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Editorial

Fractal analysis: another tool for the toolbox for dilated cardiomyopathy prognostication?

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Despite the remarkable progress in heart failure disease-modifying medical therapies over recent decades, mortality rates from dilated cardiomyopathy (DCM) remain high with 10-year survival around 60% [1,2]. Therefore, there is a pressing need to fine-tune our prognostication strategies in order to improve outcomes for patients with DCM. In the assessment of cardiomyopathy, multiparametric cardiovascular magnetic resonance (CMR) is the gold-standard imaging modality.

Traditionally, risk stratification in DCM focused solely on left ventricular ejection fraction (LVEF) as the most important criterion to determine implantable cardioverter-defibrillator (ICD) candidacy. However, the use of LVEF to predict sudden cardiac death (SCD) in DCM has proven to be imprecise given that a significant proportion of patients not eligible for ICD under current guidelines still go on to experience SCD. In addition, the clinical course of patients with DCM varies widely, ranging from rapidly progressive heart failure or SCD to left ventricular (LV) reverse remodeling following guideline-directed medical therapy, denoting complexity in assessing individual risk and the need for personalized medicine approaches. In selected highly malignant forms of DCM, such as lamin heart disease, risk assessment is algorithmically bespoke and takes into account genetic, clinical, and imaging traits [3]. But for the vast majority of patients with DCM, we are left with a "one size fits all" risk stratification framework that may well be underserving vast swathes of the DCM population. Some prognostic CMR biomarkers gaining traction in DCM include presence and pattern of late gadolinium enhancement (LGE) [4,5], myocardial strain [6,7], LV entropy [8], and native T1 and extracellular volume [9]. Authoritative guidelines have finally begun to acknowledge the clinical utility of these imaging biomarkers in risk assessment; indeed for the first time, the 2023 European Society of Cardiology guidelines for myocardial disease [10] explicitly mentions LGE as an "additional risk factor" to be considered in a subset of patients with DCM when deciding about primary prevention ICDs.

In our quest to improve the quality and quantity of life for patients with DCM, we therefore enthusiastically welcome the work by Xie et al [11]. Fractal analysis is a computational image post-processing method to quantify complex geometrical patterns encountered in the natural world or mathematical structures. The outputted unitless "fractal dimension" (FD) measures how completely a complex biological structure fills the two- or three-dimensional imaging space [12]. Greater FD represents greater complexity. CMR, with its high-spatial-resolution cine data, is well suited to fractal analysis. To date, CMR fractal analysis has been successfully used to quantify endocardial trabecular complexity in hypertrophic cardiomyopathy [12], athlete's heart [13], LV non-compaction [14,15], arrhythmogenic cardiomyopathy [16], Fabry's disease [17], and the right ventricle in pulmonary hypertension [18].

Xie et al. [11] report how they undertook CMR fractal analysis in 403 patients with non-ischemic DCM and followed them up for a median of 44 months to capture significant major adverse cardiovascular events. Patients with known prior ischemic heart disease, infarct pattern LGE, myocarditis, primary valve disease, and other cardiomyopathies were excluded. The primary endpoint was a composite of all-cause death and heart failure hospitalization while the secondary endpoint was cardiac death alone. Within this cohort, 87 patients (21%) reached the primary endpoint, of which 24 (6%) experienced heart failure death, 12 (3%) SCD, 49 (12%) heart failure hospitalization and 2 patients died from non-cardiac causes. The secondary endpoint of cardiac-only death was observed in 24 patients (6%).

Authors found that patients with higher FD had a higher risk of the experiencing the primary and secondary endpoints. The optimum diagnostic thresholds were found to be global FD $>$ 1.272, mean apical FD $>$ 1.262, and maximal apical FD $>$ 1.338. Consistent with previous studies [14], the authors found higher FD values at the LV apex and papillary muscle regions compared to the base. The authors adjusted for age, LVEF, heart rate, New York Heart Association class, N-terminal pro B-type natriuretic peptide, indexed left ventricular end-diastolic volume (LVEDVi), indexed left ventricular end-systolic volume (LVESVi), LV mass, LGE extent (%), and strain in the multivariable analysis, but not for medication use, QRS duration on the

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Abbreviations: DCM, dilatedcardiomyopathy; CMR, cardiovascularmagnetic resonance; LVEF, left ventricularejection fraction; ICD, implantablecardioverter-defibrillator; SCD, sudden cardiac death; LV, left ventricle; LGE, late gadolinium enhancement; FD, fractal dimension; LVEDVi, indexed leftventricular end diastolic volume; LVESVi, indexed leftventricular end systolic volume ; HR, hazard ratio

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electrocardiogram or left atrial size. After multivariate adjustment, LV maximal apical FD remained a significant independent predictor of outcomes [hazard ratio (HR) 1.177 for the primary endpoint, and HR 1.65 for the secondary endpoint]. The authors found that FD correlated with ventricular function (LVEF), volume (LVEDVi, LVESVi), and some strain parameters (global longitudinal strain and global circumferential strain, but not global radial strain). The study also found that the majority (84%) of patients who experienced the primary endpoint also had LGE, confirming it as a strong negative prognosticator.

This study recruited patients from two hospitals in China; the majority of whom had severe DCM (mean LVEF 21.5%), meaning they were high-risk even by conventional risk stratification criteria. Of note, it was not explicitly stated if patients had an ICD at time of recruitment, and follow-up data did not capture whether patients went on to have a device or heart transplant, which would have impacted their defined outcomes.

The study raises interesting questions: why would DCM patients with more complex LV trabeculae be at higher risk of death and heart failure outcomes? This is pertinent in light of a recent genome-wide association study of trabeculae using fractal analysis [19] suggested a potentially causal relationship for the reverse: i.e., for certain genetic loci, reduced trabecular complexity associated with cardiac dysfunction in both mixed-etiology heart failure and DCM (albeit less severe DCM than the current cohort). Is aberrant trabecular architecture really causal for DCM or is it a mere epiphenomenon, dynamically tracking LV remodeling? In this regard, it has been proposed that the excessive trabeculae in DCM are the myocardium's way of compensating for myocardial thinning or for the loss of cardiomyocyte numbers due to scarring and apoptosis. By exaggerating its trabecular meshwork and expanding its endocardial surface area, the DCM heart may seek to maintain its cardiac output even when myocardial contractility cannot be efficiently augmented. Another possibility is that eventually, compacted myocardium in the DCM heart adversely transforms into spongiform myocardium because of cardiomyocyte dysfunction and deranged gap junctions [20]. This might explain the link between abnormal trabecular architecture and arrhythmia. The reverse is equally plausible, in that a myocardial segment which is heavily fibrosed and therefore pro-arrhythmic, could become endocardially "smoother" from trabecular effacement, leading to lower regional FD values.

CMR fractal analysis can certainly provide novel insights into ventricular pathophysiology but like with any evolving translational field, it is best served by an amalgam of basic science and large-scale multicenter clinical outcome studies.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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