Fractal branching quantifies vascular changes and predicts survival in pulmonary hypertension: a proof of principle study

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Accepted 23 December 2010
Published Online First 8 February 2011

ABSTRACT

Objectives To develop a non-invasive method of assessing disease severity in pulmonary hypertension by quantifying the overall degree of vascular pruning using fractal geometry.

Design A retrospective analysis of ECG-gated CT pulmonary angiograms.

Setting A single national referral centre for the investigation and treatment of children with pulmonary hypertension.

Patients Consecutive CT pulmonary angiograms in children and young adults (mean age 10.3 years, range 0.7–19.1) with pulmonary arterial hypertension assessed between January 2007 and April 2009.

Main outcome measures The fractal dimension (FD) of skeletonised CT pulmonary angiograms was calculated using the box counting method. The FD was compared with pulmonary vascular resistance, the percentage of predicted 6-min walk distance, WHO functional class and survival.

Results Diagnostic plots confirmed that the pulmonary artery angiograms were all fractal. The FD correlated negatively with the pulmonary vascular resistance index ($r=-0.55$, $p=0.01$, $n=21$) and with WHO functional class ($p<0.01$, $n=31$) while it correlated positively with the percentage of predicted 6-min walk distance ($r=0.43$, $p=0.04$, $n=24$). A lower FD was associated with poorer survival (HR 5.6; 95% CI 1.2 to 25; $p=0.027$) for every SD reduction in FD.

Conclusion The FD derived from CT can be used to quantify vascular changes in pulmonary hypertension. This non-invasive technique may be useful in monitoring disease progression and response to therapy.

One of the most characteristic radiological features of pulmonary arterial hypertension (PAH) is vascular pruning. This is classically seen on chest x-rays or CT images and is due to vessel remodelling and loss of arterial branching. Usually it is described in purely qualitative terms, as a marker of the presence rather than the severity of PAH. However, the amount of vascular pruning is intimately linked to the pathological processes underlying this disease. Quantitative assessment of vascular pruning may thus provide a non-invasive method of assessing severity in PAH. This has been attempted using traditional morphometric analysis of pulmonary wedge angiograms. Using this technique it has been shown that the amount of vessel taper and a subjective grading of background haze correlates with haemodynamic severity in PAH.[1–3] Unfortunately, morphometry is too labour-intensive to find a place in routine clinical follow-up.

The purpose of this study is to propose an alternative approach to traditional morphometry, which relies on the fractal properties of the pulmonary arterial tree. A fractal is an object that is self-similar over different scales, and this description includes branching structures such as the pulmonary arteries. An important feature of fractals is that their complexity can be measured by their fractal dimension (FD), which is a measure of how they fill space. In tree-like structures, a higher FD suggests more abundant branching, whereas a lower FD suggests sparser branching. Therefore in PAH, vascular pruning should be associated with a lower pulmonary arterial FD. In fact, in a rat model of PAH, the FD of pulmonary arteriograms was lower in diseased animals compared with normal controls.[4] Therefore, we hypothesise that FD could be used to quantify the amount of vascular pruning in patients with PAH, providing a unique marker of disease severity. If validated in humans, measuring FD could be of value, both clinically and as a novel endpoint for therapeutic studies.

The aims of this study were to assess the feasibility of measuring the FD of CT pulmonary angiograms in patients with PAH, to investigate the relationship between FD and established markers of disease severity and to assess the relationship between FD and prognosis.

MATERIALS AND METHODS

Study population

In this study, CT pulmonary angiograms from 31 children and young adults with PAH were retrospectively analysed. All CT scans were performed as part of routine clinical management in a single referral centre for the treatment of paediatric pulmonary hypertension. Nineteen studies were performed as part of initial diagnostic assessment (to rule out lung parenchymal, veno-occlusive or thromboembolic disease) and a further 12 were performed to investigate a change in clinical status as deemed necessary by the primary physician. Data were collected consecutively between January 2007 and April 2009. Three children had two scans during the study period, for these the most recent scan was assessed. Four additional children with PAH underwent CT pulmonary angiography. These

patients were excluded from the study because of severe breathing artefacts on the CT angiograms. The clinical characteristics of the patients are summarised in table 1.

All patients underwent assessment of WHO functional status and echocardiographic estimation of right ventricular systolic pressure (derived from peak tricuspid regurgitation jet velocity using the modified Bernoulli equation as previously described)[5] during the same admission. Those who were old enough, n=24, also underwent a 6-min walk test (results expressed as a percentage of predicted distance)[6] at the time of CT. In addition, in 21 patients haemodynamic data were collected from the diagnostic cardiac catheter studies performed closest to the time of the CT scan (median time interval 1.5 years, IQR 1.6 months to 3.6 years). The local research ethics committee approved the study.

Image acquisition and processing

CT pulmonary angiography was performed on a 64-slice dual-source CT scanner with ECG gating (SOMATOM Definition; Siemens, Erlangen, Germany). Acquisition parameters were as follows: collimation 2×64×0.6 mm, rotation time 0.33 s, pitch 0.2–0.5 (depending on heart rate), kVp 80–100 (depending on size), mAs per rotation 120–220 (depending on size), breath hold 5–10 s. The mean effective radiation dose was calculated at 5.5±2.7 mSV. Images acquired in the systolic phase of the cardiac cycle were used for analysis.

Iodinated contrast agent (2 ml/kg, Omnipaque 300; GE Healthcare, Oslo, Norway) was administered at a rate of 2 ml/s via an antecubital vein. Imaging was triggered manually on visualisation of contrast in the pulmonary artery. No beta-blockers were given.

Before the measurement of FD, the CT pulmonary angiograms were processed offline (Mimics Materialise Inc, Ann Arbor, Michigan, USA) by a single investigator blinded to the clinical status of the patients. Image data were first thresholded to include the pulmonary arteries, as well as other structures of equal attenuation. A region-growing algorithm (seeded in the main pulmonary artery) was then used to segment out the pulmonary arterial tree, with manual editing enabling the exclusion of erroneously highlighted tissue (figure 1).[7] In order to prevent proximal vessel dilation from confounding FD quantification the segmented pulmonary artery data were skeletonised using an inbuilt centreline algorithm. Finally, to permit comparison between different sized patients, the skeletonised data were scaled such that the size in the z-axis or craniocaudal direction was 200 mm in all patients. This was achieved by applying a scaling factor (Sc) defined as (Sc=200/size in z axis) to the x, y and z coordinates, ie, proportional scaling. The scaled skeletonised data consisted of three-dimensional coordinate points evenly spaced (1 mm) along the centre of each branch of the pulmonary artery tree.

Table 1 Clinical characteristics of the 31 patients included in the study

Age, years	10.2 (range 0.7–19.1)
Female:male	1.38
WHO I/II/III/IV	6/8/10/7
Diagnostic group, n (%)	
CHD	14 (45)
IPAH	12 (39)
Other	5 (16)
6-Min walk distance, percentage of predicted	57.2 (46.6–65.6)
Haemodynamics	
RAP, mm Hg	6.0 (5.0–10.5)
mPAP, mm Hg	42 (34–57)
Qp, l/min/m^2	2.35 (2.0–4.0)
PVRI, units/m^2	13.2 (6.7–19.6)
Therapies n (%)	
CCB	7 (23)
Sildenafil	15 (48)
Bosentan	14 (45)
Epoprostenol	3 (10)

Figures are median (IQR) unless otherwise stated. Others are pulmonary arterial hypertension (PAH) associated with chronic lung disease, vasculitis, hereditary haemorrhagic telangectasia, primary erythrocytosis and chronic thromboembolic disease. CCB, calcium channel antagonist; CHD, congenital heart disease; IPAH, idiopathic pulmonary arterial hypertension; mPAP, mean pulmonary artery pressure; PVRI, pulmonary vascular resistance index; Qp, pulmonary blood flow index; RAP, right atrial pressure.

Fractal analysis

The FD of the skeletonised data was calculated by applying the well-validated box counting method[8] implemented using an algorithm developed in-house (MATLAB; Mathworks, Natick, Massachusetts, USA). Box counting consisted of dividing three-dimensional space into a grid of boxes of side length s and counting the number of boxes that contained part of the skeletonised data N_s.[8] This process was repeated for box sizes between 4 mm and 15 mm, with 1 mm increments in size. To account for edge effects the entire process was repeated after offsetting the starting point of the grid by 1, 2, 3 and 4 mm in each direction. Therefore, for each box size the process was performed 64 times (4×4×4) and the average number of boxes counted was taken as N_s at a given value of s. As the box size increases, the number of boxes containing the object decreases exponentially. The exponent is equivalent to the FD. A higher FD implies greater filling of space, ie, more branching. To quantify the exponent, log–log plots of the number of boxes N_s against the box size s were plotted giving a straight line of gradient −FD (figure 2). The gradient of the line and thus the FD was calculated using linear regression. The inhouse implementation of the box counting method was validated on a series of test objects of known FD (see supplementary material, available online only).

Statistical analysis

Descriptive data are expressed as mean±SD or median and IQR as appropriate. Normal distribution of data was confirmed on histogram and using D'Agostino–Pearson's omnibus normality test. The linear relation between continuous variables and FD was assessed using Pearson's correlation test. One-way analysis of variance with a Student–Newman–Keuls test was performed for the comparison of FD between patients of different WHO functional class. Patients were followed up until death or the end of the study period (1 September 2010). Univariate survival analysis was performed using a Cox proportional hazards model. Statistical analysis was performed using GraphPad Prism version 4.0 and STATA version 10.0. A two sided p value less than 0.05 was considered statistically significant.

RESULTS

Feasibility of measuring FD

It was possible to measure the FD of CT pulmonary angiograms in all patients. The total processing time was approximately 2 h for all processing steps including computation time. The log–log plots of box number N_s against box side length s produced a straight line in all of the patients (mean correlation coefficient r=−0.994; SD 0.001) confirming a fractal pattern was present

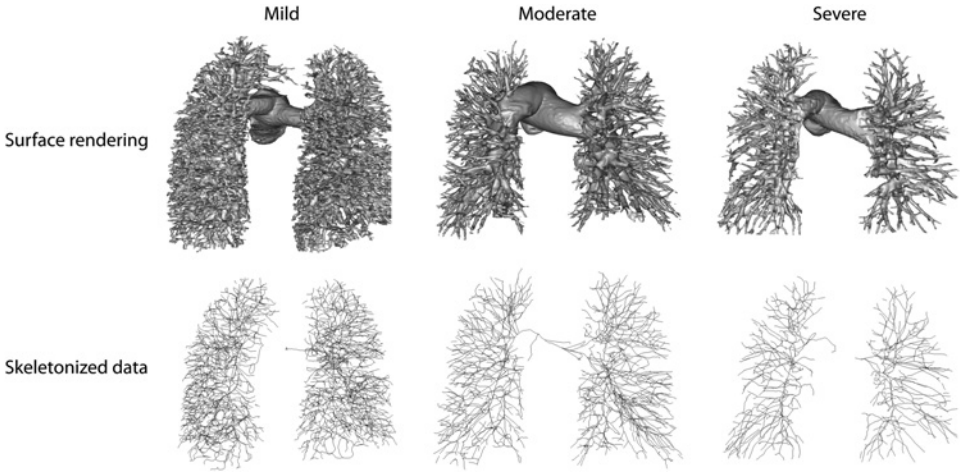

Figure 1 Representative examples of segmented pulmonary artery masks and below them the derived skeletonised representations for patients with mild, moderate and severe pulmonary hypertension. The fractal dimensions are 1.66, 1.48 and 1.27, respectively.

(figure 2). The slope of the line, the FD, ranged from 1.18 to 1.73 (mean 1.46, SD 0.15) and was normally distributed.

Relationship between FD and markers of disease severity

FD was lowest in patients with advanced WHO functional class (test for linear trend, $p<0.01$; figure 3A). In addition, FD positively correlated with the percentage of predicted walk distance

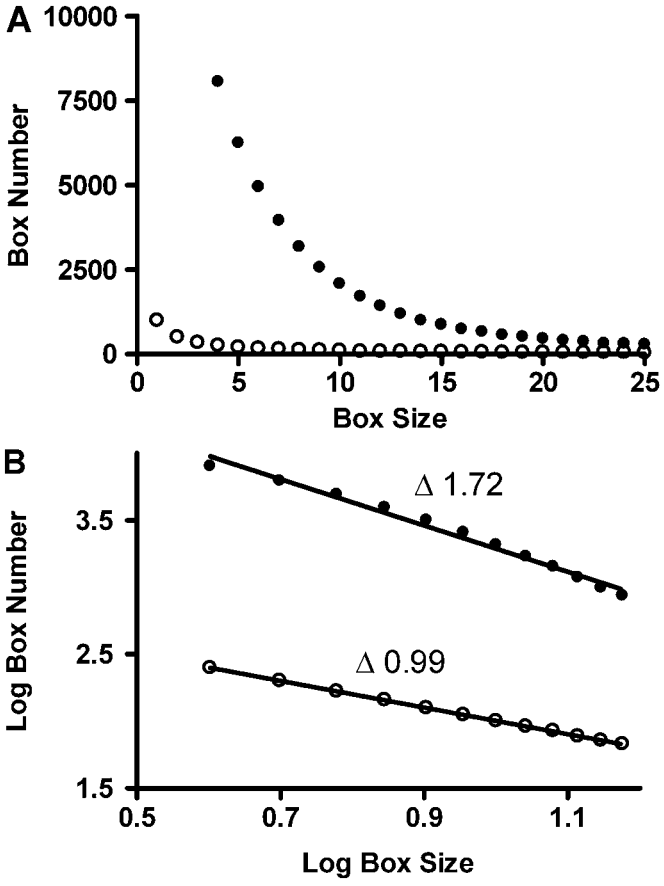

Figure 2 An example plot of box number against box size (top), and log-box number against log-box size (bottom) for a pulmonary arterial tree (closed circles) and for a line (open circles). The slope of each regression line is inset (Δ) and shows that the line has a fractal dimension (FD) of 0.99, almost the same as its topological dimension. The pulmonary artery has a non-integer FD of 1.72.

r=0.43, p=0.04 (n=24, the mean distance walked was 338±110 m, ie, 53.5±19.9% of predicted; see figure 3B).

FD correlated negatively with the pulmonary vascular resistance index (PVRI) n=21, r=−0.55, p=0.01(figure 3C). There was a positive correlation between FD and indexed pulmonary blood flow (Qp) r=0.57, p=0.01 (figure 3D). However, there was no correlation between FD and invasively measured mean pulmonary arterial pressure (r=−0.05, p=0.83), or right ventricular systolic pressure derived echocardiographically, r=0.00, p=0.97.

Relationship between FD and survival

Four patients died during a median follow-up period of 1.7 years (range 19 days–2.4 years). None of the patients underwent lung transplantation. One patient left the country and was censored at the last available follow-up. Lower FD was associated with poorer survival. The HR for death was 5.6 (95% CI 1.2 to 25; p=0.027) for every SD reduction in FD. Neither WHO functional class, percentage of predicted 6-min walk distance, pulmonary blood flow or pulmonary vascular resistance were statistically significantly associated with outcome (table 2).

DISCUSSION

The main aim of this retrospective proof of principle study was to demonstrate that pulmonary vascular FD can be used to assess disease severity in PAH. The main findings were that it is possible to determine the FD from CT pulmonary angiography acquired in a real-world setting, FD is correlated with established markers of disease severity in PAH and lower FD was associated with poorer survival.

Measuring FD

This study is based on the premise that vascular pruning can be quantified by measuring the FD of the pulmonary arterial tree. This technique is therefore completely reliant on the quality of arterial imaging. We chose to use CT to image the pulmonary arteries for three main reasons. First, it has become a routine part of non-invasive clinical assessment and is therefore available in most patients. Second, it provides three-dimensional visualisation of the pulmonary vascular tree and should therefore be more sensitive than x-ray or invasive angiograms. Finally, it provides higher resolution than other non-invasive angiographic techniques (ie, MRI), allowing better discrimination of distal pulmonary arteries. In all patients, the raw CT data were successfully segmented and subsequently skeletonised, both of

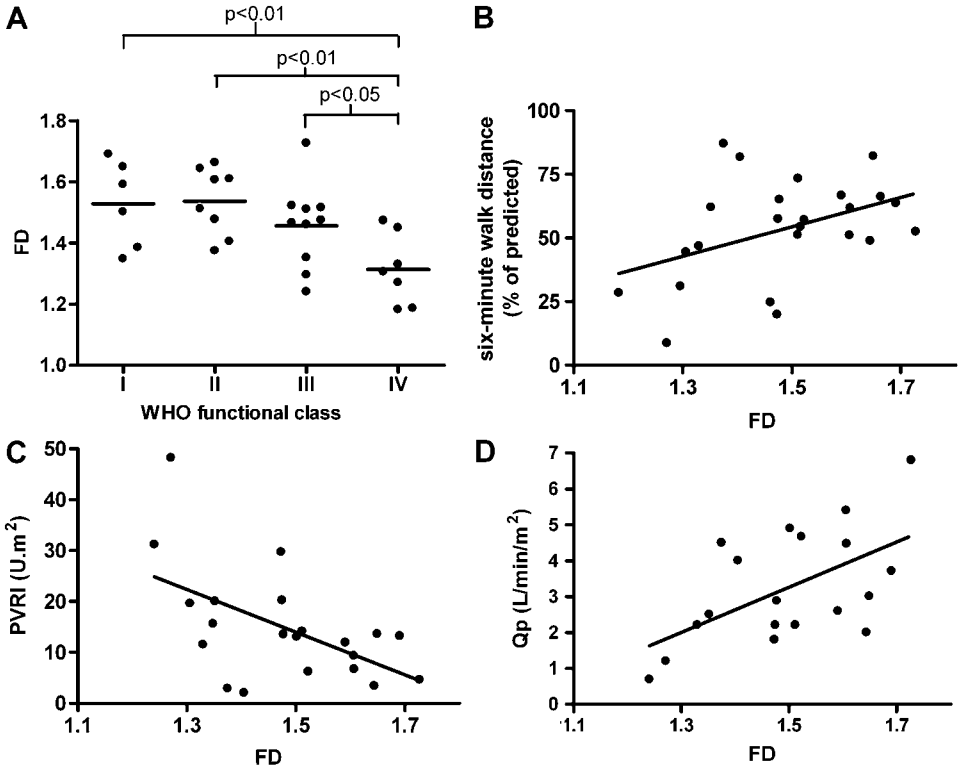

Figure 3 Plots of fractal dimension (FD) against (A) WHO functional class for the 31 patients in the study. The mean FD for each class is represented by a horizontal line. Linear trend ($p<0.01$). (B) 6-Min walk distance (expressed as percentage of predicted) ($n=24$, $r=0.43$ $p=0.04$). (C) Pulmonary vascular resistance index (PVRI) ($n=21$, $r=-0.55$, $p=0.01$). (D) Indexed pulmonary blood flow (Qp) ($n=19$, $r=0.57$, $p=0.01$). Best fit lines by linear regression are displayed.

which are important for accurate FD quantification. The FD of this post-processed data was then assessed using an inhouse implementation of the box counting method. There are a number of techniques for estimating the FD of an object.[8] However, the box counting method is well validated, commonly used and relatively simple to implement. Furthermore, we tested this method on both Euclidean and fractal objects and demonstrated good agreement with the expected FD. This suggests that the box counting method used in this study was valid. However, for this technique to be truly useful in the clinical environment it will be necessary to have all post-processing performed in a single step with minimal manual interaction. Once this has been achieved it will be important to assess interobserver and intraobserver variability.

FD in pulmonary hypertension

In a number of settings, FD has been shown to differentiate between health and disease states. For instance it has been shown that when there is reduction in branching, as seen with mucus plugging of airways in patients with asthma, FD is reduced.[9] Vascular pruning in PAH should thus lead to reduced pulmonary arterial FD. Results from animal models of PAH support this hypothesis.[4] The present study sought to determine the relationship between FD and disease severity in PAH.

Table 2 Univariate survival analysis of baseline parameters

Variable	HR	p Value
FD	5.6	0.03
WHO	6.8	0.06
Predicted walk distance	0.99	0.59
PVRI	0.96	0.76
Qp	0.69	0.66

FD, fractal dimension; PVRI, pulmonary vascular resistance index; Qp, pulmonary blood flow index.

The current reference standard method of assessing PAH severity is the invasive measurement of PVRI, which itself is associated with adverse outcomes.[10] In this study there was a moderate inverse correlation between FD and PVRI, indicating that lungs with elevated resistance have proportionately fewer small arterial branches. While the cause of this reduction in branches has not been demonstrated, it may well reflect the pathological remodelling that is known to occur in this condition.[11] There was no correlation between FD and pulmonary artery pressure, measured either at catheterisation or estimated from tricuspid regurgitation. There was, however, a positive correlation between FD and pulmonary blood flow. This can be explained by the fact that pulmonary artery pressure is not linearly related to PVRI. Progressive increases in PVRI lead to a fall in cardiac output, with pulmonary artery pressure reaching a plateau.

Although invasive catheterisation is the reference standard method of assessing PAH, functional class and exercise capacity are used to assess patients during follow-up and as endpoints in clinical trials in PAH. FD correlated with functional class and exercise capacity; however, this correlation was not as strong as with PVRI. This finding is consistent with FD being a measure of vascular structural changes rather than right ventricular function upon which the functional state predominantly depends.

Ultimately, PAH leads to premature death and an ideal marker of disease severity should provide prognostic information.[12] We have found lower FD to be associated with a significantly increased rate of death. A reduction in FD by 1 SD (0.15) is associated with a 5.6-fold increase in the risk of death. This is an important finding because survival is an unambiguous endpoint, adding strength to the argument that FD is a useful marker in PAH. In addition, FD was the only parameter to reach statistical significance as a prognostic marker, suggesting that it provides additional prognostic information over and above currently established predictors of survival.

Limitations

The main limitations to this study were largely attributable to its retrospective study design. First, most of the cardiac catheter data were not acquired contemporaneously with the CT scans. This was because additional cardiac catheterisation was not routinely performed due to the significant risks in the paediatric PAH population.[13 14] Despite this there was a significant correlation between PVRI and FD, as well as with contemporaneous assessments of functional status and most importantly with survival. Second, there was no control group in this study as normal volunteers could not be exposed to ionising radiation. Patients without pulmonary hypertension do undergo CT angiography; however, in these cases the pulmonary arteries are rarely optimally opacified. Therefore, without a control group, it was not possible to determine whether FD could be used to detect the presence or absence of disease. The CT scans acquired during the period covered by this study were ECG gated, resulting in a mean effective radiation dose of 5.5 mSV. Newer technology and the acquisition of non-gated scans has the potential to reduce the radiation burden significantly. A further limitation was that, while care was taken to segment the pulmonary arteries selectively, it was not always possible fully to exclude some more distal pulmonary veins. This adds a small amount of noise to the analysis; however, this was minimised by the timing of image acquisition (early) and the fact that veins draining areas of lung with poor arterial perfusion were themselves less likely to contain contrast.

CONCLUSION

There is strong evidence from morphometry, mathematical modelling and the present study that the pulmonary arterial tree can be described in terms of its fractal geometry.

This study has shown that FD correlates with survival, haemodynamics and functional status in patients with PAH. As such, this non-invasive technique has the potential to quantify serial changes in the pulmonary arterial bed, and to monitor disease progression (or indeed regression in response to therapy). However, before fractal analysis is applied more widely, it is important to corroborate these findings with further studies using contemporaneous haemodynamic data.

Funding This study was funded by the Pulmonary Hypertension Association and the British Heart Foundation.

Competing interests None.

Ethics approval This study was conducted with the approval of the Institute of Child Health Research Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

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