Functional respiratory imaging provides novel insights into the long-term respiratory sequelae of bronchopulmonary dysplasia

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This study assesses respiratory outcomes in adolescents born preterm. BPD patients had impaired lung function. FRI showed higher distal airway resistances and more air trapping in the BPD group and seems to be a more sensitive emerging imaging technique. https://bit.ly/2KzZytp

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ABSTRACT

Rationale: Bronchopulmonary dysplasia (BPD) is a common complication of preterm birth. Lung function and imaging are classically used to assess BPD. Functional respiratory imaging (FRI) combines a structural and functional assessment of the airways and their vasculature. We aimed to assess BPD using FRI and to correlate these findings with the clinical presentation.

Methods: We included 37 adolescents with a history of preterm birth (22 BPD cases and 15 preterm controls). The study protocol included a detailed history, lung function testing and computed tomography (CT) (at total lung capacity (TLC) and functional residual capacity (FRC)) with FRI. CT images were also assessed using the Aukland scoring system.

Results: BPD patients had lower forced expiratory volume in 1 s to forced vital capacity ratio ($p=0.02$) and impaired diffusion capacity ($p=0.02$). Aukland CT scores were not different between the two groups. FRI analysis showed higher lobar volumes in BPD patients at FRC ($p<0.01$), but not at TLC. Airway resistance was significantly higher in the BPD group, especially in the distal airways. Additionally, FRI showed more air trapping in BPD patients, in contrast to findings on conventional CT images.

Conclusion: This study is the first to use FRI in research for BPD. FRI analysis showed higher lobar volumes in BPD patients, indicating air trapping and reduced inspiratory capacity. In contrast to Aukland CT scores, FRI showed more air trapping in the BPD group, suggesting that FRI might be a more sensitive detection method. Importantly, we also showed increased distal airway resistance in BPD patients. By combining structural and functional assessment, FRI may help to better understand the long-term sequelae of BPD.

Introduction

Despite considerable advances in neonatal care and higher survival rates over the past decades, bronchopulmonary dysplasia (BPD) remains a common complication of preterm birth. The overall incidence of BPD seems to have stagnated or even increased [1–4]. Children with BPD are more often hospitalised for respiratory diseases during the first years of life [5]. Follow-up data on lung function and structural changes in adolescents with new BPD remain sparse. Most studies describe an impaired lung function, expressed as decreased forced expiratory volume in 1 s ($FEV_{1)}$ and/or FEV_1/forced vital capacity (FVC) ratio, decreased diffusion capacity and higher residual lung volumes [6–12]. Some studies report more exercise intolerance in patients with BPD [13]. However, the long-term consequences of BPD into adulthood remain poorly characterised, since follow-up studies in adulthood are limited. Currently available evidence shows that BPD patients may have significant airway obstruction early in life tracking into adulthood (up to 24 years of age) [14]. Although not yet present at age 20 years, it is likely that these BPD patients have an increased risk of developing COPD at a young age. Along with follow-up of lung function, structural imaging modalities are used to assess BPD severity, disease progression and catch-up alveolarisation [15]. Computed tomography (CT) remains the gold standard for a detailed structural assessment of the lung. Several scoring systems have been developed to judge BPD severity on CT, for instance by Aukland *et al.* [16] and by Ochiai *et al.* [17]. These scoring systems correlate with lung function parameters, but the relationship with clinical outcomes is less clear [16].

Functional respiratory imaging (FRI) is a relatively new technique based on multidetector CT (MDCT) and computational fluid dynamics (CFD) that combines a structural and functional assessment of the airways and their vasculature [18]. Patients undergo a low-dose CT scan of the lungs, while images are captured at two lung levels: functional residual capacity (FRC) and total lung capacity (TLC). Obtaining CT images at both FRC and TLC allows for an individual, patient-specific reconstruction of the airways. CFD is an established method for predicting flows and pressure distributions in complex systems. Flow patterns and corresponding airway resistances can be calculated in specific parts of the lung. Thus, it gives a clearer and more individualised idea of lung volumes and resistance in smaller airways than classically used lung function testing. FRI has been applied in a plethora of respiratory diseases, but has never been used for the assessment of lung disease in BPD. Therefore, with this study, we aimed to evaluate the long-term consequences of BPD during adolescence in the post-surfactant era, with a focus on lung function and structure using FRI in combination with classical lung function testing and CT analysis with scoring systems. In addition, we aimed to identify parameters on FRI analysis that might be of interest for long-term follow-up of BPD patients.

Materials and methods

Study population

Subject recruitment for this case–control study was based on an existing patient cohort at the Antwerp University Hospital (Edegem, Belgium) including preterm infants born <31 weeks' gestational age who needed mechanical ventilation since the day of birth, now aged 13–16 years and born between 1999 and 2002 [19]. Detailed eligibility criteria for this cohort are provided in appendix 1. Patients with severe mental or physical impairment were excluded for the present study, since some degree of cooperation is needed for lung function testing and FRI imaging. Informed consent was obtained from the parents before enrolment. This study was approved by the ethical committee of the Antwerp University Hospital.

Data collection

Clinical data

Relevant maternal and pregnancy details and neonatal data were retrieved from the infant's medical files (appendix 1). BPD diagnosis and severity assessment was recorded according to the definition proposed by Jobe and Bancalari [20].

Questionnaires

Questionnaires were used to assess clinical outcome at the time of inclusion in the present study (appendices 1 and 3). In short, these questionnaires assessed the medical history of the patient after discharge from the neonatal intensive care unit, with a focus on respiratory symptoms and their potential impact on daily life.

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Physical examination

Upon their clinic visit, patients received a physical examination. Their current weight, height and blood pressure were recorded.

Lung function testing

Lung function testing comprised of conventional spirometry with bronchodilator response (salbutamol), body plethysmography, nitrogen multiple-breath washout testing (N_2MBW) and a single-breath carbon monoxide diffusion test. A positive bronchodilator response was defined as an increase in FEV_1 >12% after administration of salbutamol. More details are provided in appendix 1.

CT imaging

All patients underwent an unenhanced low-dose MDCT of the lungs at TLC (*i.e.* at maximal inspiration) and at FRC (*i.e.* after normal expiration). Details are provided in appendix 1. The CT images were reviewed by five independent observers who were blinded to clinical data and the outcome. CT scans were reviewed using the Aukland scoring system, a validated scoring system assessing the presence or absence of nine different structural abnormalities (appendix 1) [16].

Functional respiratory imaging

FRI analyses were conducted by Fluidda (Kontich, Belgium). Methods for this imaging technique have been described in detail elsewhere [21]. In short, patient-specific anatomical structures of the lungs are

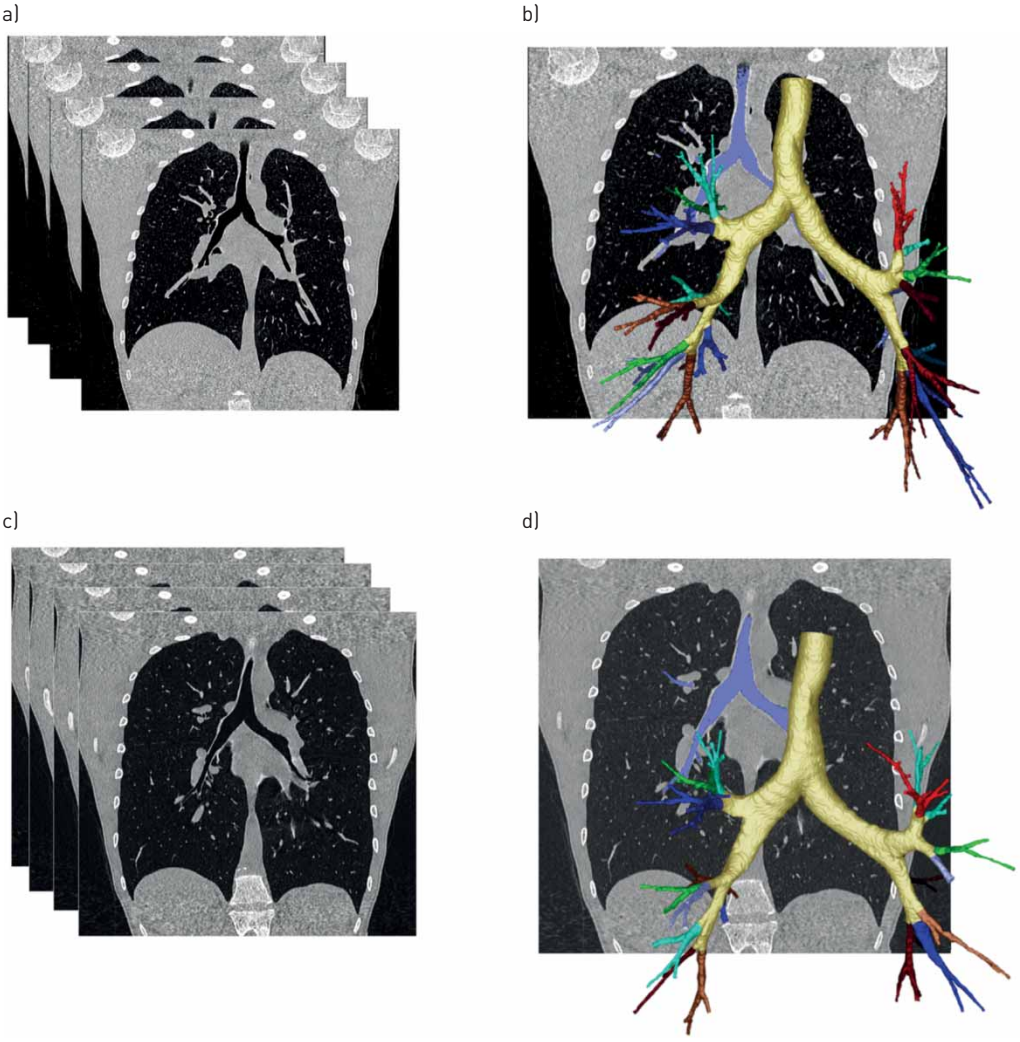

FIGURE 1 Visualisation of the functional respiratory imaging reconstruction process in a bronchopulmonary dysplasia patient (a and b) and a preterm control (c and d). From the native computed tomography image (a and c), the patient-specific three-dimensional (3D) airway is computed (b and d). Functionality is added by simulating air flow in this patient-specific 3D airway model.

reconstructed *via* segmentation of MDCT images. Air flow is simulated within this three-dimensional airway model, thus allowing a numeric, quantified assessment of several structural and functional airway parameters (figure 1). Detailed methods are provided in the supplementary material. In this study, the following parameters were assessed: 1) lung volumes at FRC and TLC, 2) airway volumes at FRC and TLC, 3) airway resistance, 4) emphysema, 5) air trapping, 6) lung vasculature and 7) ventilation/perfusion (V'/Q') ratios.

Statistical analyses

Statistical analyses were conducted in SPSS version 26 (IBM Corporation, Armonk, NY, USA). Univariate analysis, correlations and multiple regression were computed using appropriate tests and modelling strategies (appendix 1). When applicable, BPD status at 28 days was used as a grouping variable. Intraclass correlation coefficients (ICCs) were computed to evaluate interobserver variability of the Aukland CT scores. For all analyses, $p<0.05$ was considered statistically significant.

Results

Population demographics

37 patients were included, of whom 22 were diagnosed with BPD and 15 were born preterm but did not develop BPD, thus constituting a preterm control group (figure 2). General demographic information is shown in table 1. Patients with BPD had lower gestational age at birth ($p<0.01$) and lower birthweight ($p=0.04$). They more often received surfactant ($p=0.04$) and the duration of oxygen therapy was longer ($p<0.01$).

At follow-up, all patients were aged between 13 and 16 years. There was no significant difference between the two groups in occurrence of asthma, frequent respiratory symptoms (*e.g.* wheezing, waking up at night, dyspnoea, exercise intolerance, nocturnal cough), frequent respiratory infections or fatigue, nor in any other clinical outcome parameter.

Lung function testing

Spirometry

BPD patients had significantly lower FEV_1/FVC % (Tiffeneau indices), even after administration of salbutamol ($p=0.02$ and $p=0.04$, respectively). However, there was no significant difference in prevalence

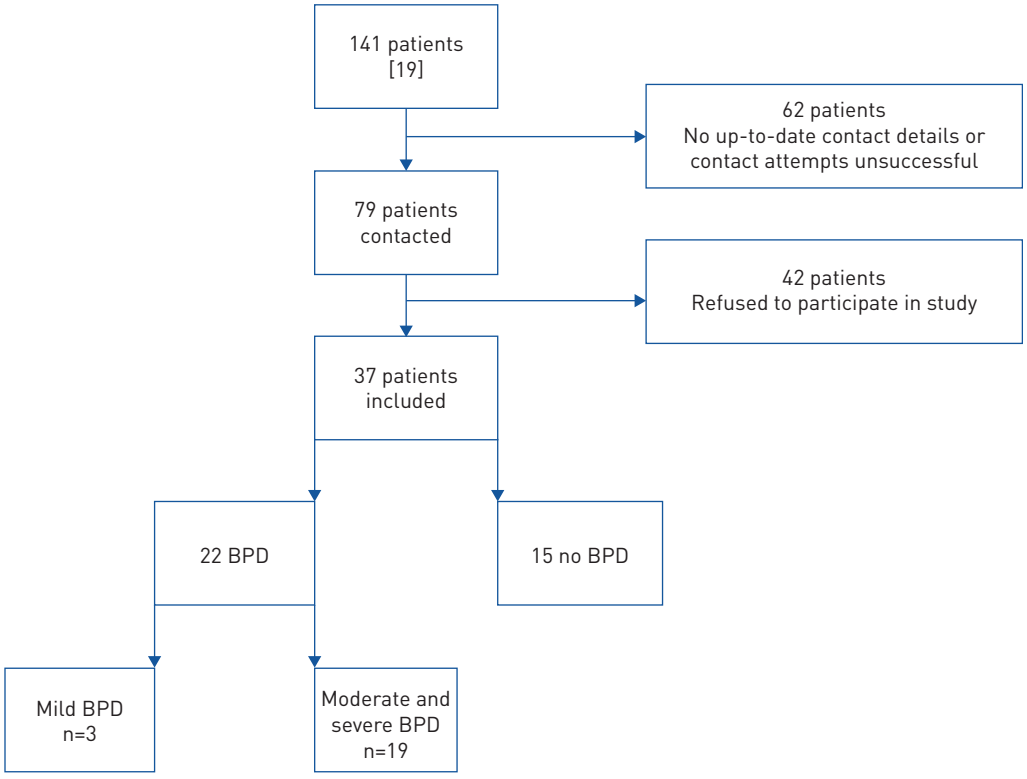

FIGURE 2 Subject recruitment flowchart. BPD: bronchopulmonary dysplasia.

TABLE 1 Patient characteristics

	No BPD	BPD	p-value
Subjects n	15	22	
Gestational age weeks	29 (26–30.6)	27.93 (24.9–30.3)	<0.01*
Birthweight g	1240 (637–1904)	973 (469–1640)	0.04*
Surfactant	5 (33)	15 (68)	0.04*
Corticosteroids	14 (93)	21 (95)	1
Days on ventilator	3 (1–11)	9 (1–45)	<0.01*
Days on oxygen	5 (1–27)	54.50 (30–133)	<0.01*
RDS	10 (67)	19 (86)	0.23
IUGR	2 (14)	3 (14)	1
Age at follow-up years	15.2 (13.5–16.7)	15.2 (14–16.9)	0.99
Psychomotor retardation	8 (57)	13 (59)	0.91
Several respiratory infections during the past 2 years	2 (14)	0 (0)	0.14
Reversibility (change FEV_1 >12%)	2 (13)	7 (32)	0.26
Inhalers	2 (14)	3 (14)	1
Wheezing in past 12 months	1 (8)	6 (30)	0.20
Nocturnal cough in past 12 months	2 (17)	1 (6)	0.55
Chronic cough[#]	1 (10)	1 (5)	1
Perennial rhinitis[¶]	2 (20)	3 (16)	1

Data are presented as median (range) or n (%), unless otherwise stated. BPD: bronchopulmonary dysplasia; RDS: respiratory distress syndrome; IUGR: intrauterine growth retardation; FEV_1: forced expiratory volume in 1 s. [#]: defined as daily cough for >4 weeks in the past year; [¶]: defined as rhinitis or sneezing without concurrent infections during the past 12 months. *: p<0.05.

TABLE 2 Lung function testing

	No BPD	BPD	p-value
Subjects n	15	22	
FVC %	111 (67–122)	108.5 (77–138)	0.94
FVC after BD[#] %	109 (70–122)	108.5 (71–141)	0.66
FEV_1 %	104 (69–121)	98 (80–125)	0.20
FEV_1 after BD[#] %	114 (73–124)	106 (78–128)	0.63
Δ FEV_1	4 (−2–13)	7.50 (−3–33)	0.10
FEV_1/FVC %	98 (88–110)	87 (68–111)	0.02*
FEV_1/FVC after BD[#] %	102 (96–115)	95 (84–115)	0.04*
PEF %	94.5 (66.1–129.9)	87 (71.1–114.5)	0.20
MEF_{50} %	92 (57–142)	66 (48–163)	0.06
MEF_{50} after BD[#] %	101 (71–153)	89.5 (61–171)	0.13
MEF_{25} %	75 (49–124)	56.5 (40–201)	0.14
MEF_{25} after BD[#] %	97 (57–148)	78.5 (48–201)	0.14
Airway resistance	1.02 (0.67–1.74)	1.29 (0.63–2.46)	0.14
RV %	107 (56–179)	135.5 (80–207)	0.09
TLC %	111 (75–128)	117.5 (77–139)	0.22
FRC %	96 (79–136)	121 (88–168)	0.02*
D_{LCO}/V_A	1.79 (1.34–2.61)	1.60 (1.17–2.09)	0.01*
D_{LCO}/V_A %	87 (64–127)	78 (58–102)	0.02*
LCI	5.40 (4.74–6.37)	5.42 (4.66–7.47)	0.75
V_A/TLC%	0.98 (0.91–1.07)	0.97 (0.88–1.07)	0.25
Reversibility	13%	32%	0.26

Data are presented as median (range), unless otherwise stated. BPD: bronchopulmonary dysplasia; FVC: forced vital capacity; BD: bronchodilation; FEV_1: forced expiratory volume in 1 s; PEF: peak expiratory flow; MEF_{50}: maximal expiratory flow at 50% of FVC; MEF_{25}: maximal expiratory flow at 75% of FVC; RV: residual volume; TLC: total lung capacity; FRC: functional residual capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; V_A: alveolar volume; LCI: lung clearance index. [#]: performed by means of salbutamol inhalation. *: p<0.05.

of asthma between both groups (p=0.3). There were no significant differences in FEV_1, FVC or maximal expiratory flows (MEFs) (table 2).

Body plethysmography

FRC volumes were significantly higher in the BPD group (p=0.02), but there was no difference in TLC or residual volume between both groups (p=0.2 and p=0.09, respectively). We did not observe a difference in airway resistance between BPD patients and preterm controls.

Diffusion capacity

Diffusion capacity was impaired in subjects with BPD, expressed by a lower diffusing capacity of the lung for carbon/alveolar volume ratio (p=0.01).

N_2MBW

Lung clearance index (LCI) was not significantly different between the two groups.

TABLE 3 Interobserver variability of the Aukland computed tomography (CT) score, presented as intraclass correlation coefficients (ICCs) for all observers combined, radiologists (M. Spinhoven, A. Snoeckx, H. El Addouli) and non-radiologists (K. Vanhaverbeke, E. Lauwers) ratings

	ICC (95% CI)
Total CT score	
All observers combined	0.8 (0.7–0.9)
Radiologists	0.6 (0.3–0.8)
Non-radiologists	0.7 (0.5–0.9)
Linear or triangular subpleural opacities	
All observers combined	0.7 (0.5–0.9)
Radiologists	0.5 (0.03–0.7)
Non-radiologists	0.8 (0.5–0.9)
Mosaic perfusion on inspiration	
All observers combined	0.7 (0.5–0.8)
Radiologists	0.6 (0.2–0.8)
Non-radiologists	0.9 (0.7–0.9)
Air trapping	
All observers combined	0.9 (0.86–0.95)
Radiologists	0.8 (0.7–0.9)
Non-radiologists	0.9 (0.8–0.96)
Decreased bronchoarterial ratio	
All observers combined	0.6 (0.4–0.8)
Radiologists	0.5 (0.1–0.7)
Non-radiologists	0.5 (−0.05–0.7)
Bronchiectasis	
All observers combined	0.5 (0.3–0.7)
Radiologists	−0.07 (−0.9–0.4)
Non-radiologists	−0.03 (−0.97–0.5)
Peribronchial thickening	
All observers combined	0.4 (0.1–0.6)
Radiologists	0.1 (−0.07–0.3)
Non-radiologists	0.3 (−0.3–0.6)
Bullae or blebs[#]	
All observers combined	
Radiologists	
Non-radiologists	
Emphysema[#]	
All observers combined	−0.09 (−0.8–0.4)
Radiologists	
Non-radiologists	
Collapse or consolidation	
All observers combined	0.9 (0.87–0.95)
Radiologists	0.8 (0.7–0.9)
Non-radiologists	1

[#]: ICCs could not be computed, as these findings were only present in one or two cases, and not scored as present by all observers.

CT imaging

Overall interobserver variability was good and there were no differences in ICCs between radiologists and non-radiologists (table 3 and appendix 2). Therefore, the mean of all observers' scores was used in subsequent analyses. All CT images showed abnormalities in at least one category when using the Aukland scoring system. We did not observe any significant difference in total Aukland CT score or any of the assessed parameters between the two groups. There was a trend towards more emphysema in the BPD group (p=0.08). Results are shown in table 4.

Functional respiratory imaging

Lung volumes

FRI analysis showed higher FRC lobar volumes in adolescents with BPD in all lobes ($p \leqslant 0.01$) (table 5). When measured at TLC, the differences were not statistically significant; indicating air trapping in the BPD group (figures 3 and 4).

Airway volumes

Airway volumes at FRC were lower in the BPD group, especially in the central airways. At TLC, distal airway volumes were decreased in the BPD group (appendix 2, supplementary figure E1).

Airway resistance

Measurements at FRC showed significantly higher total airway resistance in the BPD group (p=0.03). More specifically, airway resistance was increased in the lower lobes and distal airways of these patients (p=0.02) (figure 5).

Emphysema

We observed no difference between the groups in the occurrence of emphysema.

Air trapping

BPD patients had significantly more air trapping (lower lobes, upper lobes and total) than preterm controls ($p<0.01$) (figures 3 and 4).

Vasculature

There were no differences in absolute volume (in mL) or relative volume (expressed as % per lobe) between both groups.

Ventilation/perfusion

Ventilation/perfusion ratios were not different between BPD patients and preterm controls.

Integrating clinical outcomes, lung function and lung structure

As described earlier, FRI analysis showed that air trapping and airway resistance in the lower airways were significantly increased in adolescents with BPD. Therefore, we investigated which neonatal parameters are predictive of air trapping and airway resistance in the distal airways. Detailed results are shown in table 6. After exclusion of outliers for air trapping on FRI, multiple linear regression showed that a model

TABLE 4 Mean Aukland computed tomography (CT) score components

	No BPD	BPD	p-value
Subjects n	15	22	
Total CT score	10 (3.6–13.8)	9.1 (4.2–20)	0.7
Linear or triangular subpleural opacities	2.4 (0.6–4.8)	2.1 (0.4–5)	0.8
Mosaic perfusion on inspiration	0 (0–3.2)	0.1 (0–2.2)	0.7
Air trapping	1 (0–3.6)	0.3 (0–5.2)	0.2
Decreased bronchoarterial ratio	1.4 (0.4–3.8)	1 (0–4.4)	0.4
Bronchiectasis	0 (0–0.4)	0 (0–2)	0.9
Peribronchial thickening	4.2 (0.6–5.6)	4.5 (2–5.4)	0.8
Bullae or blebs	0 (0–0.4)	0 (0–0.2)	0.9
Emphysema	0 (0–0.8)	0 (0–1)	0.08
Collapse or consolidation	0 (0–0.2)	0 (0–1.2)	0.9

Data are presented as n or median (range), unless otherwise stated. BPD: bronchopulmonary dysplasia.

TABLE 5 Functional respiratory imaging parameters in the bronchopulmonary dysplasia (BPD) *versus* preterm control group

	No BPD	BPD	p-value
Subjects n	15	22	
Lung volumes			
FRC_*V* lobe_total L	2.1±0.74	2.70±0.71	<0.01*
FRC_*V* lobe_lower L	1.0±0.43	1.30±0.43	0.01*
FRC_*V* lobe_upper L	1.0±0.33	1.33±0.40	<0.01*
FRC_pred *V* lobe_total %	94.5±17.2	115.8±23.5	<0.01*
FRC_pred *V* lobe_lower %	103.67±26.1	124±35	0.05
FRC_pred *V* lobe_upper %	87.1±14.1	102.3±23.9	0.02*
TLC_ *V* lobe_total L	4.42±1.40	5.06±0.90	0.13
TLC_*V* lobe_lower L	2.39±0.90	2.60±0.82	0.46
TLC_*V* lobe_upper L	2.03±0.53	2.32±0.57	0.13
TLC_pred *V* lobe_total %	97.23±15.18	105.07±16.91	0.32
TLC_pred *V* lobe_lower %	103.49±22.21	106.27±27.27	0.80
TLC_pred *V* lobe_upper %	90.85±11.37	96.53±16.65	0.26
Airway volumes			
FRC_siV_{aw}_central mL·L^{-1}	5.66±1.43	5.36±0.67	<0.01*
FRC_siV_{aw}_distal mL·L^{-1}	0.98±0.33	0.86±0.25	0.15
FRC_siV_{aw}_total mL·L^{-1}	6.64±1.66	6.22±0.80	<0.01*
FRC_siV_{aw}_lower mL·L^{-1}	1.10±0.39	1.03±0.24	0.29
FRC_siV_{aw}_upper mL·L^{-1}	0.86±0.30	0.81±0.24	0.14
TLC_siV_{aw}_central mL·L^{-1}	4.57±0.90	4.53±0.56	0.20
TLC_siV_{aw}_distal mL·L^{-1}	1.29±0.44	1.05±0.31	0.04*
TLC_siV_{aw}_total mL·L^{-1}	5.87±1.04	5.58±0.73	0.07
TLC_siV_{aw}_lower mL·L^{-1}	1.39±0.51	1.22±0.51	0.86
TLC_siV_{aw}_upper mL·L^{-1}	1.18±0.39	1.00±0.28	0.33
Airway resistance			
FRC_siR_{aw}_central	0.084±0.023	0.084±0.03	0.84
FRC_siR_{aw}_distal	0.19±0.11	0.33±0.22	0.02*
FRC_siR_{aw}_total	0.27±0.12	0.42±0.24	0.03*
FRC_siR_{aw}_lower	0.17±0.10	0.32±0.21	0.02*
FRC_siR_{aw}_upper	0.23±0.14	0.34±0.26	0.19
TLC_siR_{aw}_central	0.11±0.03	0.10±0.03	0.49
TLC_siR_{aw}_distal	0.21±0.14	0.29±0.15	0.04*
TLC_siR_{aw}_total	0.31±0.15	0.39±0.17	0.14
TLC_siR_{aw}_lower	0.23±0.17	0.31±0.20	0.11
TLC_siR_{aw}_upper	0.20±0.12	0.28±0.14	0.09
Emphysema			
TLC_emphysema_total % per lobe	1.03±1.17	1.67±1.40	0.14
TLC_emphysema_lower % per lobe	1.10±1.44	1.79±1.60	0.14
TLC_emphysema_upper % per lobe	0.98±0.97	1.50±1.23	0.15
Air trapping			
FRC_airtrapping_total % per lobe	2.55±2.11	9.40±6.62	<0.01*
FRC_airtrapping_lower % per lobe	1.88±2.16	6.51±4.97	<0.01*
FRC_airtrapping_upper % per lobe	3.17±2.48	11.77±8.61	<0.01*
Vasculature			
TLC_blood absolute_total mL	129.46±32.76	126.51±31.32	0.78
TLC_blood absolute_lower mL	71.52±20.30	69.49±19.49	0.76
TLC_blood absolute_upper mL	71.52±20.30	69.49±19.49	0.61
TLC_blood relative_total % per lobe	3.58±1.50	2.90±0.71	0.14
TLC_blood relative_lower % per lobe	3.71±1.55	3.10±0.91	0.13
TLC_blood relative_upper % per lobe	3.44±1.48	2.70±0.58	0.14
Ventilation/perfusion			
V′/*Q′* distribution_total	1887.95±649.46	1952.79±644.99	0.77
V′/*Q′* distribution_lower	1957.90±605.46	1924.48±579.41	0.87
V′/*Q′* distribution_upper	1800.85±700.28	1844.95±610.32	0.84

Data are presented as mean±SD unless otherwise stated. FRC: functional residual capacity; *V*: volume; TLC: total lung capacity; siV_{aw}: specific image-based airway volume; siR_{aw}: specific image-based airway resistance; *V′*/*Q′*: ventilation/perfusion ratio. *: p<0.05.

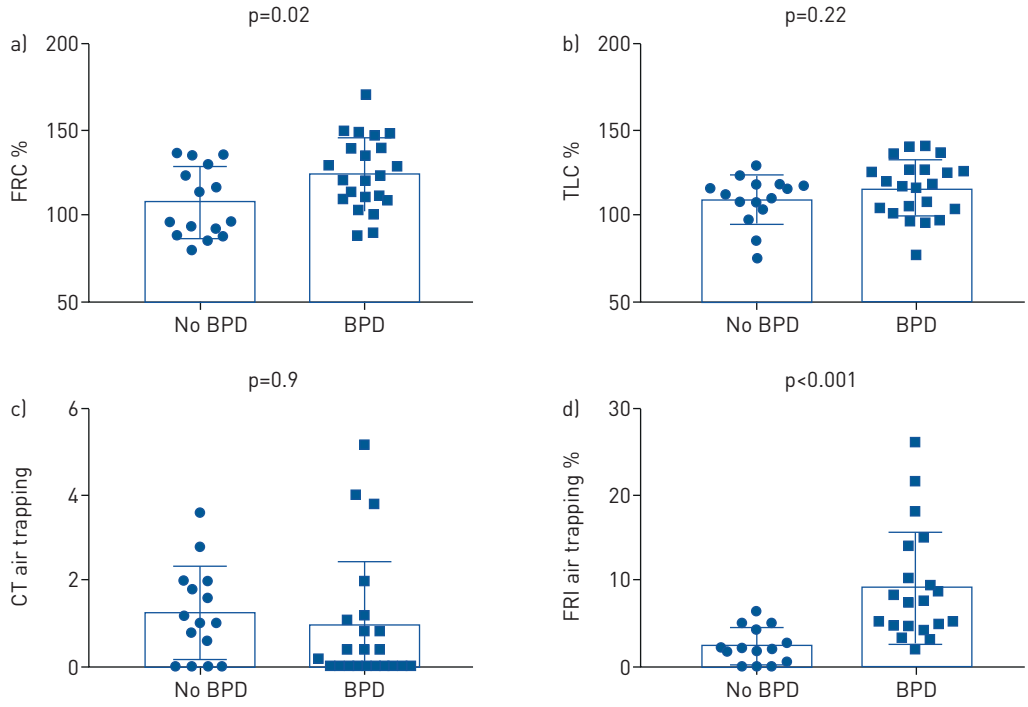

FIGURE 3 Air trapping measured by body plethysmography, computed tomography (CT) and functional respiratory imaging (FRI) in the preterm control group and the bronchopulmonary dysplasia (BPD) group. a) Functional residual capacity (FRC) measured by body plethysmography (p=0.02); b) total lung capacity (TLC) measured by body plethysmography (p=0.22); c) air trapping in all lobes combined assessed with the Aukland CT score (mean of all observers, p=0.9); d) air trapping in all lobes combined assessed using FRI (p<0.001).

containing BPD status and birthweight could explain 39% of variability in air trapping on FRI analysis. There was no significant interaction between these two independent variables. Univariate analysis with airway resistance in the distal airways as a dependent variable showed that BPD status and oxygen need at 36 weeks gestational age were significant predictors. Air trapping and airway resistance in the distal airways on FRI analysis correlated significantly with Tiffeneau indices (r=−0.47, p=0.01 and r=−0.509, p=0.001, respectively). Additionally, airway resistance on FRI analysis correlated significantly with maximal expiratory flow at 75% of FVC (MEF_{25}), at 50% of FVC (MEF_{50}) and mean maximal expiratory flow at 25–75% of FVC (MEF_{25-75}), as well as specific airway resistance as measured by conventional spirometry (appendix 2, supplementary table E1). Air trapping on FRI correlated with body box lung volume measurements (appendix 2, supplementary table E2).

Discussion

In this study, we aimed to investigate clinical, functional and radiological outcomes in adolescents with a history of preterm birth. Combined structural and functional analysis with FRI indicated more air trapping in the BPD group. In addition, BPD patients had significantly increased distal airway resistances, which indicates that these parameters might be of interest for follow-up into adulthood to assess the risk of developing COPD. While we did not observe an increase in respiratory symptoms in BPD patients, their lung function was impaired, showing lower FEV_1/FVC ratio, more air trapping and impaired diffusion capacity in the BPD group. Aukland CT scores did not differ between BPD patients and preterm controls.

In our cohort, adolescents with BPD did not have more respiratory symptoms or asthma than preterm controls. Nevertheless, an increased asthma prevalence has been described previously in adolescents with a history of preterm birth [22]. In addition, several authors observed a higher prevalence of respiratory symptoms in BPD patients compared to preterm controls [23–27]. It is possible that due to a relatively small sample size, our study was underpowered to detect these differences. Alternatively, since we did observe functional and structural abnormalities in BPD patients, it could be that these changes remain subclinical phenomena that do not cause clinical symptoms at this age.

Consistent with the literature, lung function was impaired in our BPD group [22, 28–31], with patterns suggesting obstructive lung disease, but without a positive bronchodilator response, indicating some degree of fixed airway obstruction [22, 24, 32]. In addition, we found increased FRCs in BPD patients, but no

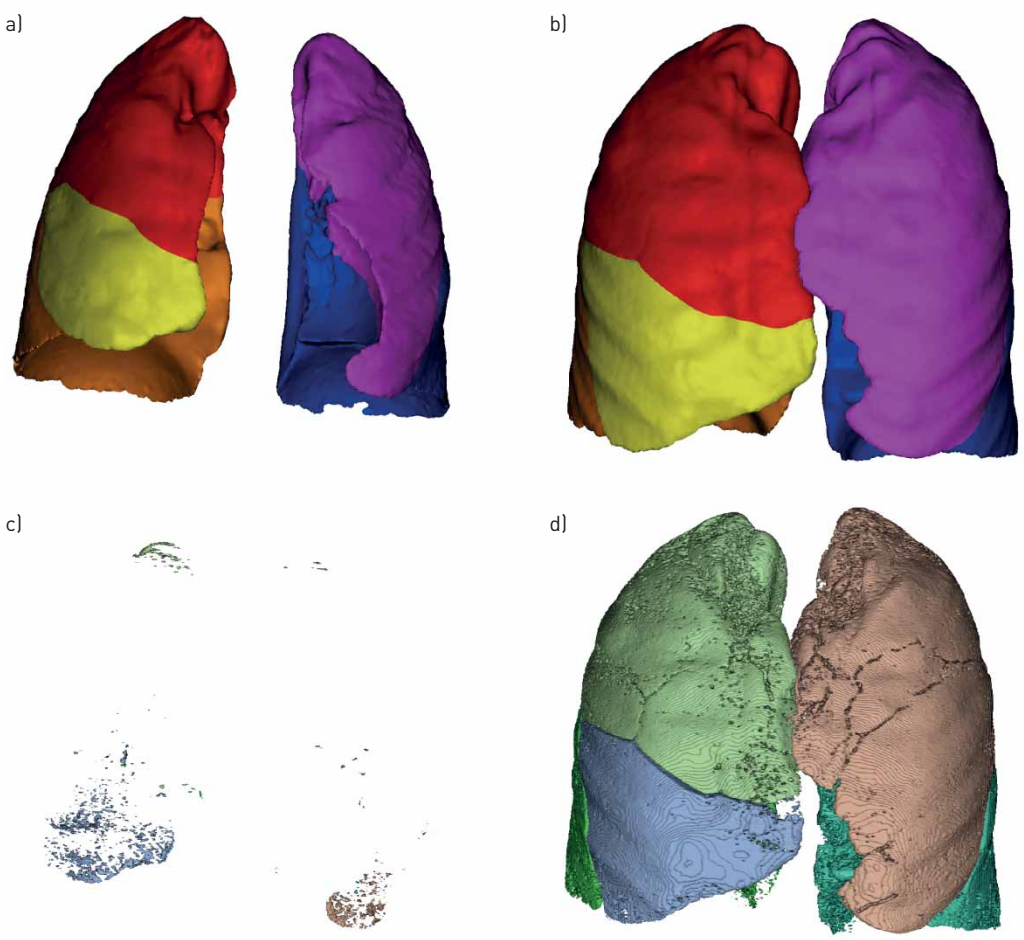

FIGURE 4 Functional respiratory imaging: visualisation of air trapping in a bronchopulmonary dysplasia (BPD) subject (a and c) and matched preterm control (b and d) showing marked air trapping in all lung lobes in the BPD subject. Figure 3b and c shows the relative amount of air trapping per lung region.

difference between TLC between groups, indicating air trapping and reduced inspiratory capacity in adolescents with BPD, as has been described in the literature [25]. Interestingly, studies that followed lung function trajectories after preterm birth have indicated that lung function worsens and becomes more obstructive over time in BPD patients [11]. While previous lung function data were not available for the patients in our cohort, these findings may support the hypothesis that airway obstruction becomes more severe over time and stress the importance of early monitoring and rigorous follow-up in children with BPD. In accordance with previous literature, we have shown lower diffusion capacity and thus impaired gas exchange in BPD patients, possibly linked with damaged alveolar compartments and changes in pulmonary vasculature that have been described in BPD [33, 34]. Interestingly, our study has been unable to demonstrate ventilation inhomogeneity based on the LCI.

Another component in long-term follow-up of respiratory morbidity is a structural assessment of the lungs. CT remains the gold standard for imaging of the lung. Numerous studies have investigated the anatomy of the BPD lung throughout childhood. Most authors describe anatomical changes in a high percentage of patients with BPD, but also in preterm controls [16, 23, 24]. Similarly, all scans in our cohort showed at least one abnormality. In contrast to previous findings, our study has been unable to demonstrate any significant difference in Aukland CT score between the BPD group and the preterm control group [16, 24]. Previous evidence, as well as our study, suggests that radiological changes might be linked to preterm birth and consequent altered lung development in general and are not necessarily indicative of a clinical BPD diagnosis only [25]. An integrated approach, taking into account both structural and functional impairment of the lung, is necessary when assessing the clinical impact of BPD.

This study is the first to use FRI in research for BPD, providing a tool for integrated structure and function assessment of the airways and their vasculature. Using FRI, we observed higher FRC but not TLC

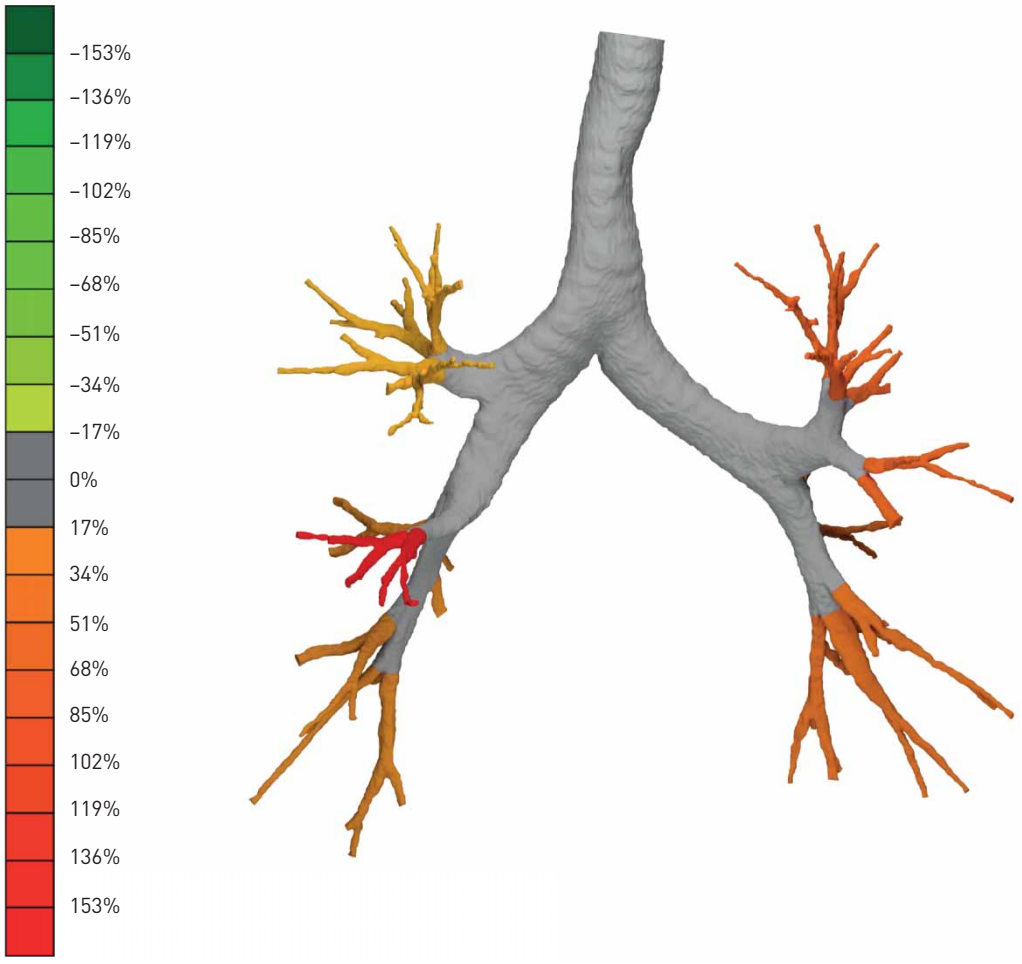

FIGURE 5 Functional respiratory imaging: visualisation of airway resistance measured at total lung capacity in a bronchopulmonary dysplasia (BPD) patient compared to a preterm control subject. In this visualisation, airway resistance of a representative BPD patient is compared to a representative preterm control patient. Thus, this image shows higher airway resistance in the distal airways (and not in the central airways) in the BPD patient compared to the preterm control (positive % values).

volumes in the BPD group, indicating air trapping. The FRI parameter "air trapping" was also increased in the BPD group. Interestingly, the peripheral airway resistance was increased in the BPD group. Several authors have hypothesised that the peripheral airways are most affected in BPD following aberrant lung development with incomplete secondary septation [5, 23]. However, lung function tests to assess these regional peripheral changes are currently not easily available in clinical practice. While oscillometric methods have been described, they have not yet found their way into routine clinical practice. Nevertheless, follow-up studies into early adulthood suggest that childhood airway obstruction tracks into adulthood, which may lead to COPD later in life [14, 35–38]. Therefore, we investigated which neonatal parameters might be predictive of air trapping and airway resistance in the distal airways upon FRI analysis. These two parameters were significantly increased in the BPD group and may be important in further COPD development. For air trapping, BPD status and birthweight were significant predictors. Airway resistance in the distal airways was significantly predicted by BPD status, and particularly moderate or severe BPD requiring oxygen therapy at 36 weeks gestational age. This suggests that a combined assessment of air trapping and distal airway resistance may be of importance in the long-term follow-up of patients with BPD, as they may reflect risk factors for the later development of COPD.

As a final aspect in the FRI analysis, we hypothesised that, in accordance with the pathophysiology, BPD patients would have lower blood vessel volumes than preterm controls. Surprisingly, we did not observe such differences. Possibly, preterm controls without BPD also show signs of impaired pulmonary vascular development. Additionally, the power of our study may not be sufficient to detect significant changes in blood vessel volume between BPD patients and preterm controls.

TABLE 6 Linear regression with FRC_air trapping_total and FRC_siR_{aw}_lower as dependent variables

	R^2	B	p-value
Univariate analysis FRC_air trapping_total			
BPD	0.33	5.22 (2.57–7.88)	<0.001*
Oxygen therapy days	0.21	0.06 (0.02–0.11)	0.01*
Preterm contractions	0.19	−3.86 (−6.89–−0.82)	0.02*
Oxygen therapy on day 7	0.17	4.07 (0.77–7.37)	0.02*
Oxygen therapy on day 14	0.23	4.42 (1.39–7.44)	0.001*
Gestational age weeks	0.14	−1.03 (−2.01–−0.06)	0.04*
Birthweight	0.14	−0.01 (−0.01–0.00)	0.04*
Multiple linear regression FRC_air trapping_total#	0.39		0.001
BPD		4.64 (1.85–7.42)	0.002*
Birthweight		−0.003 (−0.007–0.002)	0.20
Univariate analysis FRC_siR_{aw}_distal			
BPD	0.13	0.15 (0.02–0.27)	0.03*
Oxygen therapy at 36 weeks' gestational age	0.16	0.17 (0.03–0.30)	0.02*

Slopes (unstandardised coefficients) and corresponding 95% confidence intervals as well as significance levels are shown. Multiple linear regression was not performed given the multicollinearity between "BPD" and "Oxygen therapy at 36 weeks' gestational age". FRC: functional residual capacity; BPD: bronchopulmonary dysplasia; siR_{aw}: specific image-based airway resistance. #: FRC air trapping total (%) = 5.97 + 4.64 × (BPD) − 0.003 × (birthweight). *: p<0.05.

Although our study demonstrates the potential benefit of FRI in assessing patients with BPD, the results should be interpreted with caution since our work unavoidably shows some limitations.

Firstly, this is a pilot study with a relatively small sample size. The BPD group tended towards more severe forms of BPD; as only three out of 22 BPD patients had mild BPD. However, mild BPD is by far the most common presentation in clinical practice. Subgroup analysis was therefore not possible. In addition, we only included preterm controls.

Secondly, FRI imaging requires obtaining images at FRC and TLC. This implies that the patient must be able to perform a breath-hold manoeuvre for the duration of the scan, which might not be possible for all patients, including spontaneously breathing infants. However, studying newborns with this technique could provide invaluable information on the role of the small airways and pulmonary vasculature in BPD pathophysiology. FRI might be an interesting and feasible assessment method for younger children who cannot yet perform conventional spirometry, but who are capable of a breath-hold manoeuvre.

Thirdly, CT imaging is associated with exposure to ionising radiation. While the long-term effects of radiation exposure remain largely unknown, it has been shown that paediatric patients exposed to CT have an increased, dose-dependent risk of cancer [39, 40]. This is of particular importance in patients with a history of preterm birth, who are often exposed to considerable amounts of ionising radiation. Implicitly, the consideration of imaging studies must come with a clear benefit for the patient. In this respect, a possible advantage of FRI is the integrated assessment of structure and function.

Notwithstanding these limitations and the need for further confirmation of our findings, this study proposes further insights in the outcome of children with a history of BPD on a clinical, functional and structural level.

Conclusion

In this study, we assessed clinical, functional and structural respiratory outcomes in adolescents with a history of preterm birth. FRI analysis and lung function indicated significantly more air trapping in the BPD group. FRI also showed higher distal airway resistance in the BPD group, which is compatible with currently accepted theories concerning the development of BPD. FRI shows promise as a new, integrated imaging technique opening up the potential to unravel the relationship between established pathophysiological processes in BPD and specific structural and functional changes. After further exploring the role of FRI for BPD beyond this pilot study, translational research efforts including this imaging technique could play a crucial role in better understanding the process of BPD development and the potential of emerging therapeutic strategies, since FRI allows an objective and structure–function-integrated view into the BPD lung.

Conflict of interest: K. Vanhaverbeke has nothing to disclose. M. Slaats has nothing to disclose. M. Al-Nejar has nothing to disclose. N. Everaars has nothing to disclose. A. Snoeckx has nothing to disclose. M. Spinhoven has nothing to disclose. H. El Addouli has nothing to disclose. E. Lauwers has nothing to disclose. A. Van Eyck has nothing to disclose. B.Y. De Winter has nothing to disclose. K. Van Hoorenbeeck has nothing to disclose. J. De Dooy has nothing to disclose. L. Mahieu has nothing to disclose. B. Mignot is an employee of Fluidda. J. De Backer is an employee/shareholder of Fluidda. A. Mulder has nothing to disclose. S. Verhulst reports grants from Vitalaire Belgium and Josephine Neiman Foundation, during the conduct of the study.

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