JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER

VOL. 68, NO. 20, 2016
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2016.09.912

EDITORIAL COMMENT

# Left Ventricular Noncompaction, or Is It?*

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Excessive trabeculation of the human left ventricle (LV) has been found in both pediatric and adult patients, with or without manifest cardiac disease. Presence of excessive trabeculations together with extensive intertrabecular spaces that communicate with the ventricular cavity and a thin and compacted myocardium points to a diagnosis of left ventricular noncompaction (LVNC). However, a global consensus on diagnosis, management, or even the existence of this condition as a separate entity is lacking at present.

The capability of cardiac magnetic resonance (CMR) imaging to visualize trabeculae at high spatial resolution has led to several quantification methods and LVNC diagnostic criteria, ranging from measurements of trabeculae length and total trabeculae mass to the fractal dimension technique (1-3). However, overreliance on imaging criteria for LVNC poses the risk of false diagnosis, which will have tremendous impact on patients and their families. Therefore, it is vital to address 2 key questions: 1) What is the prognostic value of excessive trabeculation in an asymptomatic low risk population with normal cardiac morphology and function? 2) Is the extent of trabeculation important in the context of cardiovascular disease?

In this issue of the *Journal*, Weir-McCall et al. (4) describe a cross-sectional analysis of association between excessive LV trabeculation meeting the current diagnostic criteria for LVNC and a variety of demographic, clinical, and LV parameters in 1,480 asymptomatic participants (TASCFORCE [Tayside Screening for Cardiac Events] study cohort) free from known cardiovascular diseases. This study found that a significant proportion of the cohort (15%) met ≥1 of the current CMR-based LVNC diagnostic criteria. In addition, in multivariate analysis the long-axis noncompaction to compaction ratio was negatively correlated with systolic blood pressure and LV mass, even though the effect sizes were minimal and unlikely to have any clinical significance. These results echoed the previous study by our group published in the *Journal*, where we demonstrated similar findings of high prevalence of excessive trabeculation in the asymptomatic MESA (Multi-Ethnic Study of Atherosclerosis) study cohort, which appeared to have clinically insignificant influence on prognostically important LV parameters (5). It would certainly be interesting to see if those with excessive trabeculation in the TASCFORCE study cohort develop adverse clinical outcomes at the planned 10-year follow-up, but our own data from the larger MESA study (sample size of ~3,000) showed that the event rates in an otherwise healthy cohort were too low for any definitive conclusion.

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Most published literature on poor clinical outcomes of pediatric LVNC were relatively small in sample size and retrospective in nature, and the prognostic value of extent of trabeculation was not assessed (6-8). A recent paper by Stöllberger et al. (9) described an excellent summary on comorbidities and prognosis of published adult LVNC studies. These studies were also relatively small in size (maximum 220 participants) and typically consisted of patients with abnormal heart function or pre-existing cardiac symptoms. The adverse event rates were extremely variable in these studies and the extent of trabeculation was not found to be an independent predictor of major adverse cardiovascular events.

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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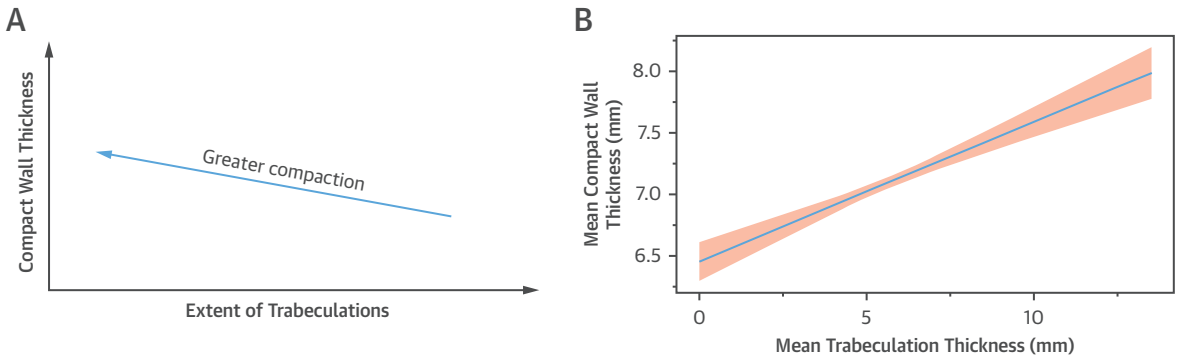
**FIGURE 1 Correlation Between Extent of Trabeculation and Compact Myocardium Thickness**




Courtesy of Bjarke Jensen, Amsterdam and Filip Zemrak, MESA data. **(A)** Expected relationship and **(B)** observed relationship in MESA (Multi-Ethnic Study of Atherosclerosis) study data.

This issue of the *Journal* also presents a paper by Andreini et al. (10), which sheds further light on the prognostic relevance of the extent of trabeculation measured by CMR. In this prospective multicenter observational study, 113 patients with imaging evidence of LVNC were followed up for a composite endpoint of adverse cardiovascular outcomes—thromboembolic events, heart failure hospitalization, ventricular arrhythmias, or cardiac death—over a course of approximately 4 years. It is important to note that a significant proportion of the study cohort had impaired cardiac function at recruitment with mean LV ejection fraction of 45%. Those with high clinical pre-test probability of LVNC made up 74% of the cohort. Thirty-six patients met the primary endpoint and 97% of those with events belonged to the high clinical pre-test probability group. The extent of trabeculation quantified by CMR was not associated with clinical outcome in the whole cohort. In multivariate analysis, LV dilation and presence of late gadolinium enhancement (LGE) were the only significant independent CMR predictors of adverse outcomes. In fact, none of the event-free patients had abnormal LV volumes or LGE.

These findings have important clinical implications. First, features of high pre-test probability of cardiomyopathy—cardiac symptoms, positive family history of nonischemic cardiomyopathy, neuromuscular diseases, or prior malignant arrhythmias and thromboembolic events—are excellent predictors of adverse outcomes in those patients with excessive trabeculation. Second, the extent of trabeculation alone does not have any additional prognostic implication above and beyond the well-established deleterious markers, such as LV dilation or LGE. The latter finding also reinforces the expanding pool of evidence suggesting trabeculation as an epiphenomenon coexisting with other forms of cardiomyopathies such as dilated cardiomyopathy (DCM) (11).

These 2 timely papers and previous literature highlight the absence of convincing evidence to consider the degree of trabeculation as prognostically relevant in asymptomatic low-risk populations and in cardiomyopathies. This conclusion leads to further open questions on whether our current trabeculation quantification or LVNC diagnostic criteria are adequate for diagnosis and risk stratification and perhaps, more importantly, on the existence of LVNC as a separate disease entity.

The nomenclature of LVNC implies that the compact or solid layer of the myocardium develops through coalescing of pre-existing embryonic trabeculation. However, the emerging evidence suggests that this commonly held belief of the mode of compact myocardium development is incorrect except for the papillary muscles (12). Using molecular staining techniques, studies by de Boer et al. (13) and Sizarov et al. (14) demonstrated the role of cellular proliferation within the solid myocardium during embryonic cardiogenesis in mouse and human, which contradicts the theory of trabecular condensation in formation of compact myocardium. If trabeculation is indeed important for the size of compact wall, we should expect the compact wall thickness to be negatively correlated with degree of trabeculation. However, the inverse was true in our data from the MESA study (**Figure 1**). A seminal paper by Jensen et al. (15) examined the evolution of ventricular trabeculation in both

endothermic (warm-blooded) and ectothermic (cold-blooded) species. They found that the hypertrabeculated ventricles in post-natal human hearts were far less trabeculated than the embryonic ventricles. In contrast, the ventricles of fully formed cold-blooded vertebrates were as trabeculated as their embryonic counterparts. These findings greatly challenge the hypothesis of LVNC because of persistence of embryonic design at least in warm-blooded vertebrates, and the term LVNC itself may be a misnomer.

In summary, there is growing evidence in the literature that presence of excessive trabeculation has no meaningful independent prognostic value in asymptomatic low-risk populations and in cardiomyopathies, particularly DCM, when other prognostic factors are considered in regression models. Compaction does not appear to be an important process for formation of the solid ventricular wall and it may be the opportune time to reconsider the term LVNC and maybe use a preferable term such as excessive trabeculation instead. Further research is needed to investigate if the extent of trabeculation plays an important prognostic role in physiological remodeling and in non-DCM cardiomyopathies.

**ACKNOWLEDGMENTS** The authors thank Robert Anderson, David MacIver, and Bjarke Jensen for the excellent discussions on LVNC, which informed this editorial.

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**KEY WORDS** CMR, LVNC, prognosis, trabeculations