Does Fractal Analysis of the Right Side of the Heart Provide Insight into Pulmonary Hypertension?

James C. Moon, MD, MBBS, MRCP • *Gabriella Captur, MD, PhD, MRCP, MSc*

From the UCL Institute of Cardiovascular Science, University College London, Gower St, London WC1E 6BT, England (J.C.M., G.C.); Cardiovascular Magnetic Resonance Imaging Unit, Barts Heart Center, St Bartholomew's Hospital, West Smithfield, London, England (J.C.M., G.C.); and UCL MRC Unit for Lifelong Health and Ageing, London, England (G.C.). Received March 26, 2018; revision requested March 30; revision received April 2; accepted April 3. **Address correspondence to** G.C. (e-mail: *gabriella.captur.11@ucl.ac.uk*).

Conflicts of interest are listed at the end of this article.
See also the article by Dawes et al in this issue.

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Terrestrial life as we know it would not have evolved were it not for the trabeculated myocardium (1). Trabeculae are nontrivial, and we know this because *(a)* the dense trabecular meshwork that occludes the embryonic ventricle acts as both the functional equivalent and the cellular ascendant of the Purkinje fiber network in mammals and birds (2), *(b)* healthy development of the mature working myocardium is tightly linked to the events taking place in the trabeculated layer, and *(c)* disruption of trabecular development leads to extreme hypotrabeculation that is incompatible with life and is frequently lethal in the embryonic mouse. To learn all this about the intricate trabecular meshwork, we have to leave the linear platonic world and get complex. In our quest for better understanding and models of the real world (here, the cardiovascular system), we discovered an ally to partner with imaging—mathematical fractal analysis.

Thus, we welcome the elegant work of Dawes and colleagues (3) in this issue of *Radiology*, which reports on a retrospective fractal analysis of the right ventricle (RV) in patients with pulmonary hypertension and healthy control subjects. Although fractal analysis of the RV had been previously used in the fetal mouse to understand cardiomorphogenesis (2), it had not been applied to the human RV. Here, with cardiac MRI, the fractal method appears reproducible (interobserver intraclass correlation of 0.97, not including test-retest correlation) and correlates with RV afterload; however, it cannot be used to independently predict survival when compared with other prognostic determinants (ie, age, sex, ethnicity, RV size or function, brain natriuretic peptide level, 6-minute walking distance, functional class, or invasive hemodynamics).

Pulmonary hypertension, nominally a disease of the pulmonary vasculature, seems to have survival determined by the cardiac response (ie, RV function), at least as we can currently measure. The fractal dimension (FD) of the RV was inversely correlated with RV ejection fraction and stroke volume. Similar to what has already been shown for the left ventricle (4), where each 10 mL of end-diastolic volume associates with 0.004 greater FD ($P < .001$), Dawes et al found a significant positive correlation ($r = 0.32$, $P < .001$) between RV volume and FD. These data suggest that trabeculae increase in either number or size as the heart dilates; however, these results must be interpreted with caution. FD measures how completely segmented endocardial contours fill the two-dimensional image space of the ventricular lumen. For a fixed volume of trabeculae (assuming no trabecular hypertrophy and no de novo trabecular formation), RV dilatation alone should theoretically reduce the FD for a given section. A dilated volume-overloaded RV from tricuspid or pulmonary regurgitation is a frequently encountered complication of longstanding pulmonary hypertension; therefore, it should have a lower FD compared with FD in an RV with the same amount of trabeculae but a smaller cavity size. In the current work on pulmonary hypertension, Dawes et al do not correct RV FD for coexistent volume overload, so it is possible that FD is being systematically underestimated precisely in the subgroup of patients with more advanced pulmonary hypertension and poorer health in the right side of the heart. Such confounding would ultimately undermine the prognostic performance of the fractal biomarker and could explain why RV FD did not retain predictive ability at multivariable testing.

Recent work using ellipsoidal two-dimensional visual models (5) has highlighted the close interaction between trabecular load, end-diastolic volume, and strain, so interpreting FD as a percentage of end-diastolic volume may be superior to FD alone. For a fixed amount of cavity strain, a larger number of trabeculations (or chunkier trabeculae) can contribute to ejecting more blood out of the ventricle, as their systolic coalescence helps reduce end-systolic volume, thus increasing stroke volume. So then, is RV hypertrabeculation a good thing or a bad thing? We think both. It is good because it allows the distressed heart to generate higher stroke volumes for a given cavity size, buying time before the establishment of frank right-sided heart failure. It is bad because if the heart were unstressed to begin with, trabeculation would not need to increase.

Interestingly, the difference between patients who survive pulmonary hypertension and those who die from this disease is greater for noncompacted RV mass index ($P = .04$) than for maximal apical FD ($P = .05$). We are not told whether noncompacted RV mass index correlated better with pulmonary vascular resistance than did the FD, but it raises the question of whether the proportion of trabeculated myocardium compared with the rest of the muscle matters more for survival in pulmonary hypertension than the FD.

Dawes et al postulate that the increased RV FD measured in patients with pulmonary hypertension is simply a reflection of RV trabecular hypertrophy (and, of course,

papillary muscle and moderator band hypertrophy as well). However, whether the afterloaded right side of the heart is instead or also sprouting de novo trabeculae, and thus further modulating its endocardial landscape, remains to be tested. The ability of the distressed ventricle to generate de novo trabeculae, if indeed this is what is happening, could be the key to unshackling the regenerative potential of the adult human myocardium. However, the majority of work on myocardial trabeculae in adults overlooks this fundamental mechanistic question: if a distressed adult ventricle can generate de novo trabeculae to maintain stroke volume, how are these trabeculae arising, and can this process be harnessed to increase stroke volume in the failing heart?

For years, developmental biologists were plagued by an analogous puzzle—trabecular fate during cardiac embryogenesis—before they seemed to have finally cracked it. We are referring to the previously upheld theory of developmental compaction. By studying the patterns of proliferation and gene expression in chamber-forming stages of the human heart and the mouse heart and confirming the proliferation that occurs in the compact myocardial layer (6), developmental biologists have clarified the origins of ventricular wall thickening before birth. However, this alone was not sufficient to prove the origins of ventricular wall thickening, nor did it enable observers to rule out compaction of trabeculae, per se. The proof required to disprove the compaction model of ventricular development requires genetic lineage tracing of the fate of trabecular tissue. There have now been some studies that have seemed to address this. Miquerol et al (7) used a transgenic ventricular conduction system reporter mouse line to study the origins of the conduction system and showed that at embryonic day 10.5, labeled descendants of trabecular cells are found in both the Purkinje fibers and the compact wall; however, by embryonic day 16.5, the lineages of the mature working myocardium and Purkinje fibers have separated. This suggests that as development proceeds, trabeculae become distinct from and do not coalesce into the compact ventricular wall (8). We will need similar approaches to unpick the trajectories of trabecular formation and hypertrophy taking place in the adult human heart.

To conclude, the origins and fate of trabeculae across the human myocardial life course and in response to disease are still being elucidated, but what potentially stands out from the current work is the extraordinary trabecular plasticity of the adult human heart. For a long time, we have been concentrating our efforts on biopsy of the compact adult myocardium, but perhaps it is the lower-hanging fruit—the unassuming trabeculae—that we ought to be sampling and studying at scale.

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