Fractal Analysis of Right Ventricular Trabeculae in Pulmonary Hypertension

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Purpose: To measure right ventricular (RV) trabecular complexity by its fractal dimension (FD) in healthy subjects and patients with pulmonary hypertension (PH) and to assess its relationship with hemodynamic and functional parameters and future cardiovascular events.

Materials and Methods: This retrospective study used data acquired from May 2004 to October 2013 in 256 patients with newly diagnosed PH who underwent cardiac MRI right-sided heart catheterization, and 6-minute walk distance testing, with median follow-up of 4.0 years. A total of 256 healthy control subjects underwent cardiac MRI only. Biventricular FD, volumes, and function were assessed on short-axis cine images. Reproducibility was assessed with the intraclass correlation coefficient, correlation between variables was assessed with the Pearson correlation test, and mortality prediction was compared by using uni- and multivariable Cox regression analyses.

Results: RV FD reproducibility had an intraclass correlation coefficient of 0.97 (95% confidence interval [CI]: 0.96, 0.98). RV FD was higher in patients with PH (median, 1.310; interquartile range [IQR], 1.242–1.295; P < .001), with the greatest difference near the apex. RV FD was associated with pulmonary vascular resistance (r = 0.30, P < .001). At univariable Cox regression analysis, RV FD was a significant predictor of death [hazard ratio (HR), 1.256; 95% CI: 1.011, 1.560; P = .04]; however, at multivariable analysis, RV FD did not enable prediction of survival independently of conventional parameters of RV remodeling (HR, 1.179; 95% CI: 0.871, 1.596; P = .29).

Conclusion: Fractal analysis of RV trabecular complexity is a highly reproducible measure of remodeling in patients with PH that is associated with afterload, although the gain in survival prediction over traditional markers is not significant.

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Online supplemental material is available for this article.

Trabeculae form a complex mesh of myocardial strands that protrude into the lumen of both ventricular chambers. In the mammalian heart, trabeculae are highly conserved structures believed to be associated with embryonic development of the coronary vasculature and conduction system (1). Their physiologic role in adults is uncertain, but numerical simulations suggest they influence vortex formation and promote mechanical efficiency (2,3). Trabecular morphology in the left ventricle (LV) is associated with environmental and hemodynamic factors, indicating that it might be a modifiable phenotype that adapts to altered loading conditions (4). A similar response is observed in the right ventricle (RV), where elevated afterload in patients with pulmonary hypertension (PH) leads to hypertrophy of both the compact myocardium and the trabeculae (5). Survival of patients with PH is closely related to RV function; however, there is substantial variability between patients (6), and quantifying trabecular adaptation could offer a sensitive marker of adverse changes in wall stress and remodeling (7).

Complex biologic structures, such as trabeculae, have self-similar properties that enable them to be quantified by their fractal dimension (FD). This semiautomated index of trabecular complexity is highly reproducible in the LV in both healthy subjects and patients with disease (4,8). To our knowledge, fractal analysis of the RV has not been previously reported, beyond assessment of tissue morphology in animal models of PH (9); therefore, its value as a marker of RV remodeling is unknown. In our study, we developed software to measure FD in both ventricles in healthy subjects and patients with PH; we assessed its relationship with hemodynamic, functional, and biochemical parameters; and we tested the hypothesis that the addition of FD to conventional risk factors would improve the accuracy of survival prediction.
**Summary**
Fractal analysis of the right ventricle is practical and reproducible in both healthy subjects and patients with disease, offering insights into cardiac efficiency, hemodynamic adaptation, and tissue characterization in right-sided heart failure; however, it does not provide incremental benefit in predicting survival.

**Implications for Patient Care**
- Fractal analysis of the right ventricle offers a highly reproducible semiautomated technique to measure trabeculation.
- Fractal analysis may be of value in assessing right ventricular functional adaptation to pulmonary hypertension, which is a key determinant of survival.
- Fractal dimension is more strongly correlated with pulmonary vascular resistance than compacted ventricular mass, suggesting that trabeculae have a greater sensitivity to hemodynamic load than does the myocardial wall.

**Materials and Methods**

**Subjects**
Our retrospective study was approved by the Health Research Authority. All participants gave written informed consent. Outcome data for all of the patient groups in this study previously have been reported (10). The prior article reported on machine learning algorithms for outcome prediction using motion-based cardiac models, whereas in this article we report on the development of fractal analysis of trabecular complexity. In our single-center observational study, patients referred to The National Pulmonary Hypertension Service at Imperial College Healthcare NHS Trust for routine diagnostic assessment and cardiac imaging between May 2004 and October 2013 were included for analysis. Survival status of subjects was monitored until September 2014 or until the date of surgery in subjects who were undergoing pulmonary endarterectomy or transplantation. A diagnosis of PH was made if the resting mean pulmonary artery pressure was 25 mmHg or higher on the status of subjects was monitored until September 2014 or until the date of surgery in subjects who were undergoing pulmonary endarterectomy or transplantation. A diagnosis of PH was made if the resting mean pulmonary artery pressure was 25 mmHg or higher at right-sided heart catheterization (11). Congenital causes of PH were excluded. Clinical classification was performed in accordance with European guidelines (11). Clinical severity was categorized in accordance with World Health Organization guidelines (12). All patients underwent standard therapy in accordance with current guidelines and NHS England treatment policy (13). In total, 256 matched healthy control subjects were drawn from 1265 participants in the United Kingdom Digital Heart Project who were investigated between February 2011 and July 2016 at the Medical Research Council London Institute of Medical Sciences (14,15).

**PH Investigations**
Right-sided heart catheterization was performed with a balloon-tipped flow-directed Swan-Ganz catheter (Baxter Healthcare, Irvine, Calif) to derive cardiac output, mean pulmonary artery pressure, mean pulmonary capillary wedge pressure, and mean pulmonary vascular resistance. We considered pulmonary vascular resistance as an estimate of RV afterload. B-type natriuretic peptide and 6-minute walk distance were measured; the latter was measured according to the American Thoracic Society guidelines (16).

**Imaging Investigations**
Cardiac MRI was performed at one site with a 1.5-T Achieva unit (Philips, Best, the Netherlands), and a standard clinical protocol was followed according to published international guidelines (17). Software updates were applied during the course of the study. Ventricular function was assessed using balanced steady-state free precession cine images acquired in conventional cardiac short- and long-axis planes. Typical parameters were as follows: repetition time msec/echo time msec, 3.2/1.6; voxel size, 1.5 × 1.5 × 8.0 mm; flip angle, 60°; and temporal resolution, 29 msec; however, parameters were adjusted from patient to patient, which was in line with routine practice, and not all parameters were constant. Images were stored on an open-source database (MRIdb; Imperial College London, England) (18).

**Quantification of Ventricular Function**
Indexed biventricular end-diastolic and end-systolic volumes were calculated by analyzing cine images with ViewForum software (Philips), and indexed stroke volume and ejection fraction derived from both ventricles. Heart rate was measured at rest, and cardiac index was calculated as the product of heart rate and stroke volume index. Endocardial borders were defined at end-diastole and end-systole using a standard published protocol (19). Indexed RV mass excluded the interventricular septum and was the sum of the compacted freewall and noncompacted (papillary muscles and trabeculae) mass. All mass and volume measurements were indexed to body surface area (BSA), as estimated with the Mosteller formula.

**FD Analysis**
FD, a scale-invariant measurement of trabecular complexity, was derived from LV short-axis cine images (Fig 1) by a reader with 5 years of experience (T.J.W.D.) who did not participate in the software development. Analysis was performed with Matlab software (Mathworks, Natick, Mass) by using a custom-written code (FracAnalyse) that has been made freely available online (20). Images were preprocessed with bicubic interpolation to 0.25 × 0.25 mm pixels to enable consistent analysis between subjects acquired at different native resolutions. For each section, a polygonal boundary for each ventricle was manually defined within the midwall myocardium on the first image of the retrospectively gated cine sequence. Subsequent image processing consisted of bias-field correction using histogram stretching, application of a region-based level-set algorithm, and binarization of the blood pool and myocardium (21). The endocardial and trabecular borders were then detected by using a Sobel filter. Trabecular mass and FD were derived from the same contours. FD was calculated by using a standard fully automated box-counting method, in which the target image was overlain by a grid of known box size, and the number of boxes containing nonzero

**Abbreviations**
BSA = body surface area, CI = confidence interval, EF = ejection fraction, FD = fractal dimension, HR = hazard ratio, IQR = interquartile range, LV = left ventricle, PH = pulmonary hypertension, RV = right ventricle.
image pixels was recorded (the box count). This process was repeated with box sizes between two pixels and 45% of the image size (8). Fractal dimension was defined as the negative gradient of an ordinary least-squares fit line to the logarithm of box size and box count. This approach to fractal analysis is similar in principle to previously published algorithms for the LV (22); however, for the RV, a convex hull was applied after image thresholding to ensure the contours were confined to the inner surface of the RV. The following summary measures were derived for both ventricles: for global FD, the mean value from all measured sections was calculated; for maximum apical FD and maximum basal FD, the maximum FD from the apical or basal halves of the ventricle was calculated, in keeping with other studies in the LV (4,23). As the number of short-axis sections varied per subject, FD values were interpolated to a 10-section model.

To test interobserver reproducibility, images from 30 patients with PH were analyzed independently by two readers (T.J.W.D., M.Q.; each with 5 years of experience).

Statistical Analyses
Data were analyzed in R version 3.4.0 by using RStudio Server, version 1.043 (RStudio, Boston, Mass). Healthy participants were selected by nearest-neighbor matching to the patient group on the basis of age, BSA, sex, and race (Afro-Caribbean, South Asian, East Asian, White) by using the matchit function in the MatchIt R software package (RStudio). Values were expressed as percentages if categorical, as mean ± standard deviation if continuous and normal, and as median ± interquartile range (IQR) if continuous and nonnormal. Baseline anthropometric data were compared between groups by using the unpaired t and Mann-Whitney U tests, pending normality (continuous variables); the Fisher exact test (nominal variables); and the Cochran-Armitage test (ordinal variables). Correlation was assessed by using the Pearson correlation test. Interobserver agreement was assessed by two-way intraclass correlation (icc function, irr R package). Missing data and tests performed at different time points were completed with Random Forests imputation to estimate synchronous phenotyping.
Mortality prediction was assessed by using univariable Cox regression analysis. Statistically significant univariable parameters were grouped into four categories: noninvasive (demographics and functional status), cardiac MRI (volumetric analysis), invasive (right-sided heart catheterization and B-type natriuretic peptide), and FD. A multivariable nested model was built by the sequential addition of categories of predictors. The purpose of this was to demonstrate the incremental benefit of each parameter group in survival prediction accuracy (pec function, pec R package). We used χ² analysis to test the significance of adding a parameter group. A baseline reference model was fitted by using a constant rate of death. To demonstrate out-of-sample accuracy, models were fitted in 80% of the patients with PH (randomly selected), and accuracy was tested in the remaining 20%. This process was repeated 50 times to avoid selection bias. To test the value of trabecular complexity in risk stratification, patients with PH were split into quartiles based on global FD, maximum apical FD, and maximum basal FD, and adjusted Cox regression analysis models were constructed with all significant univariable predictors as covariates (ggcoxfixed curves function, survminer R package). The proportional hazards assumption was checked by visualizing the Schoenfeld residuals (ggcoxzph function, survminer R package) and hazard ratio (HR) for survival calculated for each quartile.

Results

Study Population Characteristics

In total, 405 consecutive patients referred for investigation were evaluated for eligibility, and 256 subjects with confirmed PH were enrolled (Fig 2). Of these, 33% (93 of 286) died and 46 underwent either pulmonary endarterectomy or lung transplantation during follow-up. Median length of follow-up was 4.0 years (IQR, 2.0–5.7 years). In this cohort, 6% (16 of 286) of patients were unable to do the 6-minute walk test, and in 25% (66 of 286) BNP levels were unavailable. Anthropometric, hemodynamic, cardiac MRI, and subgroup data are given in Table 1 and Tables E1–E4 (online).

From a cohort of 1265 healthy control subjects, 256 matched participants were selected. Their anthropometric data are also shown in Table 1. The groups were well matched for sex (female, 44% of patients with PH vs 44% of healthy control subjects; P = .79), race (white, 82% vs 77%; P = .45), and BSA (median, 1.81 kg·m⁻² [IQR, 1.71–1.98 kg·m⁻²] vs 1.83 kg·m⁻² [IQR, 1.70–2.01 kg·m⁻²]; P = .39); however, age was lower in the control group than in the patient group (median, 59 years [IQR, 52–64 years] vs 67 years [IQR, 52–74 years]; P < .001). Patients with PH had a lower RV ejection fraction (EF) than did healthy control subjects (median, 27% [IQR, 16%–40%] vs 65% [IQR, 60%–69%]; P < .001), with higher indexed RV end-diastolic (median, 76 mL·m⁻² [IQR, 67–86 mL·m⁻²] vs 83 mL·m⁻² [IQR, 63–101 mL·m⁻²]; P < .001) and end-diastolic volume. Patients with PH who were censored for surgical intervention had significantly higher pulmonary artery pressure (median, 48 mmHg [IQR, 42–56 mmHg] vs 43 mmHg [IQR, 31–54 mmHg], P = .007), pulmonary vascular resistance (median, 9.5 Wood units [IQR, 5.4–12.3 Wood units] vs 6.3 Wood units [IQR, 27–62 Wood units] vs 26 mL·m⁻² [IQR, 22–34 mL·m⁻²]; P < .001) volume. Patients with PH who were censored for surgical intervention had significantly higher pulmonary artery pressure (median, 48 mmHg [IQR, 42–56 mmHg] vs 43 mmHg [IQR, 31–54 mmHg], P = .007), pulmonary vascular resistance (median, 9.5 Wood units [IQR, 5.4–12.3 Wood units] vs 6.3 Wood units [IQR, 3.2–10.9 Wood units], and lower RV EF (median, 35% [IQR, 27%–44%] vs 41% [IQR, 31%–51%]; P = .02); however, B-type natriuretic peptide level was also lower in censored patients (median, 157 pg/mL [IQR, 95–373 pg/mL] vs 322 pg/mL [IQR, 150–631 pg/mL]; P = .003).

Reproducibility

Analysis was performed in all 30 patients with PH. Examples from two patients are shown in Figure 3. Reproducibility between observers had an intraclass correlation coefficient of 0.97 (95% confidence interval [CI]: 0.96, 0.98).

FD Characteristics

Global FD was higher in patients with PH than in healthy control subjects in the RV (median, 1.310 [IQR, 1.281–1.341] vs 1.264 [IQR, 1.242–1.295]; P < .001) but lower in the LV (median, 1.206 [IQR, 1.176–1.231] vs 1.224 [IQR, 1.198–1.251]; P < .001) (Table 1). RV global FD varied in healthy control subjects and patients with PH by race (P < .001) (Fig E1 [online]). Afro-Caribbean subjects had higher RV global FD in both patient (median, 1.347 [IQR, 1.328–1.383]) and healthy con-
| Characteristic                  | All Patients | Patients who are Alive | Patients who are Dead | Alive vs Dead P Value | Control Subjects | Patients vs Control Subjects P Value |
|--------------------------------|--------------|------------------------|-----------------------|-----------------------|-----------------|---------------------------------------|
| Age (y)                        | 67 (52–75)   | 63 (48–71)             | 72 (65–78)            | <.001                 | 59 (52–64) | <.001                                 |
| Sex                            | ...          | ...                    | ...                   | ...                   | ...              | ...                                   |
| Male                           | 143          | 101                    | 42                    | ...                   | 144             | ...                                   |
| Female                         | 113          | 62                     | 51                    | ...                   | 112             | ...                                   |
| BSA (m²)                       | 1.85 ± 0.23  | 1.87 ± 0.22            | 1.84 ± 0.24           | .37                   | 1.84 ± 0.22 | .39                                   |
| Race*                          | ...          | ...                    | ...                   | .168                  | ...              | .21                                   |
| Afro-Caribbean                 | 22           | 18                     | 4                     | ...                   | 27              | ...                                   |
| East Asian                     | 8            | 5                      | 3                     | ...                   | 7               | ...                                   |
| South Asian                    | 15           | 127                    | 3                     | ...                   | 25              | ...                                   |
| White                          | 211          | 12                     | 86                    | ...                   | 197             | ...                                   |
| RV EDVI (mL·m⁻²)               | 83 (63–101)  | 79 (62–97)             | 92 (66–121)           | <.001                 | 76 (67–86) | <.001                                 |
| RV ESVI (mL·m⁻²)               | 41 (27–62)   | 38 (25–58)             | 49 (34–74)            | <.001                 | 26 (22–34) | <.001                                 |
| RV EF (%)                      | 27 (16–40)   | 31 (17–44)             | 24 (11–35)            | .004                  | 65 (60–69) | <.001                                 |
| RV MI (g)                      | 23 (15–39)   | 22 (13–39)             | 25 (16–38)            | .15                   | ...              | ...                                   |
| Noncompacted RV MI (g)         | 17 (13–22)   | 15 (12–21)             | 18 (14–24)            | .04                   | ...              | ...                                   |
| Compacted RV MI (g)            | 9 (6–24)     | 8 (5–24)               | 10 (7–25)             | .07                   | ...              | ...                                   |
| RV global FD                   | 1.310 (1.281–1.341) | 1.309 (1.272–1.341) | 1.312 (1.290–1.337) | .36                   | 1.264 (1.242–1.295) | <.001 |
| RV maximum apical FD           | 1.390 (1.348–1.428) | 1.389 (1.342–1.425) | 1.397 (1.370–1.434) | .05                   | 1.312 (1.264–1.357) | <.001 |
| RV maximum basal FD            | 1.319 (1.273–1.357) | 1.320 (1.265–1.361) | 1.319 (1.282–1.353) | .36                   | 1.254 (1.208–1.298) | <.001 |
| LV EDVI (mL·m⁻²)               | 59 (47–75)   | 60 (48–72)             | 57 (47–65)            | .13                   | 73 (66–82) | <.001                                 |
| LV ESVI (mL·m⁻²)               | 22 (17–30)   | 22 (16–30)             | 22 (17–28)            | .99                   | 24 (20–28) | .08                                   |
| LV EF (%)                      | 61 (54–68)   | 62 (56–68)             | 61 (53–68)            | .38                   | 67 (64–71) | ...                                   |
| LV global FD                   | 1.206 (1.176–1.231) | 1.206 (1.177–1.229) | 1.206 (1.173–1.235) | .97                   | 1.224 (1.198–1.251) | <.001 |
| LV maximum apical FD           | 1.236 (1.188–1.280) | 1.236 (1.192–1.273) | 1.231 (1.183–1.291) | .93                   | 1.283 (1.248–1.322) | <.001 |
| LV maximum basal FD            | 1.297 (1.264–1.323) | 1.300 (1.266–1.323) | 1.294 (1.263–1.323) | .60                   | 1.291 (1.261–1.315) | .06   |
| 6MWD* (m)                      | 258 (96–360) | 302 (120–395)          | 180 (90–300)          | <.001                 | ...              | ...                                   |
| BNP                            | 179 (74–602) | 127 (55–323)           | 801 (200–1164)        | <.001                 | ...              | ...                                   |
| Hemodynamics                   | ...          | ...                    | ...                   | ...                   | ...              | ...                                   |
| Mean PAP (mmHg)                | 44 (32–54)   | 43 (31–54)             | 47 (36–55)            | .09                   | ...              | ...                                   |
| Cardiac index                  | 2.3 (1.9–2.9) | 2.3 (1.9–2.9)          | 2.3 (1.9–2.9)         | .78                   | ...              | ...                                   |
| PVR (U)                        | 7.0 (3.9–11.2) | 6.1 (3.2–11.0)         | 7.4 (5.2–11.6)        | .08                   | ...              | ...                                   |
| Mean RAP                       | 10 (6–14)    | 10 (6–13)              | 12 (8–16)             | .003                  | ...              | ...                                   |
| Mean RV EDP                    | 10 (7–15)    | 10 (6–14)              | 12 (8–16)             | .004                  | ...              | ...                                   |
| PCWP                           | 12 (8–16)    | 11 (8–16)              | 13 (10–16)            | .17                   | ...              | ...                                   |
| WHO functional class†          | ...          | ...                    | ...                   | <.001                 | ...              | ...                                   |
| I                              | 3            | 3                      | 0                     | ...                   | ...              | ...                                   |
| II                             | 43           | 36                     | 7                     | ...                   | ...              | ...                                   |
| III                            | 163          | 104                    | 59                    | ...                   | ...              | ...                                   |
| IV                             | 47           | 20                     | 27                    | ...                   | ...              | ...                                   |
| Clinical classification        | ...          | ...                    | ...                   | .422                  | ...              | ...                                   |
| Group 1                        | 88           | 54                     | 34                    | ...                   | ...              | ...                                   |
| Group 1.1                      | 57           | 36                     | 21                    | ...                   | ...              | ...                                   |
| Group 1.2                      | 3            | 1                      | 2                     | ...                   | ...              | ...                                   |
In patients with PH, RV global FD was weakly associated with (a) higher indexed RV end-diastolic volume, indexed RV end-systolic volume, heart rate, and cardiac index and (b) lower indexed RV stroke volume and RV EF (Table 2). In patients with PH, RV global FD was weakly associated with pulmonary vascular resistance (r = 0.30, P < .001) and compacted indexed RV mass (r = 0.59, P < .001).
Fractal Analysis of Right Ventricular Trabeculae

Survival Prediction
In univariable Cox regression analysis, noninvasive (age, sex, race, PH subtype, World Health Organization functional class, 6-minute walk distance), invasive (mean right atrial pressure, mean RV end-diastolic pressure, B-type natriuretic peptide), and cardiac MRI (indexed RV end-diastolic volume, indexed RV end-systolic volume, and RV EF) parameters were associated with survival \((P < .001\) for all) (Table 3). RV maximum apical FD (HR, 1.256; 95% CI: 1.011, 1.560; \(P = .04\)) was also a significant univariable predictor of survival, but RV global FD (HR, 1.171; 95% CI: 0.947, 1.448; \(P = .14\)) and RV maximum basal FD (HR, 1.097; 95% CI: 0.897, 1.343; \(P = .37\)) were not (Fig 4). In the LV, indexed end-diastolic and end-systolic volumes and LV ejection fraction were not significantly associated with survival. LV maximum apical FD (HR, 1.070; 95% CI: 0.865, 1.323; \(P = .53\)), global FD (HR, 1.057; 95% CI: 0.861, 1.298; \(P = .59\)), and maximum basal FD (HR, 0.971; 95% CI: 0.791, 1.192; \(P = .78\)) also were not significant univariable predictors of survival.

Significant univariable parameters were added by category to a multivariable nested survival model (Table E5 [online]). When compared with a constant rate of death, the successive addition of noninvasive \((P < .001\) and cardiac MRI \((P = .009\) parameters cumulatively improved survival prediction. The addition of invasive parameters to the model further improved survival prediction \((\chi^2 = 42.3, P < .001\) ); however, the addition of RV maximum apical FD did not \((\chi^2 = 1.1; P = .284; HR = 1.179; 95% CI: 0.871, 1.596)\).

In adjusted Cox regression analysis, categorization by RV maximum apical FD yielded greater discrimination in 5-year survival between the first and the fourth quartiles (mean, 19.6 years; 95% CI: 19.6, 19.7) compared with RV global FD (mean, 8.9 years; 95% CI: 8.9, 9.0) or maximum basal FD (mean, 7.3 years; 95% CI: 7.3, 7.4). Out-of-sample validation suggested that gains in the accuracy of survival prediction with the addition of RV maximum apical FD were small (0.2%) compared with adding noninvasive and cardiac MRI parameters and were less than the gain in accuracy from adding invasive parameters (1.7%).

Discussion
The main findings of our study are \((a)\) fractal analysis of RV trabecular complexity is practical in both healthy participants and patients with PH, with excellent interobserver reproducibility; \((b)\) RV FD is higher in patients with PH than in healthy control subjects and weakly correlates with invasive measures of afterload (pulmonary vascular resistance); and \((c)\) FD enables prediction of survival but yields no incremental prognostic benefit over conventional parameters of RV remodeling.

Myocyte lineage tracing suggests that trabeculae have a molecular and developmental identity which is distinct from the compact layer of the RV free wall (24). Blood flow–related transmural stresses during cardiac development may influence trabecular patterning, which typically shows a base-to-apex and lateral-to-septal gradient of complexity (25). The physiologic role of trabeculae in the adult heart is uncertain, but residual

### Table 2: Correlation of Fractal Dimension with Volumetric and Hemodynamic Data in Healthy Control Subjects and Patients with Pulmonary Hypertension

| Statistic | RV EDVI | RV ESVI | RV SVI | RV EF | RV MI | mPAP | PVR | RV EDP | HR | CI |
|-----------|---------|---------|--------|-------|-------|------|-----|--------|----|----|
| Healthy Control Subjects |  |  |  |  |  |  |  |  |  |  |
| Global FD |  |  |  |  |  |  |  |  |  |  |
| \(r\) value | 0.05 | 0.05 | 0.03 | -0.01 | ... | ... | ... | 0.31 | 0.24 |
| \(P\) value | .44 | .47 | .59 | .82 | ... | ... | ... | <.001 | <.001 |
| Maximum apical FD |  |  |  |  |  |  |  |  |  |  |
| \(r\) value | 0.05 | 0.04 | 0.05 | 0.01 | ... | ... | ... | -0.14 | -0.07 |
| \(P\) value | .42 | .52 | .47 | .83 | ... | ... | ... | .03 | .29 |
| Maximum basal FD |  |  |  |  |  |  |  |  |  |  |
| \(r\) value | 0.04 | 0.01 | 0.08 | 0.04 | ... | ... | ... | -0.09 | -0.08 |
| \(P\) value | .41 | .89 | .19 | .54 | ... | ... | ... | .16 | .21 |
| Patients with Pulmonary Hypertension |  |  |  |  |  |  |  |  |  |  |
| Global FD |  |  |  |  |  |  |  |  |  |  |
| \(r\) value | 0.24 | 0.24 | -0.27 | -0.42 | 0.19 | 0.42 | 0.30 | 0.12 | 0.18 | 0.14 |
| \(P\) value | <.001 | <.001 | <.001 | <.001 | <.003 | <.001 | <.001 | .06 | .004 | .022 |
| MAFD |  |  |  |  |  |  |  |  |  |  |
| \(r\) value | 0.32 | 0.33 | -0.32 | -0.51 | 0.31 | 0.46 | 0.29 | 0.14 | 0.19 | 0.15 |
| \(P\) value | <.001 | <.001 | <.001 | <.001 | <.001 | <.001 | <.001 | <.021 | <.002 | <.02 |
| MBFD |  |  |  |  |  |  |  |  |  |  |
| \(r\) value | 0.19 | 0.17 | -0.18 | -0.29 | 0.09 | 0.27 | 0.23 | 0.06 | 0.15 | 0.16 |
| \(P\) value | .002 | .007 | .004 | <.001 | .161 | <.001 | <.001 | .33 | .018 | .009 |

Note.—CI = cardiac index, EDP = end-diastolic pressure, EDVI = end-diastolic volume index, EF = ejection fraction, ESVI = end-systolic volume index, FD = fractal dimension, HR = heart rate, MI = mass index, mPAP = mean pulmonary artery pressure, PVR = pulmonary vascular resistance, RV = right ventricle, SVI = stroke volume index.
### Table 3: Uni- and Multivariable Survival Data in Patients with Pulmonary Hypertension

| Variable                        | Univariable           | Multivariable         |
|---------------------------------|-----------------------|-----------------------|
|                                 | Hazard Ratio          | P Value               | Hazard Ratio          | P Value               |
| Age                             | 1.739 (1.423, 2.126)  | <.001                 | 1.395 (0.717, 1.044)  | .02                   |
| Sex                             | 1.321 (1.077, 1.619)  | .007                  | 2.734 (1.723, 4.339)  | <.001                 |
| BSA                             | 0.886 (0.720, 1.090)  | .25                   | ...                  | ...                   |
| Race                            | ...                   | ...                   | 2.913 (1.249, 6.797)  | .013                  |
| Afro-Caribbean                  | ...                   | ...                   | ...                  | ...                   |
| East Asian                      | 0.855 (0.607, 1.206)  | .37                   | ...                  | ...                   |
| South Asian                     | 0.835 (0.637, 1.094)  | .19                   | ...                  | ...                   |
| White                           | 1.421 (1.078, 1.874)  | .01                   | ...                  | ...                   |
| Cardiac MRI                     | ...                   | ...                   | ...                  | ...                   |
| RV EDVI*                         | 1.327 (1.111, 1.586)  | .002                  | 1.349 (0.377, 1.459)  | .39                   |
| RV ESVI*                        | 1.342 (1.127, 1.598)  | <.001                 | 1.868 (0.789, 4.425)  | .16                   |
| RV EF                           | 0.712 (0.579, 0.877)  | .001                  | 1.257 (0.745, 2.120)  | .39                   |
| RV global FD                    | 1.171 (0.947, 1.448)  | .14                   | ...                  | ...                   |
| RV maximum apical FD            | 1.256 (1.011, 1.560)  | .04                   | 1.128 (0.833, 1.529)  | .44                   |
| RV maximum basal FD             | 1.097 (0.897, 1.343)  | .37                   | ...                  | ...                   |
| LV EDVI*                        | 0.946 (0.755, 1.185)  | .63                   | ...                  | ...                   |
| LV ESVI*                        | 1.002 (0.821, 1.223)  | .98                   | ...                  | ...                   |
| LV EF                           | 0.868 (0.712, 1.059)  | .16                   | ...                  | ...                   |
| LV global FD                    | 1.057 (0.861, 1.298)  | .59                   | ...                  | ...                   |
| LV maximum apical FD            | 1.070 (0.865, 1.323)  | .53                   | ...                  | ...                   |
| LV maximum basal FD             | 0.971 (0.791, 1.192)  | .78                   | ...                  | ...                   |
| 6MWD†                           | 0.519 (0.404, 0.666)  | <.001                 | 0.606 (0.434, 0.846)  | .003                  |
| BNP                             | 1.757 (1.559, 1.980)  | <.001                 | 1.749 (1.448, 2.112)  | <.001                 |
| Hemodynamics                    | ...                   | ...                   | ...                  | ...                   |
| Mean PAP                        | 1.137 (0.932, 1.386)  | .21                   | ...                  | ...                   |
| Cardiac index                   | 0.963 (0.781, 1.188)  | .73                   | ...                  | ...                   |
| PVR                             | 1.135 (0.935, 1.378)  | .20                   | ...                  | ...                   |
| Mean RAP                        | 1.418 (1.156, 1.740)  | <.001                 | 1.203 (0.874, 1.657)  | .26                   |
| Mean RV EDP                     | 1.404 (1.148, 1.718)  | <.001                 | 0.970 (0.745, 1.262)  | .82                   |
| PCWP                            | 1.081 (0.889, 1.314)  | .44                   | ...                  | ...                   |
| WHO functional class‡           | 1.602 (1.295, 1.982)  | <.001                 | 1.272 (0.971, 1.668)  | .08                   |
| Clinical classification          | ...                   | ...                   | ...                  | ...                   |
| Group 1                         | 1.087 (0.890, 1.328)  | .41                   | ...                  | ...                   |
| Group 2                         | 0.987 (0.803, 1.214)  | .90                   | ...                  | ...                   |
| Group 3                         | 1.527 (1.332, 1.750)  | <.001                 | 1.510 (1.282, 1.777)  | <.001                 |
| Group 4                         | 0.701 (0.560, 0.878)  | .002                  | 0.742 (0.563, 0.978)  | .03                   |
| Group 5                         | 1.031 (0.866, 1.228)  | .73                   | ...                  | ...                   |

Note.—Unless otherwise indicated, data are hazard ratios, with 95% confidence intervals in parentheses. BNP = B-type natriuretic peptide, BSA = body surface area, EDP = end-diastolic pressure, EDVI = end-diastolic volume index, EF = ejection fraction, ESVI = end-systolic volume index, FD = fractal dimension, LV = left ventricular, MAFD = maximum apical fractal dimension, MBFD = maximum basal fractal dimension, PAP = pulmonary artery pressure, PCWP = pulmonary capillary wedge pressure, PH = pulmonary hypertension, PVR = pulmonary vascular resistance, RAP = right atrial pressure, RV = right ventricle, 6MWD = 6-minute walk distance, WHO = World Health Organization.

* Indexed to body surface area.
† Excluding 16 subjects who were unable to undergo testing.
‡ WHO functional class I–IV. Higher numbers indicate lower functional capacity. Group 1, pulmonary arterial hypertension; group 1.1, idiopathic; group 1.2, heritable; group 1.3, drug and toxin induced; group 1.4, associated with other conditions (except congenital heart disease); group 1′, peripheral veno-occlusive disease and/or pulmonary capillary hemangiomatosis; group 2, pulmonary hypertension due to left-sided heart disease; group 3, pulmonary hypertension due to lung diseases, hypoxia, or both; group 4, chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions; group 5, pulmonary hypertension with unclear or multifactorial mechanisms.
Fractal Analysis of Right Ventricular Trabeculae

Fractal Analysis of Right Ventricular Trabeculae

blood volume within the trabecular recesses may preserve the kinetic energy of in-flowing blood and enhance apical washout (2,26). Fractal analysis provides a quantitative measure of trabeculations, revealing a relationship with hemodynamic factors in the LV and high accuracy in the identification of patients with hypertrabecular phenotypes (4,8). However, excessive LV trabeculation has not been shown to provide independent prognostic value in asymptomatic low-risk populations or cardiomyopathies when other prognostic factors are considered (27). Fractal analysis of the RV has not been previously reported in healthy subjects or in patients with disease; however, trabecular hypertrophy has long been recognized as an important feature of RV adaptation to pressure overload and a noninvasive marker in the diagnosis of PH (5,28).

We showed that fractal analysis of the RV is practical and highly reproducible, reflecting the robustness of automated trabecular segmentation. Patients with PH have a higher FD than do healthy control subjects; however, both share a similar base-to-apex gradient in trabecular complexity. Racial variation in RV FD was similar to that previously reported in LV FD (8). In patients, RV FD was weakly positively associated with pulmonary vascular resistance and indexed RV mass; however, only RV FD was associated with survival at univariable analysis. A meta-analysis of cardiac MRI findings in patients with PH has shown that RV EF is the strongest determinant of outcome (29); however, our data suggest that other markers of RV adaptation beyond global volume and function also predict all-cause mortality. Change in RV apical FD showed the strongest association with afterload and survival, in keeping with other reports demonstrating that apical markers of function may become abnormal before global and basal markers in PH (30,31).

In conclusion, FD is a reproducible measure of RV trabecular complexity on cardiac MR images, a marker of elevated afterload in patients with PH, and enables prediction of all-cause mortality, though the gains over traditional volumetric markers are not significant.

Acknowledgments: We thank our radiographers Ben Statton and Alaine Berry and our research nurse Tamara Diamond. We also acknowledge the staff of the National Institute for Health Research/Wellcome Trust Imperial Clinical Research Facility, Hammersmith Hospital (London, England), and George Villa for work on the TRIPHIC (Translational Research in Pulmonary Hypertension at Imperial College) database.
Author contributions: Guarantor of integrity of entire study, D.P.O.; study concept and design or data acquisition and analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, T.J.W.D., M.Q., A.d.M., D.P.O.; clinical studies, T.J.W.D., M.Q., G.M.J.W., L.S.G.E.H., J.S.R.G., S.A.C., D.P.O.; statistical analysis, T.J.W.D., M.Q., A.d.M., D.P.O.; and manuscript editing, T.J.W.D., J.C., M.Q., A.d.M., J.W., L.S.G.E.H., S.A.C., M.R.W., D.P.O.

Disclosures of Conflicts of Interest: T.J.W.D. disclosed no relevant relationships. J.C. disclosed no relevant relationships. M.Q. disclosed no relevant relationships. A.d.M. disclosed no relevant relationships. P.E.T. disclosed no relevant relationships. G.J.W. disclosed no relevant relationships. J.W. disclosed no relevant relationships. L.S.G.E.H. disclosed no relevant relationships. J.S.R.G. Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: is on the board of Actelion, Bayer, Arena, Complexa, and GlaxoSmithKline; is a consultant for Pfizer, Belleghoron, Bayer, and Actelion; received grants from Actelion, Bayer, Amco, GlaxoSmithKline, and Merck Sharp & Dohme; gave lectures for Actelion, Bayer, GlaxoSmithKline, Merck Sharp & Dohme, and AOP Orphan Pharmaceuticals. Other relationships: disclosed no relevant relationships. S.A.C. disclosed no relevant relationships. M.R.W. Activities related to the present article: disclosed no relevant relationships. M.R.W. Activities related to the present article: is on the board of Actelion, Bayer, Amco, GlaxoSmithKline, and Merck Sharp & Dohme; gave lectures for Actelion, Bayer, GlaxoSmithKline, Merck Sharp & Dohme, and AOP Orphan Pharmaceuticals. Other relationships: disclosed no relevant relationships. J.S.R.G. Activities related to the present article: is on the board of Actelion, Bayer, Arena, Complexa, and GlaxoSmithKline; is a consultant for Pfizer, Belleghoron, Bayer, and Actelion; received grants from Actelion, Bayer, Amco, GlaxoSmithKline, and Merck Sharp & Dohme; gave lectures for Actelion, Bayer, GlaxoSmithKline, Merck Sharp & Dohme, and AOP Orphan Pharmaceuticals. Other relationships: disclosed no relevant relationships. D.P.O. disclosed no relevant relationships.

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