Fractal Dimension of Hypertrophic Cardiomyopathy Trabeculation
A Window to an Unpredictable Future?

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Genetic analysis has revolutionized our understanding of the pathophysiology of hypertrophic cardiomyopathy (HCM) and has led to an evolving approach to both screening and diagnosis of patients with HCM and their relatives in recent years. Phenotypically, HCM was characterized and defined by left ventricular hypertrophy (LVH) unexplained by other conditions and LV outflow tract obstruction. Current genetic evaluation can now identify mutations within sarcomeric proteins that form the basic contractile unit of the heart in >60% of HCM cases. Despite the advancement of genetic diagnosis and cascade screening, the clinical impact of genetic testing for HCM remains somewhat uncertain. Genetic mutations in HCM have both variable expressivity and incomplete penetrance, thus current mutation-specific risk stratification of patients with HCM lacks precision. Screened relatives who are genotype positive may never progress to overt clinical disease, and even patients who have the same genetic mutation may manifest highly variable phenotypic severity over time. Furthermore, there has been no reliably established link between the type of genetic mutation and patient prognosis. These factors have resulted in a hybrid of genetic and cardiac imaging to improve profiling of preclinical disease in patients who are genotype positive but phenotype negative. In accordance, cardiac magnetic resonance has emerged as a valuable imaging tool to complement genetic evaluation, attributable to its high spatial resolution and ability to assess myocardial tissue characteristics. With unrestricted scan planes and imaging field, cardiac magnetic resonance allows imaging of the heart volumetrically and may identify focal ventricular hypertrophy and subtle structural abnormalities, such as myocardial crypts, less easily detected by 2-dimensional echocardiography. Recent data have also emphasized the prognostic significance of quantifying the extent of myocardial fibrosis by late gadolinium enhancement imaging in this heterogeneous disease.

Fractal analysis assesses how complex biological structures occupy space. Its initial application in medicine was for mapping of neurons and the dendritic fields and it is based on the key observation that growth of biological structures follows a geometry that contains some degree of scale invariant symmetry. Fractal dimension, a unitless parameter that fractal analysis measures, describes the spatial orientation and geometric complexities of a structure. Compared with conventional methods, fractal analysis represents the irregularity and scaling relationships of complex anatomic patterns more completely. In this issue of Circulation: Cardiovascular Genetics, Captur et al performed fractal analysis of an HCM patient cohort and matched controls. Patients with unexplained LVH or a genetic profile consistent with HCM underwent cardiac magnetic resonance and genotyping for mutations in the sarcomere genes. The fractal dimension measured in this study aimed to quantify the extent of LV trabeculation (LVT) based on inhomogeneity of image signal intensity in cohorts of 39 genotype-positive HCM patients without unexplained LVH, 67 with LVH (31 of whom were genotype positive), and age- and sex-matched controls. The authors reported that although LVT was markedly increased in patients with LVH (regardless of presence of sarcomere gene mutations), genotype-positive patients without LVH demonstrated increased fractal dimensions in the apical part of the LV. They concluded that this structural feature of the LV, in conjunction with myocardial crypts and evidence of myocardial fibrosis, might represent sentinel phenotypic features of preclinical HCM. Captur et al should be commended for their effort in studying the complex myocardial shapes of this heterogeneous condition using a novel automated quantitative method. The results are intriguing, inferring that evidence of abnormal myocardial development as influenced by sarcomere gene mutations can be detected in preclinical patients with HCM. The potential impact of their findings may be substantial. Abnormal trabeculation seemed to be detected sensitively by fractal analysis, even when LV wall thickness, myocardial mass, and ECG voltage remained within the normal range. In addition, in genotype-positive patients without overt LVH, it is reasonable to hope that fractal analysis of LVT may forecast the development of debilitating cardiac manifestations marked by LVH and heart failure and may allow early intervention for novel therapeutic intervention.

However, measurement of the LVT by fractal analysis faces several challenges. Endocardial complexity is a 3-dimensional entity, whereas the current fractal analysis is only 2-dimensional; thus, the accuracy of the fractal dimension measurement can be affected by parameters, such as slice thickness,
in-plane spatial resolution, and angulation of the imaging plane. A single fractal dimension may not adequately represent the 3-dimensional endocardial complexity of the LVT, which may be more accurately represented by multiple fractal dimensions. Measurement of fractal dimension is also dependent on the method applied, so consistency of the methodology will need to be maintained for future prospective clinical studies.\textsuperscript{11} Most importantly, fractal dimension is a descriptive parameter and does not imply a specific biological process, pathophysiology, or mechanism involved in the early development of the myocardium. From the standpoint of technical development, fractal analysis of LVT needs further evaluation with histological correlation, in addition to assessing the consistency of this measure across different methods and fractal criteria. Further development of fractal analysis in quantifying regional and global endocardial complexities may provide further insight into understanding the derangement in embryological myocardial development and its potential genetic influence. Its reliability as a clinical measurement will also need substantially more vigorous multicenter testing.

The penetrance of sarcomeric protein mutations is highly variable and remains poorly understood. From a clinical standpoint, the interesting observations reported by Captur et al\textsuperscript{10} will need to be replicated in larger cohorts of genotype-positive and phenotype-negative patients with preclinical HCM. Larger studies would also help to determine whether a diagnostic cutoff for fractional dimension of LVT exists to offer robust prognostication for those patients who will manifest future adverse phenotypic changes. It may also be imperative to assess whether serial fractal analysis can serve as a longitudinal tool in monitoring disease progression.

At present, there are no preclinical imaging markers that have established association with adverse prognosis in patients with preclinical HCM, with regard to either the development of overt phenotypic disease or sudden cardiac death. Genotype-positive patients without overt LVH have not been shown to be at increased risk of sudden death,\textsuperscript{12} and current consensus recommendations do not exclude these patients from engaging in competitive sports.\textsuperscript{13} On the basis of these present-day recommendations, and clear need for continual surveillance of these patients, how novel imaging observations may impact clinical management remains speculative but warrants further focused investigation.

**Disclosures**

None.

**References**


**Key Words:** Editorials ■ cardiomyopathy, hypertrophic ■ genetic testing ■ magnetic resonance imaging
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Circ Cardiovasc Genet. 2014;7:228-229
doi: 10.1161/CIRCGENETICS.114.000649

Circulation: Cardiovascular Genetics is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1942-325X. Online ISSN: 1942-3268

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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