Adherence to Thresholds:

Overdiagnosis of Left Ventricular Noncompaction Cardiomyopathy

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Thresholds derived from quantification in imaging are increasingly used to define disease. This derivation is not an exact science. When one uses a threshold to define a disease, one does not clearly demarcate disease from normality because the threshold includes overlapping spectra of mild disease and normality. Thus, use of the threshold will mislabel normal individuals with disease. In this perspective, we will describe how the threshold has been derived for left ventricular noncompaction cardiomyopathy, the statistical biases in the design of studies used to derive the threshold, and the dangers of overdiagnosis when the threshold is used to rule out left ventricular noncompaction cardiomyopathy.

Key Words: Overdiagnosis; cardiovascular imaging; ventricular noncompaction.

Definitions are important to diagnose, prognosticate, and treat a disease. To increase consistency and reduce uncertainty, we increasingly ask for objective criteria to establish disease. For example, chronic bronchitis is defined by a productive cough on most days for at least 3 months for 2 years.

It is neither always desirable nor feasible to obtain tissue for confirmation of disease, particularly cardiac disease, as biopsies have morbidity and sampling error. There is reliance on imaging for diagnosis, and imaging is therefore increasingly used to objectify the positivity of disease. A threshold is the minimum required to fulfill disease status.

Thresholds oversimplify the complexity of diagnosis by assuming a dichotomy between those with a particular disease and those without (1). In reality, there exists spectrum of disease, as well as spectrum of "nondisease." The compositions of groups can vary from one study and one clinical situation to another, which affects the generalizability of measurements made on any group. This leads to the establishment of diagnostic thresholds that are inaccurate when used in real-world clinical scenarios.

Left ventricular noncompaction cardiomyopathy (LVNC) is a rare disease, previously under-recognized, characterized by a bilayered myocardium with an abnormally trabeculated subendocardial layer of the myocardium with prominent trabeculae and recesses (2).

The clinical and phenotypic presentations are variable, and it is recognized that patients with a severe phenotype have a poor prognosis from progressive heart failure, embolic phenomena, and malignant arrhythmias.

Diagnosis of LVNC is based on a threshold. However, proposed thresholds are controversial because ever since their implementation, there have been increasing rates of diagnosis, and likely overdiagnosis, of LVNC (3).

LVNC is instructive in how thresholds in imaging are derived and the problems inherent in establishing a diagnosis based on fulfillment of a threshold. We will critically analyze the studies used to develop thresholds for LVNC on echocardiography and cardiac magnetic resonance (CMR). We will explain why these thresholds increase overdiagnosis.

ESTABLISHMENT OF A THRESHOLD

Although isolated reports of LVNC date back to the 1960s, the first major study of patients with LVNC was in 1990 (4). The authors reported a series of eight patients who were thought to have a congenital abnormality of the myocardium characterized by "numerous, excessively prominent trabeculations and deep, intertrabecular recesses." They reported a high rate of cardiovascular complications associated with this entity and attempted to provide a diagnostic tool using echocardiography.

The authors developed a ratio between two distances X and Y. X is the distance from the epicardial surface to the trough of the trabecular recess. Y is the distance from the epicardial surface to the peak of trabeculation.

They compared the ratio to eight controls and noted that all patients with LVNC had an X/Y ratio that decreased to <0.5 from the midcavity to the apex of the heart, whereas all controls had X/Y ratios that remained >0.5 at the apex. They therefore proposed an X/Y threshold of <0.5 on echocardiography for the diagnosis of LVNC.

Jenni et al. refined the echocardiographic threshold for LVNC. They identified, retrospectively, 17 of 37,555

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echocardiograms with hypertrabeculation and deep intertrabecular recesses. Chart review of these 17 patients revealed that most patients had clinical manifestations of disease such as systolic dysfunction, arrhythmia, or embolic phenomena (5,6). Pathologic confirmation was available for 10 patients who either died or received heart transplants and was used as the gold standard for diagnosis (7).

Echocardiograms of these 10 patients were compared to patients with left ventricular hypertrophy (LVH) or idiopathic dilated cardiomyopathy (DCM) because these patients often have prominent trabeculations. They found that the ratio of noncompacted to compacted myocardium (NC/C ratio) in systole at the site of maximum wall thickness averaged 3.5 for the LVNC group, 0.8 for the DCM group, and 1.1 for the LVH group.

No patient in the LVH or DCM group had an NC/C ratio >2.0; therefore, they proposed a threshold of 2.0 for the diagnosis of LVNC. In their conclusion, they wrote, "classification of isolated ventricular noncompaction as a distinct cardiomyopathy would facilitate its diagnosis and most probably contribute to unmasking a much higher incidence of this disorder." The authors also emphasized the long-time frame from symptom onset to diagnosis of LVNC (8). The threshold was widely adopted.

Still, the limitations of echo including difficulty in assessing the left ventricular apex because of the near-field effect and dependence on good imaging windows were widely recognized. CMR is not afflicted by these technical limitations and offered an alternative to echo in the diagnosis of cardiomyopathies.

The most widely used threshold on CMR was developed by Petersen et al. (9) in 2005. The authors compared the CMR findings of seven patients with a known diagnosis of LVNC to CMR findings from small cohorts of the following: competitive athletes, patients with DCM, hypertrophic cardiomyopathy, LVH, or aortic stenosis. They found that the average diastolic NC/C ratio of the LVNC group was 3.0 (95% confidence interval, 1.5–4.5) and was significantly higher than the other groups. They calculated that an NC/C ratio of >2.3 would provide a diagnosis of LVNC with a sensitivity, specificity, positive predictive value, and negative predictive value of 86%, 99%, 75%, and 99%, respectively. The authors concluded that "the diastolic ratio of >2.3 showed high diagnostic accuracy for distinguishing pathologic LVNC from the degrees of noncompaction observed in healthy, dilated, and hypertrophied hearts."

APPLICATION OF THRESHOLDS TO WIDER POPULATIONS

The aforementioned studies are methodologically reasonable, and the authors should be commended for providing diagnostic criteria for such a rare and recently discovered entity. Indeed, they are the best in the circumstances. However, this does not mean they are without significant flaws.

A threshold was derived for a very rare disease (a reported prevalence in these early studies of 0.3%) based on very small cohorts with poorly defined disease states. The imaging findings of these patients were then compared to small control groups of distinctly normal patients or to those with other distinct diseases. In effect, a diagnostic threshold was established with very small representations of normal or diseased states, when the phenotypes of both groups are in reality quite varied. It would be improbable that a group of 10 normal or a group of 10 patients determined to have LVNC could provide an accurate representation of all the phenotypic manifestations of those groups. The problems that arise from such assumptions become clear when these diagnostic thresholds are applied to larger populations.

In 2008, Kohli et al. evaluated the echocardiographic criteria proposed by Chin et al., Jenni et al., and a third set of criteria previously proposed by Stollberger et al. (10). They applied three thresholds for LVNC to the echocardiograms of 202 consecutive patients with left ventricular systolic dysfunction who were referred to a heart failure program at a tertiary hospital (11). They also applied the criteria to the echocardiograms of 60 normal healthy volunteers. They found that nearly 25% of the heart failure patients, as well as 8% of the healthy controls, fulfilled one or more of the criteria for LVNC. This was in stark comparison to the earlier reported prevalence of <0.3%. Their findings, combined with an increasing number of reports of LVNC in the literature, led the authors to question whether LVNC was being overdiagnosed.

Some years later, Kawel et al. (12) applied the CMR threshold (NC/C > 2.3) for diagnosis of LVNC to a large cohort of patients participating in the Multi-Ethnic Study of Atherosclerosis (MESA). Of 323 patients without cardiac disease or hypertension, 140 (43%) had an NC/C ratio >2.3 in at least one segment. The maximum thickness of trabeculation was positively associated with Chinese and black races, and left ventricular end diastolic volume (ie, the larger the ventricle, the more likely it was to have significant trabeculation.)

Several questions arise from the two studies. The most obvious question is by what means did established plausible thresholds with high specificity flag LVNC in so many normal subjects. Recall that the specificity from the study by Peterson et al. is 99%, and yet, 43% of asymptomatic patients in MESA fulfilled the threshold of 2.3.

Furthermore, there are larger questions regarding the nature of diagnosis and subsequent management. Should normal study participants be concerned that they meet definition for LVNC and seek treatment with warfarin? If so many "normal" subjects have features of LVNC on cardiac imaging, is it possible that the disease is much more common than previously believed? Or were the initially developed thresholds too sensitive, overdiagnosing patients who in reality have no underlying pathology? From the standpoint of cardiac imagers, is it better to err on the side of overdiagnosis, potentially exposing normal patients to unnecessary testing and