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EDITORIAL COMMENT

CMR and LV Noncompaction*

Does it Matter How We Measure Trabeculations?

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Left ventricular noncompaction (LVNC) is an intriguing, but poorly understood, condition that can lead to heart failure, malignant arrhythmias, and thromboembolic events. It can be associated with neuromuscular disorders and can coexist with other cardiac malformations (1).

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Diagnostic imaging criteria were first described for native echocardiography by Chin et al. (2), Jenni et al. (3), and Stöllberger et al. (1) and followed by cardiac magnetic resonance (CMR) criteria proposed by Petersen et al. (4) and Jacquier et al. (5). It is important to emphasize here that currently there is no diagnostic tool, neither genetic nor imaging, that can, in all patients, reveal the underlying truth of whether or not somebody is affected by LVNC. The absence of such a "gold standard" is the main reason why all cardiac imaging studies have limitations when attempting to determine their diagnostic accuracies with a basis of a *likely* diagnosis of LVNC and not a *definitive* diagnosis. To avoid a circular argument in diagnostic accuracy studies for LVNC, the imaging findings alone should not be considered sufficient for a diagnosis of LVNC but should be supported with evidence of malignant arrhythmias, neuromuscular disorders, or a family history of LVNC or thromboembolic events. Another observation holds true for most LVNC diagnostic accuracy studies: in a derivation dataset, cutoff values for continuous variables, such as the noncompaction-to-compaction ratio, are typically determined using receiver-operating characteristics curves and tradeoff sensitivity and specificity according to the purpose of the test; rarely is the diagnostic accuracy of a cutoff value validated in a validation dataset.

Sensitivity and specificity are independent of the prevalence of disease. A useful diagnostic test provides information that changes the likelihood of having a disease (post-test probability) from the likelihood of having disease without the test information (pre-test probability). The positive and negative predictive values quantify this information of the test as a function of sensitivity, specificity, and pre-test probability (this may be the prevalence of disease). Figure 1 represents the relationships between pre- and post-test probabilities over the entire range of pre-test probabilities given the sensitivities and specificities published (4,5). An uninformative test (50% sensitivity and 50% specificity) does not change the probabilities and equals the identity line (45° line) in Figure 1. The graph also shows that in the range of pre-test probabilities that are consistent with the currently published range of LVNC prevalence (0.014% to 0.05%) (6), both CMR criteria do not provide sufficient diagnostic information, as the post-test probability remains low. Both CMR criteria help to refine the post-test probability in the low and intermediate pre-test range. Above a pre-test probability of 10%, the post-test probability is above 90% for the Petersen criteria, showing the value of CMR as a rule-in test in such a population. Similarly, the negative CMR test result in the same population reduced the post-test probabilities to very

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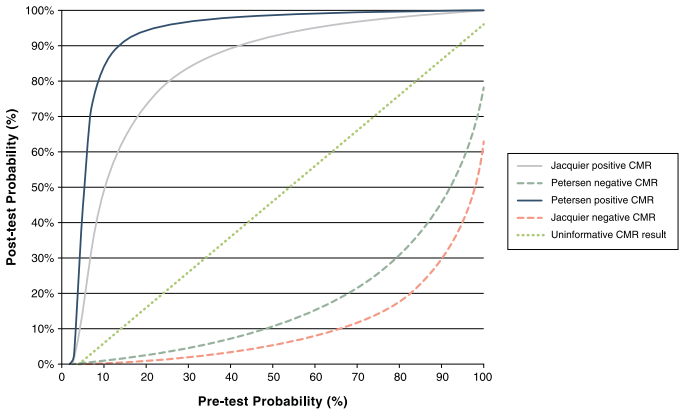

Figure 1. Relationship Between Pre- and Post-Test Probability for Published Sensitivities and Specificities to Diagnose LVNC

Petersen criteria: sensitivity: 86%; specificity: 99%. Jacquier criteria: sensitivity: 93.7%; specificity: 93.7%. An uninformative test has a sensitivity and specificity of 50%. In very low pre-test probabilities consistent with the reported left ventricular noncompaction (LVNC) prevalence of 0.014% to 0.5%, neither cardiac magnetic resonance (CMR) criteria are very informative. In low and intermediate pre-test probabilities both CMR criteria are informative, one slightly better at ruling out disease and one better at ruling in disease.

low likelihoods and thus underlines its potential use as a rule-out test.

Currently no prediction rule is available based on the above clinical information to determine the pre-test probability for LVNC. Patients with a family history of LVNC, known LVNC complications, associated muscular disorders, or regional wall motion abnormalities would have higher than background prevalence pre-test probabilities of having LVNC. To illustrate the use of CMR in diagnosing or excluding LVNC in intermediate probabilities, consider the following CMR screening in a family with an autosomal dominant inheritance pattern. The nephew of an index patient has a pre-test probability of 25% compared with that of the index patient's child, which is 50%. Here, positive CMR scans using Petersen criteria lead to post-test probabilities of having LVNC of 96.6% and 98.9%, respectively. Negative CMR scans lead to post-test probabilities of having LVNC of 4.5% and 12.4% (4).

The clinical value of CMR in the diagnosis of LVNC is currently unclear due to a lack of prospective population-based studies including cardiac imaging and LVNC cohorts. The natural history of LVNC with normal ejection fraction compared to normally functioning and normally trabeculated hearts remains unknown, and the natural history of LVNC with impaired LV systolic function compared to that in matched dilated cardiomyopathy patients is unclear. This information could inform how to best manage such patients. Many open questions remain, such as: should patients with heavily trabeculated hearts and normal function be treated to reduce the likelihood of adverse remodelling or thromboembolic events? And should LVNC patients with impaired systolic function be managed differently from those with dilated cardiomyopathy?

In this issue of *iJACC*, Stacey et al. (7) present, for a number of diagnostic CMR criteria that are similar but slightly modified compared to those in previously published studies, associations with prevalent (existing) heart failure and with incident (future) combined clinical events (death, heart failure readmission, embolic events, or ventricular arrhythmias). The motivation for this retrospective study with chart reviews to determine outcomes was to investigate whether end-systolic measures of LVNC are feasible and can improve clinical recognition of LVNC. A total of 122 patients (2.5% of the 4,762 patients screened) were included as reports mention trabeculations or LVNC. The authors find that measures of end-systolic non-compaction-to-compaction ratios (ES-NCCR) are the strongest predictors of not only prevalent heart failure (adjusted odds ratio: 29.4; confidence interval [CI]: 6.6 to 125) but also incident combined clinical events (adjusted odds ratio: 8.6; CI: 2.5 to 33), albeit with very wide CIs, reflecting uncertainty. This study is welcomed as it provides some much-needed insight into the not entirely benign natural history of some patients with a LVNC diagnosis based on the CMR findings. However, no firm conclusions can be drawn as to whether ES-NCCR is superior to end-diastolic measures for the diagnosis of LVNC leading to related events. Given the above explanations regarding the relationship of pre- and post-test probabilities of LVNC and the arguments presented in Figure 1, it is likely that a large proportion of the so-called LVNC population does not have the disease. In particular, patients with normal ejection fraction may have no disease. It is possible that ES-NCCR may identify LVNC patients with more pronounced impairment of regional or global dysfunction due to the reduced contraction of the trabeculations. Whether this approach is superior to using a diastolic measure with attention to regional and global function is unclear. Even though the authors adjusted the odds ratios for covariates including heart failure, it is possible that the adjusted odds ratios for end-systolic parameters were higher compared with the end-diastolic ones due to the lack of contraction of trabeculations when ejection fraction was impaired. Whether end-systolic parameters are more useful in diagnosing

LVNC or predicting clinical events in normal ejection fraction remains unclear.

The study by Stacey et al. (7) was limited by its retrospective nature and relatively small sample size, leaving it unable to provide sufficient information on the natural history of patients with normal ejection fraction and impaired ejection fraction separately (and to compare the latter group to dilated cardiomyopathy patients).

Prospective studies are needed to document the natural progression of LVNC and to determine clinical and imaging predictors of adverse outcomes, which could be the basis for a simple diagnostic prediction rule. This is a task for a coordinated effort between the international imaging and heart muscle disease communities to come together to plan, raise funds for, and organize such a study.

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Key Words: Bayes ■ cardiovascular magnetic resonance ■ CMR ■ diagnostic accuracy ■ left ventricular noncompaction ■ LVNC ■ post-test probability ■ pre-test probability ■ prognosis.