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

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

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⁷Neonatal Intensive Care Unit, Antwerp University Hospital, Edegem, Belgium
⁸Fluidda, Kontich, Belgium

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Take home message
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.
1. 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 with 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 CT (at TLC and FRC) with FRI. CT images were also assessed using the Auckland scoring system.

RESULTS: BPD patients had lower FEV$_1$/FVC ($p=0.02$) and impaired diffusion capacity ($p=0.02$). Auckland 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 Auckland 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.
2. **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 hospitalized 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 FEV₁ and/or FEV₁/FVC, decreased diffusion capacity and higher residual lung volumes [6–12]. Some studies report more exercise intolerance in patients with BPD [13]. The long-term consequences of BPD into adulthood remain however poorly characterized, 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 20 years of age, it is likely that these BPD patients have an increased risk of developing chronic obstructive pulmonary disease (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 alveolarization [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 and colleagues [17]. These scoring systems correlate with lung function parameters, but the relation 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 (iRaw) can be calculated in specific parts of the lung. It thus gives a clearer and more individualized 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. With this study, we therefore 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.
3. **Materials and methods**

   a. **Study population**

   Subject recruitment for this case-control study was based on an existing patient cohort at the Antwerp University Hospital including preterm infants born before 31 weeks gestational age (GA) who needed mechanical ventilation since the day of birth, now aged 13 to 16 years old 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.

   b. **Data collection**

      i. **Clinical data**

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

      II. **Questionnaires**

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

   c. **Physical examination**

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

   d. **Lung function testing**

   Lung function testing comprised of conventional spirometry with bronchodilator response (salbutamol), body plethysmography, nitrogen multiple-breath washout testing (N₂MBW) and a single breath carbon monoxide diffusion test. A positive bronchodilator response was defined as an increase in FEV₁ > 12% after administration of salbutamol. More details are provided in Appendix 1.

   e. **CT imaging**

   All patients underwent an unenhanced low-dose MDCT of the lungs at total lung capacity (TLC) (i.e. at maximal inspiration) and at functional residual capacity (FRC) (i.e. after normal expiration). Details are provided in Appendix 1. The CT images were reviewed by 5 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 9 different structural abnormalities (see Table 4 and Appendix 1) [16].

   f. **Functional Respiratory Imaging**

   FRI analyses were conducted by Fluida (Kontich, Belgium). Methods for this imaging technique have been described in detail elsewhere [21]. In short, patient-specific anatomical structures of the lungs are reconstructed via segmentation of MDCT images. Air flow is simulated within this 3D airway model, thus allowing a numeric, quantified assessment of several structural and functional airway parameters (Figure 1). Detailed methods are provided in the online supplement. 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.
g. Statistical analyses

Statistical analyses were conducted in SPSS version 26 (IBM Corporation, USA). Univariate analysis, correlations and multiple regression were computed using appropriate tests and modelling strategies (see 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 Auckland CT scores. For all analyses, p<0.05 was considered statistically significant.
4. Results

a. Population demographics (Figure 2 and Table 1)

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. General demographic information is shown in Table 1. Patients with BPD had lower GA at birth (p <0.01) and lower birth weight (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 between 13 and 16 years old. There was no significant difference between the two groups in occurrence of asthma, frequent respiratory symptoms (e.g. wheezing, waking up at night, dyspnea, exercise intolerance, nocturnal cough), frequent respiratory infections or fatigue, nor in any other clinical outcome parameter.

b. Lung function testing (Table 2)

   i. Spirometry

BPD patients had significantly lower FEV\textsubscript{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 of asthma between both groups (p = 0.3). There were no significant differences in FEV\textsubscript{1}, FVC or MEFs.

   ii. Body plethysmography

FRC volumes were significantly higher in the BPD group (p = 0.02), but there was no difference in TLC or RV 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.

   iii. Diffusion capacity

Diffusion capacity was impaired in subjects with BPD, expressed by a lower DLCO/VA (p = 0.01).

   iv. N\textsubscript{2}MBW

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

c. CT imaging

Overall interobserver variability was good and there were no differences in ICCs between radiologists and non-radiologists (see Table 3 and Appendix 2 in the online supplement). 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 Auckland scoring system. We did not observe any significant difference in total Auckland CT score or any of the assessed parameters between both groups. There was a trend towards more emphysema in the BPD group (p = 0.08). Results are shown in Table 4.

d. Functional Respiratory Imaging (Table 5)

   i. Lung volumes

FRI analysis showed higher FRC lobar volumes in adolescents with BPD in all lobes (p≤0.01). When measured at TLC, the differences were not statistically significant; indicating air trapping in the BPD group (see Figure 3 and 4).
ii. Airway volumes (online supplement, Appendix 2, Figure E1)

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.

iii. 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; see Figure 5).

iv. Emphysema

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

v. Air trapping

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

vi. Vasculature

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

vii. Ventilation perfusion

V/Q ratios were not different between BPD patients and preterm controls.

e. Integrating clinical outcomes, lung function and lung structure

As described above, 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 respectively. Detailed results are shown in Table 6. After exclusion of outliers for air trapping on FRI, multiple linear regression showed that a model containing BPD status and birth weight 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 GA 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. Airway resistance on FRI analysis also correlated significantly with MEF25, MEF50, MEF25-75 as well as specific airway resistance as measured by conventional spirometry (see online supplement, appendix 2, Table E1). Air trapping on FRI correlated with body box lung volume measurements (see online supplement, appendix 2, Table E2).
5. 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 air trapping and 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, more air trapping and impaired diffusion capacity in the BPD group. Auckland 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 previously been described in adolescents with a history of preterm birth [22]. Several authors also 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]. We also found increased FRCs in BPD patients but no 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 also 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 Auckland CT score between the BPD group and the preterm control group [16, 24]. Previous evidence as well as our study suggest 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 volumes in the BPD group, indicating air trapping. The FRI variable ‘air trapping’ was also increased in the BPD group. Interestingly, the peripheral airway resistance was increased in the BPD group. Several authors have hypothesized 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, 35–37]. 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 birth weight 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 GA.
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 hypothesized 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. Also, the power of our study may not be sufficient to detect significant changes in blood vessel volume between BPD patients and preterm controls.

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 3 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. Also, 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. On the other hand, 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 ionizing 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 [38, 39]. This is of particular importance in patients with a history of preterm birth, who are often exposed to considerable amounts of ionizing radiation. Implicitly, considering 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.
6. **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.
7. **Funding**

This research is supported by grants from the Josephine Neiman Foundation and Vitalaire to the UZA Foundation.
### 8. Tables

<table>
<thead>
<tr>
<th></th>
<th>No BPD (n=15)</th>
<th>BPD (n=22)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (wks)</td>
<td>29 [26; 30.6]</td>
<td>27.93 [24.9; 30.3]</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>1240 [637; 1904]</td>
<td>973 [469; 1640]</td>
<td>0.04*</td>
</tr>
<tr>
<td>Surfactant</td>
<td>5 (33%)</td>
<td>15 (68%)</td>
<td>0.04*</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>14 (93%)</td>
<td>21 (95%)</td>
<td>1</td>
</tr>
<tr>
<td>Days on ventilator</td>
<td>3 [1; 11]</td>
<td>9 [1; 45]</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Days on O₂</td>
<td>5 [1; 27]</td>
<td>54.50 [30; 133]</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>RDS</td>
<td>10 (67%)</td>
<td>19 (86%)</td>
<td>0.23</td>
</tr>
<tr>
<td>IUGR</td>
<td>2 (14%)</td>
<td>3 (14%)</td>
<td>1</td>
</tr>
<tr>
<td>Age at follow-up</td>
<td>15.2 [13.5; 16.7]</td>
<td>15.2 [14; 16.9]</td>
<td>0.99</td>
</tr>
<tr>
<td>Psychomotor retardation</td>
<td>8 (57%)</td>
<td>13 (59%)</td>
<td>0.91</td>
</tr>
<tr>
<td>Several respiratory infections during the last 2 years</td>
<td>2 (14%)</td>
<td>0 (0%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Reversibility (ΔFEV₁&gt;12%)</td>
<td>2 (13%)</td>
<td>7 (32%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Inhalers</td>
<td>2 (14%)</td>
<td>3 (14%)</td>
<td>1</td>
</tr>
<tr>
<td>Wheezing (last 12m)</td>
<td>1 (8%)</td>
<td>6 (30%)</td>
<td>0.20</td>
</tr>
<tr>
<td>Nocturnal cough (last 12m)</td>
<td>2 (17%)</td>
<td>1 (6%)</td>
<td>0.55</td>
</tr>
<tr>
<td>Chronic cough</td>
<td>1 (10%)</td>
<td>1 (5%)</td>
<td>1</td>
</tr>
<tr>
<td>Perennial rhinitis</td>
<td>2 (20%)</td>
<td>3 (16%)</td>
<td>1</td>
</tr>
</tbody>
</table>

**Table 1.** Patient characteristics. Expressed as median, minimum and maximum and corresponding P-values for continuous variables. Categorical variables are expressed as total number per group in which the symptom was present and % affected per group. Abbreviations: wks=weeks, g=grams, m=months, RDS= respiratory distress syndrome, IUGR = intrauterine growth retardation. Chronic cough was defined as daily cough for more than 4 weeks in the last year. Perennial rhinitis was defined as rhinitis or sneezing without concurrent infections during the last 12 months.
<table>
<thead>
<tr>
<th></th>
<th>No BPD (n=15)</th>
<th>BPD (n=22)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC %</td>
<td>111 [67; 122]</td>
<td>108.5 [77; 138]</td>
<td>0.94</td>
</tr>
<tr>
<td>FVC after BD %</td>
<td>109 [70; 122]</td>
<td>108.5 [71; 141]</td>
<td>0.66</td>
</tr>
<tr>
<td>FEV₁ %</td>
<td>104 [69; 121]</td>
<td>98 [80; 125]</td>
<td>0.20</td>
</tr>
<tr>
<td>FEV₁ after BD %</td>
<td>114 [73; 124]</td>
<td>106 [78; 128]</td>
<td>0.63</td>
</tr>
<tr>
<td>Δ FEV₁</td>
<td>4 [-2; 13]</td>
<td>7.50 [-3; 33]</td>
<td>0.10</td>
</tr>
<tr>
<td>FEV₁ %</td>
<td>98 [88; 110]</td>
<td>87 [68; 111]</td>
<td>0.02*</td>
</tr>
<tr>
<td>FEV₁ after BD %</td>
<td>102 [96; 115]</td>
<td>95 [84; 115]</td>
<td>0.04*</td>
</tr>
<tr>
<td>PEF %</td>
<td>94.5 [66.1; 129.9]</td>
<td>87 [71.1; 114.5]</td>
<td>0.20</td>
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<tr>
<td>MEF50 %</td>
<td>92 [57; 142]</td>
<td>66 [48; 163]</td>
<td>0.06</td>
</tr>
<tr>
<td>MEF50 after BD %</td>
<td>101 [71; 153]</td>
<td>89.5 [61; 171]</td>
<td>0.13</td>
</tr>
<tr>
<td>MEF25 %</td>
<td>75 [49; 124]</td>
<td>56.5 [40; 201]</td>
<td>0.14</td>
</tr>
<tr>
<td>MEF25 after BD %</td>
<td>97 [57; 148]</td>
<td>78.5 [48; 201]</td>
<td>0.14</td>
</tr>
<tr>
<td>Airway resistance</td>
<td>1.02 [0.67; 1.74]</td>
<td>1.29 [0.63; 2.46]</td>
<td>0.14</td>
</tr>
<tr>
<td>RV %</td>
<td>107 [56; 179]</td>
<td>135.5 [80; 207]</td>
<td>0.09</td>
</tr>
<tr>
<td>TLC %</td>
<td>111 [75; 128]</td>
<td>117.5 [77; 139]</td>
<td>0.22</td>
</tr>
<tr>
<td>FRC %</td>
<td>96 [79; 136]</td>
<td>121 [88; 168]</td>
<td>0.02*</td>
</tr>
<tr>
<td>TCO/VA</td>
<td>1.79 [1.34; 2.61]</td>
<td>1.60 [1.17; 2.09]</td>
<td>0.01*</td>
</tr>
<tr>
<td>TCO/VA %</td>
<td>87 [64; 127]</td>
<td>78 [58; 102]</td>
<td>0.02*</td>
</tr>
<tr>
<td>LCI</td>
<td>5.40 [4.74; 6.37]</td>
<td>5.42 [4.66; 7.47]</td>
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<tr>
<td>VA/TLC %</td>
<td>0.98 [0.91; 1.07]</td>
<td>0.97 [0.88; 1.07]</td>
<td>0.25</td>
</tr>
<tr>
<td>Reversibility</td>
<td>13%</td>
<td>32%</td>
<td>0.26</td>
</tr>
</tbody>
</table>

**Table 2.** Lung function testing. Expressed as median, minimum, maximum and corresponding P-values. Abbreviations: BD=bronchodilation. Bronchodilation was performed by means of salbutamol inhalation.
<table>
<thead>
<tr>
<th>Observers</th>
<th>ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total CT score</strong></td>
<td></td>
</tr>
<tr>
<td>All observers combined</td>
<td>0.8 [0.7; 0.9]</td>
</tr>
<tr>
<td>Radiologists</td>
<td>0.6 [0.3; 0.8]</td>
</tr>
<tr>
<td>Non-radiologists</td>
<td>0.7 [0.5; 0.9]</td>
</tr>
<tr>
<td><strong>Linear or triangular subpleural opacities</strong></td>
<td></td>
</tr>
<tr>
<td>All observers combined</td>
<td>0.7 [0.5; 0.9]</td>
</tr>
<tr>
<td>Radiologists</td>
<td>0.5 [0.03; 0.7]</td>
</tr>
<tr>
<td>Non-radiologists</td>
<td>0.8 [0.5; 0.9]</td>
</tr>
<tr>
<td><strong>Mosaic perfusion on inspiration</strong></td>
<td></td>
</tr>
<tr>
<td>All observers combined</td>
<td>0.7 [0.5; 0.8]</td>
</tr>
<tr>
<td>Radiologists</td>
<td>0.6 [0.2; 0.8]</td>
</tr>
<tr>
<td>Non-radiologists</td>
<td>0.9 [0.7; 0.9]</td>
</tr>
<tr>
<td><strong>Air trapping</strong></td>
<td></td>
</tr>
<tr>
<td>All observers combined</td>
<td>0.9 [0.86; 0.95]</td>
</tr>
<tr>
<td>Radiologists</td>
<td>0.8 [0.7; 0.9]</td>
</tr>
<tr>
<td>Non-radiologists</td>
<td>0.9 [0.8; 0.96]</td>
</tr>
<tr>
<td><strong>Decreased bronchoarterial ratio</strong></td>
<td></td>
</tr>
<tr>
<td>All observers combined</td>
<td>0.6 [0.4; 0.8]</td>
</tr>
<tr>
<td>Radiologists</td>
<td>0.5 [0.1; 0.7]</td>
</tr>
<tr>
<td>Non-radiologists</td>
<td>0.5 [-0.05; 0.7]</td>
</tr>
<tr>
<td><strong>Bronchiectasis</strong></td>
<td></td>
</tr>
<tr>
<td>All observers combined</td>
<td>0.5 [0.3; 0.7]</td>
</tr>
<tr>
<td>Radiologists</td>
<td>-0.07 [-0.9; 0.4]</td>
</tr>
<tr>
<td>Non-radiologists</td>
<td>-0.03 [-0.97; 0.5]</td>
</tr>
<tr>
<td><strong>Peribronchial thickening</strong></td>
<td></td>
</tr>
<tr>
<td>All observers combined</td>
<td>0.4 [0.1; 0.6]</td>
</tr>
<tr>
<td>Radiologists</td>
<td>0.1 [-0.07; 0.3]</td>
</tr>
<tr>
<td>Non-radiologists</td>
<td>0.3 [-0.3; 0.6]</td>
</tr>
<tr>
<td><strong>Bullae or blebs</strong></td>
<td></td>
</tr>
<tr>
<td>All observers combined</td>
<td>/</td>
</tr>
<tr>
<td>Radiologists</td>
<td>/</td>
</tr>
<tr>
<td>Non-radiologists</td>
<td>/</td>
</tr>
<tr>
<td><strong>Emphysema</strong></td>
<td></td>
</tr>
<tr>
<td>All observers combined</td>
<td>-0.09 [-0.8; 0.4]</td>
</tr>
<tr>
<td>Radiologists</td>
<td>/</td>
</tr>
<tr>
<td>Non-radiologists</td>
<td>/</td>
</tr>
<tr>
<td><strong>Collapse or consolidation</strong></td>
<td></td>
</tr>
<tr>
<td>All observers combined</td>
<td>0.9 [0.87; 0.95]</td>
</tr>
<tr>
<td>Radiologists</td>
<td>0.8 [0.7; 0.9]</td>
</tr>
<tr>
<td>Non-radiologists</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 3. Interobserver variability of the Aukland CT score; presented as intraclass correlation coefficients with 95% confidence intervals for all observers combined, radiologists (MS, AS, HEA) and non-radiologists’ (KV, EL) ratings respectively. ICCs for ‘bullae or blebs’ and ‘emphysema’ could not be computed given these findings were only present in one or two cases, and not scored as present by all observers.
<table>
<thead>
<tr>
<th></th>
<th>no BPD (n = 15)</th>
<th>BPD (n = 22)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total CT score</td>
<td>10 [3.6; 13.8]</td>
<td>9.1 [4.2; 20]</td>
<td>0.7</td>
</tr>
<tr>
<td>Linear or triangular</td>
<td>2.4 [0.6; 4.8]</td>
<td>2.1 [0.4; 5]</td>
<td>0.8</td>
</tr>
<tr>
<td>subpleural opacities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mosaic perfusion on</td>
<td>0 [0; 3.2]</td>
<td>0.1 [0; 2.2]</td>
<td>0.7</td>
</tr>
<tr>
<td>inspiration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Air trapping</td>
<td>1 [0; 3.6]</td>
<td>0.3 [0; 5.2]</td>
<td>0.2</td>
</tr>
<tr>
<td>Decreased</td>
<td>1.4 [0.4; 3.8]</td>
<td>1 [0; 4.4]</td>
<td>0.4</td>
</tr>
<tr>
<td>bronchoarterial ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>0 [0; 0.4]</td>
<td>0 [0; 2]</td>
<td>0.9</td>
</tr>
<tr>
<td>Peribronchial thickening</td>
<td>4.2 [0.6; 5.6]</td>
<td>4.5 [2; 5.4]</td>
<td>0.8</td>
</tr>
<tr>
<td>Bullae or blebs</td>
<td>0 [0; 0.4]</td>
<td>0 [0; 0.2]</td>
<td>0.9</td>
</tr>
<tr>
<td>Emphysema</td>
<td>0 [0; 0.8]</td>
<td>0 [0; 1]</td>
<td>0.08</td>
</tr>
<tr>
<td>Collapse or consolidation</td>
<td>0 [0; 0.2]</td>
<td>0 [0; 1.2]</td>
<td>0.9</td>
</tr>
</tbody>
</table>

**Table 4.** Mean Auckland CT score components, expressed as median, minimum, maximum and corresponding p-values.
<table>
<thead>
<tr>
<th></th>
<th>No BPD (n=15)</th>
<th>BPD (n=22)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lung volumes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FRC_V lobe_total (l)</td>
<td>2.1 (+0.74)</td>
<td>2.70 (+0.71)</td>
<td>&lt; 0.01*</td>
</tr>
<tr>
<td>FRC_V lobe_lower (l)</td>
<td>1.0 (+0.43)</td>
<td>1.30 (+0.43)</td>
<td>0.01*</td>
</tr>
<tr>
<td>FRC_V lobe_upper (l)</td>
<td>1.0 (+0.33)</td>
<td>1.33 (+0.40)</td>
<td>&lt; 0.01*</td>
</tr>
<tr>
<td>FRC_pred V lobe_total (%)</td>
<td>94.5 (+17.2)</td>
<td>115.8 (+23.5)</td>
<td>&lt; 0.01*</td>
</tr>
<tr>
<td>FRC_pred V lobe_lower (%)</td>
<td>103.67 (+26.1)</td>
<td>124 (+35)</td>
<td>0.05</td>
</tr>
<tr>
<td>FRC_pred V lobe_upper (%)</td>
<td>87.1 (+14.1)</td>
<td>102.3 (+23.9)</td>
<td>0.02*</td>
</tr>
<tr>
<td>TLC_V lobe_total (l)</td>
<td>4.42 (+1.40)</td>
<td>5.06 (+0.90)</td>
<td>0.13</td>
</tr>
<tr>
<td>TLC_V lobe_lower (l)</td>
<td>2.39 (+0.90)</td>
<td>2.60 (+0.82)</td>
<td>0.46</td>
</tr>
<tr>
<td>TLC_V lobe_upper (l)</td>
<td>2.03 (+0.53)</td>
<td>2.32 (+0.57)</td>
<td>0.13</td>
</tr>
<tr>
<td>FRC_pred V lobe_total (%)</td>
<td>97.23 (+15.18)</td>
<td>105.07 (+16.91)</td>
<td>0.32</td>
</tr>
<tr>
<td>FRC_pred V lobe_lower (%)</td>
<td>103.49 (+22.21)</td>
<td>106.27 (+27.27)</td>
<td>0.80</td>
</tr>
<tr>
<td>TLC_pred V lobe_upper (%)</td>
<td>90.85 (+11.37)</td>
<td>96.53 (+16.65)</td>
<td>0.26</td>
</tr>
<tr>
<td><strong>Airway volumes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FRC_siVaw_central (ml/l)</td>
<td>5.66 (+1.43)</td>
<td>5.36 (+0.67)</td>
<td>&lt; 0.01*</td>
</tr>
<tr>
<td>FRC_siVaw_distal (ml/l)</td>
<td>0.98 (+0.33)</td>
<td>0.86 (+0.25)</td>
<td>0.15</td>
</tr>
<tr>
<td>FRC_siVaw_total (ml/l)</td>
<td>6.64 (+1.66)</td>
<td>6.22 (+0.80)</td>
<td>&lt; 0.01*</td>
</tr>
<tr>
<td>FRC_siVaw_lower (ml/l)</td>
<td>1.10 (+0.39)</td>
<td>1.03 (+0.24)</td>
<td>0.29</td>
</tr>
<tr>
<td>FRC_siVaw_upper (ml/l)</td>
<td>0.86 (+0.30)</td>
<td>0.81 (+0.24)</td>
<td>0.14</td>
</tr>
<tr>
<td>TLC_siVaw_central (ml/l)</td>
<td>4.57 (+0.90)</td>
<td>4.53 (+0.56)</td>
<td>0.20</td>
</tr>
<tr>
<td>TLC_siVaw_distal (ml/l)</td>
<td>1.29 (+0.44)</td>
<td>1.05 (+0.31)</td>
<td>0.04*</td>
</tr>
<tr>
<td>TLC_siVaw_total (ml/l)</td>
<td>5.87 (+1.04)</td>
<td>5.58 (+0.73)</td>
<td>0.07</td>
</tr>
<tr>
<td>TLC_siVaw_lower (ml/l)</td>
<td>1.39 (+0.51)</td>
<td>1.22 (+0.51)</td>
<td>0.86</td>
</tr>
<tr>
<td>TLC_siVaw_upper (ml/l)</td>
<td>1.18 (+0.39)</td>
<td>1.00 (+0.28)</td>
<td>0.33</td>
</tr>
<tr>
<td><strong>Airway resistance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FRC_siRaw_central</td>
<td>0.084 (+0.023)</td>
<td>0.084 (+0.03)</td>
<td>0.84</td>
</tr>
<tr>
<td>FRC_siRaw_distal</td>
<td>0.19 (+0.11)</td>
<td>0.33 (+0.22)</td>
<td>0.02*</td>
</tr>
<tr>
<td>FRC_siRaw_total</td>
<td>0.27 (+0.12)</td>
<td>0.42 (+0.24)</td>
<td>0.03*</td>
</tr>
<tr>
<td>FRC_siRaw_lower</td>
<td>0.17 (+0.10)</td>
<td>0.32 (+0.21)</td>
<td>0.02*</td>
</tr>
<tr>
<td>FRC_siRaw_upper</td>
<td>0.23 (+0.14)</td>
<td>0.34 (+0.26)</td>
<td>0.19</td>
</tr>
<tr>
<td>TLC_siRaw_central</td>
<td>0.11 (+0.03)</td>
<td>0.10 (+0.03)</td>
<td>0.49</td>
</tr>
<tr>
<td>TLC_siRaw_distal</td>
<td>0.21 (+0.14)</td>
<td>0.29 (+0.15)</td>
<td>0.04*</td>
</tr>
<tr>
<td>TLC_siRaw_total</td>
<td>0.31 (+0.15)</td>
<td>0.39 (+0.17)</td>
<td>0.14</td>
</tr>
<tr>
<td>TLC_siRaw_lower</td>
<td>0.23 (+0.17)</td>
<td>0.31 (+0.20)</td>
<td>0.11</td>
</tr>
<tr>
<td>TLC_siRaw_upper</td>
<td>0.20 (+0.12)</td>
<td>0.28 (+0.14)</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Emphysema</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TLC_emphysema_total (%) per lobe</td>
<td>1.03 (+1.17)</td>
<td>1.67 (+1.40)</td>
<td>0.14</td>
</tr>
<tr>
<td>TLC_emphysema_lower (%) per lobe</td>
<td>1.10 (+1.44)</td>
<td>1.79 (+1.60)</td>
<td>0.14</td>
</tr>
<tr>
<td>TLC_emphysema_upper (%) per lobe</td>
<td>0.98 (0.97)</td>
<td>1.50 (+1.23)</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>Air trapping</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FRC_airtrapping_total (%) per lobe</td>
<td>2.55 (+2.11)</td>
<td>9.40 (+6.62)</td>
<td>&lt; 0.01*</td>
</tr>
<tr>
<td>FRC_airtrapping_lower (%) per lobe</td>
<td>1.88 (+2.16)</td>
<td>6.51 (+4.97)</td>
<td>&lt; 0.01*</td>
</tr>
<tr>
<td>FRC_airtrapping_upper (%) per lobe</td>
<td>3.17 (+2.48)</td>
<td>11.77 (+8.61)</td>
<td>&lt; 0.01*</td>
</tr>
<tr>
<td><strong>Vasculature</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TLC_blood absolute_total (ml)</td>
<td>129.46 (+32.76)</td>
<td>126.51 (+31.32)</td>
<td>0.78</td>
</tr>
<tr>
<td>TLC_blood absolute_lower (ml)</td>
<td>71.52 (+20.30)</td>
<td>69.49 (+19.49)</td>
<td>0.76</td>
</tr>
<tr>
<td>TLC_blood absolute_upper (ml)</td>
<td>71.52 (+20.30)</td>
<td>69.49 (+19.49)</td>
<td>0.61</td>
</tr>
<tr>
<td>TLC_blood relative_total (%) per lobe</td>
<td>3.58 (+1.50)</td>
<td>2.90 (+0.71)</td>
<td>0.14</td>
</tr>
<tr>
<td>TLC_blood relative_lower (%) per lobe</td>
<td>3.71 (+1.55)</td>
<td>3.10 (+0.91)</td>
<td>0.13</td>
</tr>
<tr>
<td>TLC_blood relative_upper (%) per lobe</td>
<td>3.44 (+1.48)</td>
<td>2.70 (+0.58)</td>
<td>0.14</td>
</tr>
</tbody>
</table>
Table 5. FRI parameters in the BPD versus preterm control group. Expressed as mean, standard deviation and corresponding P-values. Vascular parameters are expressed as amount of volume per lobe or as % per lobe respectively.

<table>
<thead>
<tr>
<th>Ventilation perfusion</th>
<th>V/Q distribution_total</th>
<th>1887.95 ( \pm 649.46 )</th>
<th>1952.79 ( \pm 644.99 )</th>
<th>0.77</th>
</tr>
</thead>
<tbody>
<tr>
<td>V/Q distribution_lower</td>
<td>1957.90 ( \pm 605.46 )</td>
<td>1924.48 ( \pm 579.41 )</td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td>V/Q distribution_upper</td>
<td>1800.85 ( \pm 700.28 )</td>
<td>1844.95 ( \pm 610.32 )</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>Variable</td>
<td>$R^2$</td>
<td>$B$</td>
<td>p-value</td>
<td></td>
</tr>
<tr>
<td>----------------------------------</td>
<td>-------</td>
<td>--------------</td>
<td>-------------</td>
<td></td>
</tr>
<tr>
<td>BPD</td>
<td>0.33</td>
<td>5.22 [2.57; 7.88]</td>
<td>&lt; 0.001*</td>
<td></td>
</tr>
<tr>
<td>Oxygen therapy (days)</td>
<td>0.21</td>
<td>0.06 [0.02; 0.11]</td>
<td>0.01*</td>
<td></td>
</tr>
<tr>
<td>Preterm contractions</td>
<td>0.19</td>
<td>-3.86 [-6.89; -0.82]</td>
<td>0.02*</td>
<td></td>
</tr>
<tr>
<td>Oxygen therapy on day 7</td>
<td>0.17</td>
<td>4.07 [0.77; 7.37]</td>
<td>0.02*</td>
<td></td>
</tr>
<tr>
<td>Oxygen therapy on day 14</td>
<td>0.23</td>
<td>4.42 [1.39; 7.44]</td>
<td>0.001*</td>
<td></td>
</tr>
<tr>
<td>Gestational age (wks)</td>
<td>0.14</td>
<td>-1.03 [-2.01; -0.06]</td>
<td>0.04*</td>
<td></td>
</tr>
<tr>
<td>Birth weight</td>
<td>0.14</td>
<td>-0.01 [-0.01; 0.00]</td>
<td>0.04*</td>
<td></td>
</tr>
</tbody>
</table>

**Table 6.** Linear regression with FRC_air trapping_total and FRC_siRaw_lower as dependent variables respectively. Slopes (unstandardized coefficients) and corresponding 95% confidence intervals as well as significance levels are shown. (A) Univariate analysis FRC_air trapping_total, (B) Multiple linear regression model for FRC_air trapping_total and the corresponding equation. $R^2 = 0.39$; p = 0.001. (C) Univariate analysis for FRC_siRaw_distal. Multiple linear regression was not performed given the multicollinearity between ‘BPD’ and ‘O$_2$ therapy at 36w GA’.
9. References


Figure 1. Visualisation of the functional respiratory imaging reconstruction process in a BPD patient (figures 1a and 1b) and a preterm control (figure 1c and 1d). From the native CT image (figures 1a and 1c), the patient-specific 3D airway is computed (figures 1b and 1d). Functionality is added by simulating air flow in this patient-specific 3D airway model.
Figure 2. Flowchart subject recruitment

141 patients JDD

79 patients contacted

37 patients included

22 BPD

Mild BPD N = 3

Moderate and severe BPD N = 19

62 patients
No up-to-date contact details or contact attempts unsuccessful

60 patients
Refused to participate in study

15 no BPD
Figure 3. Air trapping measured by body plethysmography, CT and FRI. The preterm control group is shown on the left, the BPD group on the right. (A) FRC measured by body plethysmography (p = 0.02); (B) TLC measured by body plethysmography (p = 0.22); (C) Air trapping in all lobes combined assessed with the Auckland CT score (mean of all observers, p = 0.9); (D) Air trapping in all lobes combined assessed with FRI (p < 0.001).
Figure 4. Functional respiratory imaging: visualisation of air trapping in a BPD subject (figures 4 and 4c) and matched preterm control (figures 4b and 4d) showing marked air trapping in all lung lobes in the BPD subject. Figures 3b and 3c show the relative amount of air trapping per lung region.
Figure 5. Functional respiratory imaging: visualisation of airway resistance measured at TLC in a BPD patient compared to a preterm control subject. In this visualization, 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).
Appendix 1. Detailed methods

a. Study population

Subject recruitment was based on an existing patient cohort at the Antwerp University Hospital included in a study investigating the relationship between histologic chorioamnionitis and early inflammatory variables in preterm infants [1]. Recruitment for this cohort spanned from September 1999 and February 2002. The inclusion criteria were as follows: (1) born at a gestational age < 31 weeks; (2) need for mechanical ventilation starting from day one. Patients who were mechanically ventilated for non-pulmonary reasons (e.g. diaphragmatic hernia, congenital malformations, cardiac defects, ...) were excluded from the study. Additionally, for the present study, patients with severe mental or physical impairment were excluded since some degree of cooperation is needed for lung function testing and FRI imaging.

b. Data collection

All clinical follow-up data into adolescence, including a medical history (partly assessed through questionnaires), lung function testing and MDCT imaging were obtained during a single clinic visit at the Antwerp University Hospital.

1. Clinical data

The following clinical data were collected: (1) maternal and pregnancy details; (2) neonatal data such as gestational age, birth weight, number of days on ventilator, number of days on oxygen, diagnosis of RDS based on Edwards score [2], diagnosis of BPD and severity, administration of surfactant, administration of steroids. BPD was defined as the need for oxygen > 21% for at least 28 days. Severity was assessed at 36 weeks post-menstrual age or discharge (whichever came first). BPD was categorized as ‘mild’ if the patient was breathing room air, ‘moderate’ if there was oxygen need < 30% and as ‘severe’ if oxygen needs exceeded 30%. Because the percentage of oxygen at any given moment was not recorded in the original study, we could only discriminate BPD patients into 2 groups: mild BPD versus moderate and severe BPD combined.

II. Questionnaires

Questionnaires were used to assess clinical outcome and quality of life at time of inclusion in the present study. These questionnaires comprised 4 domains: (1) family history, including but not limited to pregnancy details, (2) patient history: illnesses, infections, surgeries, hospital admissions,... (3) psychomotor development; (4) current patient characteristics focusing on the respiratory tract, based on the ISAAC-questionnaire and assessing for, amongst other variables, respiratory infections, asthma, atopic constitution, use of inhalers, (nocturnal) cough, wheezing, exercise intolerance,... [3]. The questionnaire was completed in the presence of the adolescent, his or her parents and a trained investigator (MA, NE or MS).

c. Physical examination

Upon their clinic visit, patients received a physical examination (cardiopulmonary auscultation, abdominal auscultation, percussion and palpation). Their current weight, height, blood pressure, Mallampati score and tonsil score were recorded.

d. Lung function testing

Lung function testing comprised conventional spirometry (Jaeger Masterscreen PFT, CareFusion), body box plethysmography (Jaeger Masterscreen Body, CareFusion), determination of the lung clearance index (LCI) via N2-washout (Exhalyzer D with Spiroware software, Eco Medics) and a single breath carbon monoxide diffusion test (Jaeger MasterScreen, CareFusion). All tests were repeated after administration of a bronchodilator (salbutamol). Salbutamol was administered after HRCT with
FRI. Thus, patients first underwent lung function testing before HRCT, were then administered a bronchodilator and subsequently underwent a second round of lung function testing. A positive bronchodilator response was defined as an increase in $\text{FEV}_1 > 12\%$ after administration of salbutamol.

e. **CT imaging**

After the first round of lung function testing, but before administration of the bronchodilator, all patients underwent an unenhanced low-dose MDCT (GE VCT Lightspeed 64-slice scanner, GE Healthcare). The scanned area spanned from the upper part of the trachea to the diaphragm. To enable FRI analysis, HRCT images were obtained at 2 specific lung levels: at total lung capacity (TLC) (i.e., at maximal inspiration) and at functional residual capacity (FRC) (i.e., after normal expiration). In order to capture a clear image without artefacts, the patient had to perform a breath-hold manoeuvre at TLC and FRC for a few seconds. Breathing was monitored using ‘Blue Cherry’ technology that provides spirometry information during the scanning process (Geratherm, Germany). The mean total radiation dose was 2.4 mSv. The CT images were reviewed by 5 independent observers who were blinded to the outcome. Three observers (MS, AS, HEA) were experienced radiologists, two observers (KV, EL) did not have a background in radiology but received prior training in CT scoring systems for BPD. CTs were reviewed using the Aukland scoring system, a validated scoring system assessing the presence or absence of the following structural abnormalities: (1) linear or triangular subpleural opacities, (2) mosaic perfusion on inspiration, (3) air trapping, (4) decreased bronchoarterial ratio, (5) bronchiectasis, (6) peribronchial thickening, (7) bullae or blebs, (8) emphysema and (9) collapse or consolidation [4]. A training session for all observers was provided before scoring the patients’ images.

f. **Functional Respiratory Imaging**

HRCT images were imported into Mimics, a commercial FDA-approved medical image processing software package (Materialise, Leuven, Belgium; Food and Drug Administration, K073468; CE certificate, BE 05/1191 CE01). This software package converts HRCT images into patient-specific, three-dimensional computer models of the lung structures. The FRI process includes segmentation of the lung volumes at FRC and TLC from the HRCT images by using a HU threshold of [-1024; -400]. In addition, the fissures that separate the individual lung lobes are identified. By using the fissure lines as cutting planes, the individual lobe volumes can be determined. The airway tree, i.e., intraluminal air, could be segmented down to bronchi with a diameter of about 1–2 mm. Beyond this point, the HRCT resolution is insufficient to distinguish alveolar and intraluminal air. A typical airway model includes 5–10 generations, depending mainly on the disease state of the individual patient.

Functionality is added to the static segmented images by applying computational fluid dynamics methods to characterize airway resistance. The airway models are converted into a computational grid in order to solve the Navier-Stokes flow equations numerically, using commercial software packages (Ansys Inc., Canonsburg, PA, USA). Resistance was defined as the total pressure drop over an airway divided by the flow rate through that airway. Air trapping can be determined through segmentation based on Hounsfield unit (HU) thresholds of [-1024; -850] performed on the FRC scan. Blood vessels density and emphysema score can be extracted the same way but from the TLC scan, using HU thresholds of [-600; 600] and [-1024; -950], respectively.

g. **Statistical analyses**

Statistical analyses were computed in SPSS version 24 (IBM Corporation, USA). Normality was assessed based on graphical representation of the data as well as the Kolmogorov-Smirnov test. The independent t-test and Mann-Whitney U test were used to compare categorical and continuous variables as deemed appropriate after normality assessment. When appropriate, the chi-square or Fisher exact tests were used to compare 2 categorical variables. Spearman correlation coefficients were calculated to assess the relation between 2 continuous variables. Logistic regression was used for building prediction models with a categorical dependent variable, linear regression for continuous dependent variables. Intraclass correlation coefficients (ICCs) were computed to evaluate interobserver variability of the Aukland CT scores. For all analyses, $p \leq 0.05$ was considered statistically significant.
Appendix 2. Supplementary results

a. CT imaging

ICCs for the Auckland CT score were calculated for the following groups: (1) all 5 observers combined, (2) radiologists (MS, AS, HEA) and (3) non-radiologists (KV, EL). Interobserver variability (MS, AS, HEA, KV, EL) of total CT score was good (ICC=0.8). ICCs for the items of the Auckland CT score are shown in Table 3 and Appendix 2. Overall, there were no differences in ICCs between radiologists and non-radiologists. Therefore, the mean of all observers’ scores was obtained and used in all subsequent analyses. We did not observe any significant difference in total Auckland CT score or one of the assessed parameters between both groups. There was a trend towards more emphysema in the BPD group (p = 0.08). Results are shown in Table 4. In addition, when comparing CT scores for children with and without respiratory symptoms (wheezing, nocturnal cough, dyspnea, exercise intolerance) and for children with and without a physician-made asthma diagnosis, no significant differences in structural abnormalities on CT were observed.

b. Functional respiratory imaging

Figure E1. Functional respiratory imaging: visualisation of specific airway volumes. Specific airway volume is defined as the airway volume divided by the corresponding lobe volume. In this visualization, specific airway volumes of a representative BPD patient are compared to a representative preterm control patient. Thus, this image shows smaller specific airway volumes in the BPD patient compared to the preterm control (negative % values).
### c. Integrating clinical outcomes, lung function and lung structure

<table>
<thead>
<tr>
<th></th>
<th>FRC$_{siRaw}$</th>
<th>FRC$_{siRaw}$</th>
<th>FRC$_{siRaw}$</th>
<th>TLC$_{siRaw}$</th>
<th>TLC$_{siRaw}$</th>
<th>TLC$_{siRaw}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>_central</td>
<td>_distal</td>
<td>_total</td>
<td>_central</td>
<td>_distal</td>
<td>_total</td>
</tr>
<tr>
<td><strong>FEV$_1$</strong></td>
<td>-0.272</td>
<td>-0.133</td>
<td>-0.177</td>
<td>-0.336</td>
<td>-0.346</td>
<td>-0.372</td>
</tr>
<tr>
<td></td>
<td>0.103</td>
<td>0.433</td>
<td>0.295</td>
<td>0.042*</td>
<td>0.036*</td>
<td>0.023*</td>
</tr>
<tr>
<td><strong>ΔFEV$_1$</strong></td>
<td>0.142</td>
<td>0.421</td>
<td>0.433</td>
<td>0.503</td>
<td>0.594</td>
<td>0.570</td>
</tr>
<tr>
<td></td>
<td>0.402</td>
<td>0.009*</td>
<td>0.007*</td>
<td>0.002*</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
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<tr>
<td><strong>FVC</strong></td>
<td>-0.091</td>
<td>0.299</td>
<td>0.262</td>
<td>0.103</td>
<td>0.183</td>
<td>0.176</td>
</tr>
<tr>
<td></td>
<td>0.593</td>
<td>0.073</td>
<td>0.117</td>
<td>0.544</td>
<td>0.280</td>
<td>0.297</td>
</tr>
<tr>
<td><strong>FEV$_1$/FVC</strong></td>
<td>-0.188</td>
<td>-0.509</td>
<td>-0.504</td>
<td>-0.455</td>
<td>-0.691</td>
<td>-0.666</td>
</tr>
<tr>
<td></td>
<td>0.266</td>
<td>0.001*</td>
<td>0.001*</td>
<td>0.005*</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
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<tr>
<td><strong>MEF50</strong></td>
<td>-0.226</td>
<td>-0.385</td>
<td>-0.401</td>
<td>-0.471</td>
<td>-0.578</td>
<td>-0.626</td>
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<tr>
<td></td>
<td>0.179</td>
<td>0.019*</td>
<td>0.014*</td>
<td>0.003*</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
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<tr>
<td><strong>MEF25</strong></td>
<td>-0.268</td>
<td>-0.303</td>
<td>-0.325</td>
<td>-0.468</td>
<td>-0.534</td>
<td>-0.575</td>
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<tr>
<td></td>
<td>0.108</td>
<td>0.069</td>
<td>0.049*</td>
<td>0.004*</td>
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<td><strong>MEF75-25</strong></td>
<td>-0.276</td>
<td>-0.261</td>
<td>-0.287</td>
<td>-0.473</td>
<td>-0.469</td>
<td>-0.524</td>
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<tr>
<td><strong>Specific airway</strong></td>
<td>0.098</td>
<td>0.119</td>
<td>0.086</td>
<td>0.003*</td>
<td>0.003*</td>
<td>0.001*</td>
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<tr>
<td><strong>resistance</strong></td>
<td>0.175</td>
<td>0.416</td>
<td>0.422</td>
<td>0.527</td>
<td>0.583</td>
<td>0.582</td>
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<tr>
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<td>0.301</td>
<td>0.011*</td>
<td>0.009*</td>
<td>0.001*</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
</tr>
</tbody>
</table>

**Table E1.** Correlations between spirometry and FRI airway resistance analysis. Spearman or Pearson correlation coefficients and respective p-values are shown. Significant values are indicated with an asterisk. Spirometry parameters are expressed as % predicted, except for MEFs (l/s) and specific airway resistance (kPas). FRI airway resistance parameters are expressed in kPas.

<table>
<thead>
<tr>
<th></th>
<th>FRC$_{air\trapping_total}$</th>
<th>FRC$_{air\trapping_lower}$</th>
<th>FRC$_{air\trapping_upper}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RV</strong></td>
<td>0.663</td>
<td>0.650</td>
<td>0.615</td>
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<tr>
<td></td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td><strong>FRC</strong></td>
<td>0.685</td>
<td>0.715</td>
<td>0.618</td>
</tr>
<tr>
<td></td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td><strong>TLC</strong></td>
<td>0.582</td>
<td>0.622</td>
<td>0.554</td>
</tr>
<tr>
<td></td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
</tr>
</tbody>
</table>

**Table E2.** Correlations between body plethysmography lung volume measurements and FRI air trapping analysis. Spearman correlations and respective p-values are shown. Significant values are indicated with an asterisk. Lung volume parameters are expressed as % predicted; FRI air trapping parameters are expressed in % of air trapping compared to total lung volume, lower lobes and upper lobes respectively.
Appendix 3. Questionnaire

Patients and their parents were asked to complete the following questionnaire before the study clinic visit. Note: original questionnaires were distributed in Dutch.

A. Family history – to be completed by the parents

Please provide the details listed below.

1. Concerning the mother of the patient
   a. Age at the time of giving birth to the patient
   b. Ethnicity
   c. Medical history

2. Concerning the father of the patient
   a. Age at the time of giving birth to the patient
   b. Ethnicity
   c. Medical history

3. Other children
   a. Were there other pregnancies before the pregnancy with this patient?
   b. Were other children born preterm, and if yes, how many?
   c. How many children are currently alive, and do they have a significant medical history?
   d. Are there abortions in the mother’s history?
      i. Number of abortions
      ii. Spontaneous abortions and number?
      iii. Therapeutic abortions and number?
   e. Are there deceased children?
      i. Before birth
      ii. At birth
      iii. After birth? At which age?

B. Pregnancy details – to be completed by the mother of the patient

1. Did the pregnancy occur spontaneously or after medical intervention?
2. Single pregnancy or multiples?
3. Did you have a regular follow-up during this pregnancy?
4. Was any form of prenatal diagnostics performed?
   a. No
   b. Chorion villus sampling
   c. Cordocentesis
   d. Amniocentesis
5. Did you smoke during pregnancy? If yes, how many cigarettes per day?
6. Did you drink coffee during pregnancy? If yes, how many cups per day?
7. Did you drink alcohol during pregnancy? If yes, how many units per day?
8. Pregnancy details. Please indicate if any of the following events occurred during pregnancy, and if yes, when/how long.
   a. Vaginal bleeding
   b. Pre-existing hypertension (diagnosed before pregnancy)
   c. Hypertension
   d. Pre-existing diabetes (diagnosed before pregnancy)
   e. Cardiovascular disease
   f. Renal disease
   g. Neurological disease
   h. Respiratory disease
   i. Iso immunisation
   j. Other disease
   k. Growth retardation of the foetus
   l. Preterm contractions
   m. Congenital malformations in the foetus
   n. Hospitalisation before delivery
   o. Chorioamnionitis
p. Pre-eclampsia
q. Medication during pregnancy, in particular one of the following
   i. Tocolysis
   ii. Corticoids
   iii. Antihypertensive medication
   iv. Antibiotics
   v. Anti-epileptics
   vi. Narcotics
   vii. Other medication

9. Concerning the delivery
   a. Vaginal delivery or C section?
   b. Gestational age at delivery

C. Neonatal events – to be completed by the parents

1. Biometry
   a. Birth weight
   b. Length at birth
   c. Head circumference at birth
2. APGAR scores
   a. At 1 minute
   b. At 5 minutes
3. Please indicate if any of the following occurred during the neonatal period
   a. Asphyxia
   b. Respiratory system
      i. Hyaline membrane disease
      ii. Transient tachypnea of the neonate
      iii. Pneumonia
      iv. Mechanical ventilation (intubation). If yes, how long?
      v. CPAP (intubation). If yes, how long?
      vi. Oxygen therapy (intubation). If yes, how long?
      vii. Surfactant therapy
   c. Neurological system
      i. Brain bleeding
      ii. Leukomalacia
      iii. Convulsions
      iv. Apnea
   d. Cardiovascular system
      i. Patent ductus arteriosus
      ii. Other
   e. Infections
   f. Metabolic problems or diseases
      i. Hypoglycaemia
      ii. Hypocalcaemia
   g. Intra uterine growth retardation
   h. Gastrointestinal system
      i. Necrotising enterocolitis
      ii. Feeding difficulties and/or problems
   i. Congenital abnormalities
      i. Spina bifida
      ii. Hydrocephalus
      iii. (palato)schisis
4. How was the psychomotor development of your child during the following periods?
   - Pre school
   - Primary school
   - High school
5. Was your child immunised? If not or not entirely, please indicate which vaccinations your child
did not receive.
6. Did your child suffer from serious diseases or medical problems beyond the neonatal period?
7. Did your child undergo surgical procedures beyond the neonatal period?
D. Current health assessment – to be completed by the parents and patient together

1. Did your child suffer from frequent respiratory infections in the past 2 years?
2. Did your child ever have pneumonia? If yes, when?
3. Does your child have asthma? If yes, when was this diagnosed?
4. Did your child have asthma symptoms in the past 12 months?
5. Did your child present with wheezing during the past 12 months?
   If yes, how often did your child present with wheezing during the past 12 months?
6. Did your child use medication for wheezing during the past 12 months?
7. Does your child regularly use nebulizers? If yes, what is the medication regimen?
8. Did your child wake up during the night due to wheezing during the past 12 months?
   a. Not at all
   b. Less than once a week
   c. More than once a week
9. Did your child experience shortness of breath at night during the past 12 months?
   a. Not at all
   b. Sometimes
   c. Often
   d. All the time
10. Did your child experience wheezing during physical activity during the past 12 months?
11. Did your child present with a dry cough at night (without concurrent respiratory infection at that moment) during the past 12 months?
12. Did your child cough daily for at least 4 consecutive weeks during the past 12 months?
13. Did your child use medication for chronic cough during the past 12 months? If yes, which medication?
14. Does your child snore?
15. Is your child allergic? If yes, was this confirmed with objective testing?
16. Does your child have nasal obstruction?
17. Did your child present with sneezing, a runny or blocked nose (without concurrent respiratory infection at that moment) during the past 12 months?
18. Did your child have symptoms of hay fever during the past 12 months?
19. Did your child use medication for hay fever or nasal symptoms during the past 12 months?
20. Did your child have an itching skin rash (coming and going) for at least 6 months during the past 12 months?
21. Did your child have eczema during the past 12 months?
22. Did your child use medication to treat itching skin rash during the past 12 months?
23. Does your child suffer from significant fatigue?
24. Does your child have learning difficulties?
25. Does your child have heart problems?
26. Does your child smoke?
27. Is your child exposed to second-hand smoking in the home environment?
28. Does your child currently present with symptoms that were not yet addressed in this questionnaire?
29. Does your child currently use medication that was not yet mentioned above?
References


