Radiology – Commissioned Editorial

TITLE

Topcats often begin as underdogs: Ascent of the trabeculae

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We quote Bernard C. Meltzer in the title.

Main Text

The concept of using fractal algorithms to quantify cardiac trabeculae[1] was not an immediate success – in 2011, the proposal was turned down three times for funding and the methods paper rejected 7 times. Thereafter however, it was validated in the mouse[2,3], successfully applied to patients and population-based cohorts, disseminated as user-friendly plugins[4], and has recently underpinned a Nature paper probing the genetic basis of trabeculae and cardiovascular risk[5].

The unitless fractal dimension (FD) from fractal analysis, measures how completely a complex biological structure fills the 2- or 3-dimensional imaging space. It is better suited to natural irregular, scaling biological architectures than traditional Euclidean approaches such as linear measurement or fitting simple contours. The box-counting method typically used for its quantification is also relatively image resolution independent. Cardiovascular magnetic resonance imaging (MRI) with its high-resolution cine data, is well suited to fractal analysis. In this issue of *Radiology*, XXX et al.[REF 6] performed fractal analysis in 378 patients with hypertrophic cardiomyopathy (HCM) and 100 controls to understand its prognostic value. Participants were assessed for endpoints over a median of 33±18 months. Consistent with previous studies, authors found that the FD in HCM was higher than controls, and a FD >1.352 associated with the primary and secondary endpoints. FD was independently predictive on multivariable analysis and provided incremental prognostic value over and above the traditional risk factors considered by the European Society of Cardiology sudden cardiac death risk algorithm[7].

XXX et al should be commended for their efforts to explore new biomarkers to improve HCM risk stratification. This is needed. Current approaches are simplistic measuring a basket of late parameters (wall thickness, atrial size, outflow tract obstruction, arrhythmia) distant from the active substrate changes in the heart muscle that lead to adverse outcomes. Current approaches could potentially lead to (for example) misallocation of implantable cardioverter defibrillators, with the risk of inappropriate therapies. There is progress using new more direct biomarkers such as fibrosis and late gadolinium enhancement by cardiac MRI that have successfully infiltrated the North American HCM sudden cardiac death risk stratification strategy,[8] but it remains early days.

Here, another approach is taken: HCM patients with more complex trabeculae are shown to be a higher risk group. Why would that be? We know that trabeculae are a unique biometric marker similar to fingerprints. They are measurable early in the embryo as soon as ventricular septation has occurred.[9] Pathogenic sarcomere gene mutations causing HCM in adults also disrupt the normal embryologic compaction processes leaving a signature: the "subclincal HCM" phenotype, than can be seen before measurable hypertrophy or electrocardiographic changes. It is therefore plausible that mutations which alter signalling and cardiomorphogenesis would impact adult life risk. There may however be other phenomena. Firstly, hypertrophy is at least in part a protective mechanism. It seems remarkable, but there are still so many fundamental disease mechanisms in HCM that we do not understand: *where* does hypertrophy occur in HCM–at the endocardium or epicardium or trabeculae?; *how* do myocyte disarray, small vessel disease, fibrosis and hypertrophy inter-relate?; and *what* is the actual sequence of architectural changes in HCM phenotype development? Mutations are at the coding DNA sequence level, but imaging is macroscopic–an imaging voxel may perhaps contain 100,000 myocytes. There is however cause for optimism: firstly, as Richard Feynman once said, "*Nature uses only the longest threads to weave her patterns, so each small piece of her fabric reveals the organization of the entire tapestry*." Secondly, only around half (depending on the cohort) of HCM patients will have an identifiable pathogenic gene mutation, even with the most massive and advanced sequencing approaches. It is therefore biologically plausible (and testable) that mutation-negative patients, could be at lower risk and that these will be the ones with lower FD reflecting the lack of genetic causality.

This study is preliminary, single-center and the cohort relatively low-risk, so larger multi-center data will be needed to validate its findings. FD performance in a health care system needs robust assessment: repeatability via test:retest imaging and vendor neutral performance of the assay. Other scenarios may need exploring: extreme hypertrophy, cavity obliteration, or apical aneurysm formation are likely to degrade FD performance whilst abnormal papillary muscle insertion in HCM may swamp the apical trabecular signal. Other associated features–anterior mitral valve elongation and myocardial crypts may contribute to the constellation of subtle

"architectural abnormalities" that predict risk in gene mutation carriers. In this paper Authors' use of resting left ventricular outflow tract gradients without Valsalva provocation may have flattered FD as a biomarker.

What of the future? We should not look to higher resolution imaging for all the answers–cardiac MRI is caught between two opposing forces: one for technical advancement with higher resolution (e.g. 7T is remarkable for crypts), and another for faster scans with "good enough" image quality but greater access at lower cost. Image analysis developments such as this are however highly promising as they are automatable and may provide improved objectivity and precision in image measurement with the potential to cascade clinical benefit. This is needed. HCM affects millions globally. Concerted transatlantic efforts led by imagers in partnership with clinicians and computer scientists have the potential to deliver improved, vendor agnostic imaging analysis tools to improve HCM risk stratification algorithms. Myocardial trabeculae may be shown to be a part of such approaches–they feel vindicated already.

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BIOGRAPHIES

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