictive form of LVNC, (7) the biventricular form of LVNC, (8) the right ventricular hypertrabeculation with normal LV form, and (9) the congenital heart disease form of LVNC. The authors thoughtfully excluded patients with congenital heart disease from their analysis. However, the other subtypes were not completely identified, which may impact some of the findings being reported. The dilated form of LVNC (subtype 3) is characterized by depressed systolic function, which is often accompanied by LV dilation. The outcome of this group is similar to that in patients with isolated dilated cardiomyopathy. This provides support to the finding of the investigators that an LVEF <50% was an independent predictor

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Correspondence to: John L. Jefferies, MD, MPH, University of Tennessee Health Science Center, Heart Institute, 956 Court Ave, Memphis, TN 38163. E-mail: [jjeffe15@uthsc.edu](mailto:jjeffe15@uthsc.edu)

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of all-cause mortality. Although not described in detail within the article, Table 5 reports the finding of “any right ventricular dysfunction” as a variable associated with overall mortality (hazard ratio [HR], 1.98; 95% CI, 1.10–3.54). This may represent patients with the biventricular form of LVNC. Historically, these patients are difficult to diagnose by echocardiography and are typically identified by use of CMR. As only 118 subjects (35%) in the cohort in this study underwent CMR, it is worth considering that the biventricular form of LVNC (subtype 7) may have been present but was not identified.

An important consideration in interpreting the data from this recent report is recognizing the reported experience in children. Brescia and colleagues reported on 242 children diagnosed with LVNC at Texas Children’s Hospital.<sup>9</sup> In this retrospective evaluation, the presence of cardiac dysfunction (LVEF <55%) was strongly associated with mortality (HR, 11;  $P<0.001$ ). The clinical presentation and symptoms in this pediatric cohort are similar to those in the current report. The presenting symptoms in the childhood cohort were as follows: (1) congestive heart failure (25%), (2) abnormal cardiac examination (19%), abnormal ECG or chest x-ray film (16%), arrhythmia (10%), chest pain (9%), and syncope (5%). These findings reported in children have some obvious commonalities with the Mayo Clinic data. ECG abnormalities were present in 87% of the patients. Repolarization abnormalities were associated with increased mortality (HR, 2.1;  $P=0.02$ ). Eighty children had an arrhythmia that resulted in increased mortality (HR, 2.8;  $P=0.002$ ). During the evaluation period, there were 15 cases of sudden cardiac death (6.2%). Nearly all patients who experienced sudden death had abnormal cardiac dimensions or evidence of cardiac dysfunction. Notably, no patient with normal cardiac dimensions and function without evidence of a preceding arrhythmia died. These findings mirror the report by Vaidya and colleagues in many ways. The presenting symptoms in both groups are similar. This is remarkable considering that many of the patients described from Texas Children’s Hospital were too young to reliably voice symptoms, such as chest pain. No patient with normal LV size or systolic dysfunction in the absence of arrhythmia died. This is the same finding reported in the Mayo adult cohort with the exception that arrhythmias were not identified as an independent predictor of mortality.

The lack of robust arrhythmia analysis in the current report is a limitation and should be recognized by those caring for children and adults with LVNC. The arrhythmogenic form of LVNC (subtype 2) is an important component of longitudinal surveillance in these patients. As noted above, the presence of an arrhythmia and/or a repolarization abnormality resulted in increased mortality. Although identifying patients

with normal LV systolic function and isolated apical LV trabeculations may provide some comfort to providers, these are not the only important phenotypic characteristics. The impact of significant arrhythmias cannot be underestimated and mandates thoughtful surveillance. The opportunity to accrue meaningful arrhythmia data is underleveraged in the current management of cardiomyopathies, including LVNC. This is unfortunate as it would add valuable information in the development of risk stratification instruments and inform clinical decision-making.

Although the data set provides typical clinical information about the LVNC phenotype, the article fails to provide any genetic information. The authors appropriately recognize the need for genotyping in this population. The focus of their study was to identify clinical and imaging variables that are routinely available in practice. However, in 2020, genetic testing is routinely available in clinical practice and should be considered in the overall assessment of patients with LVNC. We have reported on the importance of potential genetic triggers and genotype-phenotype correlations in adult patients with LVNC.<sup>10</sup> In our study, 190 adults from 174 families with concern of LVNC by echocardiography were prospectively analyzed by CMR and whole exome sequencing. This provided the foundation to attempt genotype-phenotype correlations. We included 425 controls to assess for genetic variants of interest (VOIs). In one of the largest reported CMR studies in LVNC, we found 138 VOIs in 102 unrelated patients in 54 genes that have been previously associated with LVNC or other cardiomyopathy phenotypes. VOIs were identified in 68 of 90 probands (76%) with LVNC and 34 of 84 probands (40%) with LV hypertrabeculation. We also identified 0, 1, and  $\geq 2$  VOIs in 72, 74, and 28 probands, respectively. More importantly, we found that the presence of an increasing number of VOIs in individual patients correlated with several phenotypic markers, including the ratio of noncompacted/compacted myocardium ( $P<0.001$ ) and LVEF ( $P=0.01$ ). Furthermore, the presence of sarcomere gene mutations was associated with increased occurrence of late gadolinium enhancement ( $P=0.004$ ). A report from the Netherlands by van Waning and colleagues again documented the importance of using genetic information in the risk stratification of children and adults with LVNC.<sup>11</sup> On review of 327 unrelated cases of LVNC, the highest risk for cardiac events in both age groups was related to LV systolic dysfunction in mutation carriers. Of note, mutations in *MYH7* had a low risk for major cardiac events. Li and colleagues also reported on the importance of pathogenic mutations predicting adverse outcomes in an adult Chinese cohort with LVNC.<sup>12</sup> These 3 reports underscore the important role that genotyping plays in risk stratification for patients with LVNC. This also strengthens the

hypothesis that LVNC is a distinct and genetically triggered cardiomyopathy.

As Maya Angelou humbly noted, we are learning that we still have a lot to learn about many things, including LVNC. Routine care for patients with LVNC continues to be greatly confounded by the lack of consensus about the cause, diagnostic criteria, surveillance, and management of this increasingly common diagnosis. Furthermore, over the past 3 decades, the ability to differentiate “benign” from “pathologic” has become increasingly challenging given the morphologic spectrum and diverse populations described in the literature. In a recent report from the PESA (Progression of Early Subclinical Atherosclerosis) study, de la Chica et al found that vigorous physical activity was associated with a higher prevalence of CMR-detected LVNC.<sup>13</sup> This association was maintained using the Petersen, Jacquier, and Grothoff CMR criteria for LVNC.<sup>3,4,14</sup> This reflects our limited understanding of the drivers of noncompaction but does suggest that underpinning genetics may help differentiate those with “real disease.” The authors are to be congratulated on their report. However, one must recognize that these identified predictors are only a small piece in a large and complex puzzle.

## ARTICLE INFORMATION

### Affiliations

From the University of Tennessee Health Science Center, Memphis, TN.

### Disclosures

None.

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