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EDITORIAL COMMENT

Left Ventricular Noncompaction

From Physiologic Remodeling to Noncompaction Cardiomyopathy*

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Left ventricular noncompaction (LVNC) or noncompaction cardiomyopathy (NCCM) has reached popularity like that of a Hollywood star and has been promoted to one of "Topic of Fame" in the current publications, along with increased awareness of this myocardial phenotype, high quality cardiovascular imaging modalities, appropriate and probably inappropriate implementation of diagnostic criteria that have culminated in a plethora of publications about LVNC (1). Controversies regarding myocardial embryogenesis, classification as primary genetic or unclassified cardiomyopathy, and the presence of different diagnostic criteria, with their limitations and, last but not least, small case series and the lack of robust data, which have contributed to a fragmented picture of LVNC and to uncertainties about risk stratification of these patients (2-8).

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In this issue of the *Journal*, van Waning et al. (9) describe in their retrospective multicenter study from 4 cardiogenetic centers in the Netherlands, the correlations between genetics, clinical features, and outcomes in 1 of the largest populations consisting of 327 unrelated children and adults with NCCM. To our knowledge, this is 1 of the first and largest studies with a comprehensive assessment to bridge some knowledge gaps between clinical features and genetics regarding risk stratification for outcome. Previous studies, with their own limitations, focused on the identification of clinical risk factors and echocardiographic predictors, but the authors of the present study have broken down the silo mentality among clinicians, radiologists, and geneticists and have combined genetics, clinical features at presentation, and myocardial performance to define the risks and occurrences of major adverse cardiac events (MACE) (9-14).

The authors divided the 327 patients referred for genetic counseling and DNA testing into 3 groups: 1) genetic NCCM with a mutation (n = 104 or 32% [45% in children, 30% in adults]); 2) probably genetic without a mutation but a family history of cardiomyopathy (n = 53 or 16% [15% in children, 16% in adults]); and 3) sporadic NCCM without family history or a mutation (n = 164 or 52% [40% in children, 54% in adults]). Mutations were significantly more frequent in children than in adults (45% vs. 30%, respectively; p = 0.036); sarcomere genes were involved in 82% of the 104 genetic cases, including mutations in *MYH7*, *MYBPC3*, and *TTN*, which were the most common (71%), followed by mutations in *ACTC1*, *ACTN2*, *MYL2*, *TNNC1*, *TNNT2*, and *TPM1* (11%). The yield per tested gene was highest for *MYH7* (13%), *TTN* (11%), and *MYBPC3* (5%). Non-sarcomere gene mutations were identified in a minority of genetic cases (12% in children, 5% in adults). A minority of cases presented with complex genotypes (multiple mutations in 1 patient) in cardiomyopathy genes that were more prevalent in children (10%) than in adults (3%) (p = 0.038) (9).

Interestingly, the presence of LV systolic dysfunction was significantly more frequent in genetic patients than in those whose condition was probably genetic and in sporadic cases (p = 0.024). LV systolic

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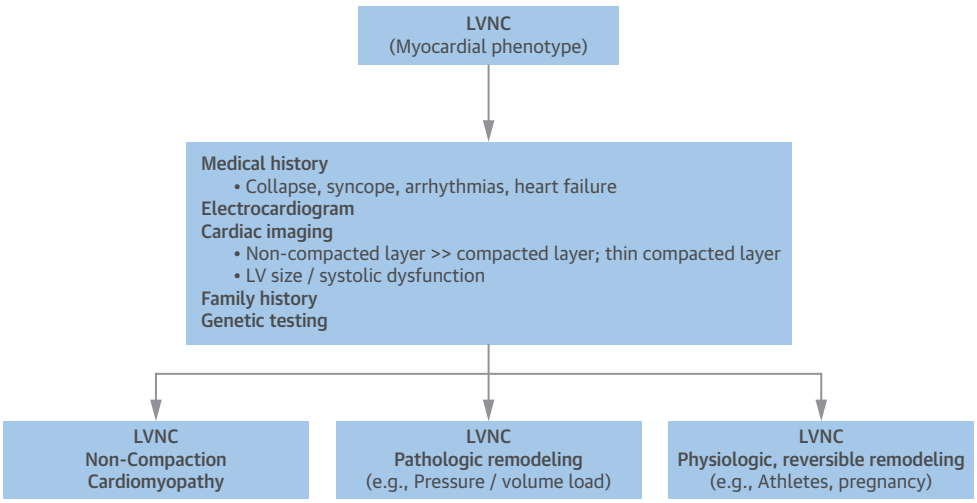
FIGURE 1 Myocardial Phenotype of LVNC to Noncompaction Cardiomyopathy



From the myocardial phenotype of LVNC to noncompaction cardiomyopathy, pathologic or physiologic reversible remodeling. LVNC = left ventricular noncompaction.

dysfunction was a risk factor for MACE in carriers of mutations but not in sporadic cases (9).

LVNC: PHYSIOLOGIC OR PATHOLOGIC REMODELING OF THE MYOCARDIUM?

Noncompaction is the description of a myocardial phenotype with a severely thickened myocardium presenting with a prominent noncompacted layer (excessive trabeculations, deep intertrabecular recesses), which is at least twice as thick as the compacted layer. Different diagnostic criteria are used to diagnose LVNC; although the Jenni criteria are most frequently applied to diagnose LVNC, each of them has its own limitations and pitfalls (15-18).

Recently, clinicians and researchers have debated whether LVNC is a physiologic or a pathologic phenotype of the myocardium. Genetic mutation(s) and nongenetic factors such as loading conditions (volume/pressure load) drive ventricular remodeling (concentric remodeling, concentric/eccentric hypertrophy) and the myocardial phenotype of dilated cardiomyopathy, hypertrophic cardiomyopathy, or LVNC (18-24). Obviously, there seems to be a physiologic, reversible remodeling of the LV myocardium with prominent trabeculations in athletes or pregnant women as opposed to a pathologic ventricular remodeling in patients with a cardiomyopathy of any cause or pathologic remodeling of the myocardium due to pathological loading conditions (**Figure 1**) (8).

The identification of significantly more frequent genetic mutations in children than in adults, associated with LV systolic dysfunction as a risk factor for MACE, enhances our understanding of LVNC (9). The association between a genetic mutation and LV dysfunction as a risk factor for outcome, with LVNC as the myocardial phenotype, strengthens the hypothesis that LVNC is a genetically determined cardiomyopathy. The results of this study emphasize the importance of routine genetic testing to establish a genotype-phenotype correlation and to move to the next step, from the description of the myocardial phenotype and morphological diagnosis to a genetically confirmed diagnosis. LVNC can occur in isolation or in association with other pathologies of the heart (e.g., congenital heart defects), with or without associated gene mutation(s).

We are concerned that a healthy subject not be labeled as a patient with LVNC, with a life-long impact on this individual and on the health care system, with unjustified regular follow-up visits and tests. This is a call for precaution not to over-diagnose LVNC and to establish the diagnosis of LVNC after a careful comprehensive assessment including genetic testing and concordant morphologic findings on the echocardiogram and advanced cardiac imaging (e.g., cardiac magnetic resonance).

As volume or pressure load results in hypertrophy of the myocardium, it can also result in the morphological appearance of LVNC, which is different from