Gas exchanges in children with cystic fibrosis or primary ciliary dyskinesia: A retrospective study

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Abstract

Primary ciliary dyskinesia (PCD) and cystic fibrosis (CF) both entail bronchiectasis and pulmonary impairment as measured using spirometry, during childhood. We aimed at looking whether blood gas exchanges progressed differently between CF and PCD children in a retrospective study of repeated measurements. Comparisons between groups (Wilcoxon-Mann-Whitney and Chi-squared tests) and a mixed linear model, adjusted for age, evaluated associations between diseases and PaO_2, $PaCO_2$, or PaO_2-$PaCO_2$ ratio.

Among 42 PCD and 73 CF children, 62% and 59% had respectively bronchiectasis (*P*=0.75). Spirometry and blood gases were similar at inclusion (PaO_2 median [IQR] PCD -1.80 [-3.40;-0.40]; CF -1.80 [-4.20;0.60] z-scores; *P*=0.72). PaO_2 and PaO_2-$PaCO_2$ ratio similarly and significantly decreased with age in both groups (*P*<0.01) whereas $PaCO_2$ increased more in CF (*P*=0.02) remaining within the range of normal (except for one child).

To conclude, gas exchange characteristics, similarly initially impaired in PCD and CF children, tended to less deteriorate with time in PCD children who could benefit from an early diagnosis.

Keywords: Primary Ciliary Dyskinesia, Clinical Aspects of Cystic Fibrosis, Pulmonary Gas Exchange, Childhood Respiratory Disease

1. Introduction

Cystic fibrosis (CF) and primary ciliary dyskinesia (PCD) diseases show similarities as they both involve congenital impairment of mucociliary clearance leading to recurrent or chronic rhinosinusitis, airway infection, and bronchiectasis at paediatric age (Knowles and Boucher, 2002). Studies conducted in PCD or CF patients showed close lung function (LF) impairment as measured by static pulmonary volumes (Kraemer et al., 2006, Pifferi et al., 2012), forced expiratory volumes and flows (Magnin et al., 2012, Ren et al., 2008) and ventilation inhomogeneity assessed using the lung clearance index (LCI) with different study protocols (Aurora et al., 2005, Green et al., 2012, Kraemer et al., 2005). However, the latter index was correlated to Forced Expiratory Volume in 1 s (FEV_1) in CF but not PCD in adolescents and adults, where Forced Expiratory Flows between 25% and 75% of FVC ($FEF_{25\%-75\%}$) were significantly correlated with LCI in both populations (Irving et al., 2013). FEV_1 is the most frequently used index to evaluate the severity of PCD and CF respiratory disease even though its relevance might differ between these two diseases. In CF patients, FEV_1 was one of the characteristics significantly related to the clinical outcome, including survival (Kerem et al., 2014, Konstan et al., 2007, Liou et al., 2001) whereas the correlation between FEV_1 and future symptoms seemed weaker in PCD children (Ellerman and Bisgaard, 1997, Hellinckx et al., 1998, Marthin et al., 2010). In addition to the presence of ventilation heterogeneity measured by LCI impairment, the deficit in respiratory Nitric Oxide (NO) production could further alter ventilation-to-perfusion ratios in these diseases. NO acts in the lung (among other effects) as an aerocrine messenger with vasodilator effect increasing PaO_2 in patients with respiratory distress or in healthy subjects (Lundberg et al., 1996a, Lundberg et al.; 1996b). The nasal production of NO was measured low in PCD and CF subjects

but lower in PCD subjects (Marthin et al., 2011). Moreover, despite a similar total level of orally exhaled NO, PCD patients exhibited lower NO bronchial output and alveolar concentration than healthy subjects, whereas CF patients had only a decrease in NO alveolar concentration (Walker et al., 2013). Finally, unlike CF, PCD first hits lower lung territories where a majority of gas exchanges takes place (Cohen-Cymberknoh et al., 2014), supporting the hypothesis of dissimilar gas exchanges progression in PCD and CF children (the latter experiencing initially apical lesions). In CF children, partial pressure of Oxygen (PaO_2) steeply decreased in parallel to (but earlier than) FEV_1 reaching low level in school age children while $PaCO_2$ slightly increased from low to normal level (Kraemer et al., 2009). In PCD children, PaO_2 also significantly decreased with age and could be altered in school age children but $PaCO_2$ remained stable or slightly increased without association with age (Magnin et al., 2012).

We hypothesized that, independently of central airway impairment, ventilation-perfusion mismatch would start earlier in PCD than in CF children and would worsen quicker in CF children. The demonstration of earlier lung impairment with gentler progression in PCD children compared to CF children would promote the importance of an early diagnosis in PCD in order to limit lung damages.

Our objective was to compare the evolution of gas exchange characteristics, i.e. PaO_2, $PaCO_2$ and PaO_2-$PaCO_2$ ratio, as a marker of ventilation/perfusion mismatch in CF and PCD children from 4 to 18 years of age. We also compared characteristics, respiratory history and other LF indexes between CF and PCD children.

2. Methods

2.1. Subjects

Children were recruited from monocenter retrospective cohorts in the National Centre for Respiratory Rare Disease and the Paediatric Cystic Fibrosis Centre of Trousseau Hospital (Paris, France). Data recording started in 2000 up to 2015. Diagnosis retained was CF for children with causal CF mutations and/or positive sweat tests and PCD for children with sino-pulmonary syndrome and *situs inversus* (i.e. Kartagener syndrome), or suggestive clinical features and typical abnormal ciliary ultrastructure, or causal biallelic mutations in a known PCD gene. In all children, immunodeficiency was excluded as well as diseases which could alter PaO_2 (e.g. heart disease with shunt, scoliosis, obesity, airway malacia). Pancreatic sufficient CF children were secondarily excluded because these children are known to have milder respiratory disease and there were too few of them (n=8) to allow statistical analysis. Bronchiectasis was diagnosed from a standardised computed tomography performed in all PCD children at diagnosis or before depending on lower respiratory symptoms, and in CF children at 5 years of age or before depending on lower respiratory symptoms. Bronchiectasis was confirmed when bronchoarterial ratio was over 1, or when bronchus lacked tapering or were visualised within 1cm of pleural surface.

We looked for all LFTs including PaO_2 measurements and excluded results obtained during acute airway infection or respiratory exacerbation (i.e. change in treatment because of respiratory symptoms during the previous week), or showing a significant bronchodilator response as PaO_2 was measured before bronchodilator administration. It is to be noted that in our laboratory, blood gas analyses considered as unreliable are not recorded, and therefore were not available for the present study. Routine criteria for blood gas unreliability and, therefore, non-inclusion were: only one capillary sampled; between-capillary PaO_2 difference larger than 1 Standard Deviation (5 mmHg (Gaultier et al., 1979)); child with obvious altered breathing pattern (usually

because of cry). Eligible children were included at the time of their first PaO_2 measurement available (cross-sectional study), then all subsequent LFT including blood gas analysis performed in stable conditions were recorded (longitudinal study).

2.2. Lung function measurements

Ear lobe capillary blood gas was performed as previously described in our laboratory (Gaultier et al., 1979). The mean of 2 to 4 capillary results was recorded. Lung function results from children able to perform lung volumes and forced expiratory volumes and flows measurements (Masterscreen, Vyair Medical, CareFusion, Adhésia, France, or BodyBox, Medisoft, Belgium) according to international recommendations were recorded (Beydon et al., 2007, Miller et al., 2005, Wanger et al., 2005). We used the database e-RespiRare® software national register (elaborated by UMR_S707 and 719, INSERM) to record clinical, microbiological, and therapeutic features.

Children over 8 years of age and their parents gave their consents to perform investigations; the ethical review board of the National Centre approved the retrospective use of the database register on 20/03/2008 (CCTIRS, no.08.015bis).

2.3. Statistical Analysis

This study conducted in children with rare respiratory diseases was not based on a power calculation but on the feasibility to retrospectively include repeated PaO_2 measurements from our national register of Rare Respiratory Diseases. Quantitative variables were expressed in median and interquartile range [IQR], range and percentage when appropriate. Chi2 or Fisher's exact tests were applied to compare qualitative data and Wilcoxon's test to quantitative data. Anthropometric measures and lung function indexes, including PaO_2 and $PaCO_2$, were expressed or as z-scores

(standard deviations from the mean) (Gaultier et al., 1979, Quanjer et al., 2012, Rolland-Cachera et al., 1991, Stocks and Quanjer, 1995). To take into account repeated measures in individuals, the effect of the disease on PaO_2, $PaCO_2$ and $PaCO_2$-$PaCO_2$ ratio was studied using a random-intercept mixed model, adjusted for age. Further bivariate analyses assessed the association of the following covariates with PaO_2 (as, in contrast to $PaCO_2$, PaO_2 was altered in more than one children): sex, Body Mass Index (BMI), Forced Expiratory Capacity (FVC), FEV_1, FEV_1/FVC and $FEF_{25\%-75\%}$; and genotypes. Then, significant covariates at a 20% threshold were retained in two final multivariate models (one including FVC and the second FEV_1 because they were collinear variables). The *P*-value confirmed a statistical relationship when <0.05 (two-sided). All analyses were performed using the statistical software (V.9.4; SAS institute).

3. Results

3.1. Participating children

One hundred and twenty-eight patients were eligible. Thirteen patients were excluded; five for being over 18 years at the date of inclusion and eight for being sufficient pancreatic CF. The number of children with data at different age groups in the remaining 115 children (42 PCD and 73 CF) is displayed in Figure 1. The median [IQR] duration of follow-up of patients was 2.3 [0.8;3.8] years. The median [IQR] number of blood gas measurements per child was 3 [2;4] and the median [IQR] delay between two measurements in a child was 13.1 [11.7;19.4] months.

The 42 PCD and 73 CF children were included at a similar age with characteristics at inclusion (cross-sectional study) displayed in Table 1. As expected, CF children were younger than PCD children at diagnosis due to neonatal screening. Frequency of

bronchiectasis was similar between the two groups (61.9 % in PCD versus 58.9% in CF; *P*=0.75), but bronchiectasis was diagnosed at a younger age in PCD. Despite the later onset of bronchiectasis in CF children, *Pseudomonas aeruginosa* (*P. aeruginosa*) was more frequently detected in CF than in PCD children.

3.2. Comparison of lung function measurements at inclusion (cross-sectional study)

At time of inclusion, measured LF indexes were similar between the two groups except for static volumes in a sub-group of 16 (38%) and 25 (34%) of PCD and CF children; respectively (more hyperinflation in PCD group) (Table 2). In particular, PaO_2 and $PaCO_2$ were similar in PCD compared to CF children (median [IQR] -1.80 [-3.40; -0.40] versus -1.80 [-4.20; 0.60], *P*=0.72 and 0.20 [-0.20; 0.60] versus 0.40 [0.00; 0.60], *P*=0.15; respectively).

3.3. Comparison of lung function measurements at follow-up (longitudinal study)

In all study children, increasing age was associated with a decrease in PaO_2, FEV_1, $FEF_{25-75\%}$ and FEV_1/FVC but with an increase in $PaCO_2$, (Figures 2a, 2b, 2d, E1). The change per year was significant with ß coefficients [95%CI] of -0.21 [-0.29;-0.13] z-score for PaO_2 (*P*<0.0001), 0.06 [0.04;0.08] z-score for $PaCO_2$ (*P*<0.0001), -0.15 [-0.22;-0.09] z-score for FEV_1 (*P*<0.0001), and -0.09 [-0.13;-0.05] z-score for FEV_1/FVC (all *P*<0.0001).

$PaCO_2$ was within the range of normal in all samples, except for three measurements performed in one CF teenager (Figure 2b). $PaCO_2$ slowly increased with age in both diseases but with a gentler slope in PCD compared to CF children (ß

coefficients [95%CI] -0.22 [-0.42;-0.03]; *P*=0.02). Among the 107 children who fitted the mixed model for the PaO_2-$PaCO_2$ ratio (calculated from raw PaO_2 and $PaCO_2$ values), no significant effect of disease on PaO_2-$PaCO_2$ ratio progression was evidenced (*P*=0.07) (Figure 2c).

In 60 CF children with identified mutations and a longitudinal follow-up of PaO_2 and $PaCO_2$, different *CFTR* genotypes (classified into 5 classes according to the type of mutations: inframe/inframe [F508del/ F508del], n=27; inframe [F508del]/nonsense, n=7; inframe [F508del]/frameshift, n=13; [non-F508del]/frameshift, n=4; inframe [F508del]/splicesite, n=9) were not associated with PaO_2 (*P*=0.62) or with $PaCO_2$ (*P*=0.16). Among the 21 PCD children with genetic diagnosis, 11 different genes were involved preventing any statistical analysis in such small groups of children.

Variables associated with PaO_2 in bivariate analyses were spirometry indexes (FVC, FEV_1, FEV_1/FVC, $FEF_{25\%-75\%}$) (241 observations in 99 children), but not disease, sex, or BMI (278 observations in 110 children) (Table 3). In multivariates models (241 observations in 99 children) (Table 4), PaO_2 was independently associated with forced volumes (0.65 [0.44;0.85] and 0.71 [0.44;0.97] PaO_2 z-score increase for 1 z-score increase in FVC or FEV_1, respectively; *P*<0.0001) but not with forced expiratory flows (*P*>0.35). Moreover, FEV_1/FVC was associated with PaO_2 only in the model including FVC (0.82 [0.43;1.21] PaO_2 z-score increase for 1 z-score increase in FEV_1/FVC; *P*<0.0001)(Table 4).

4. Discussion

The present monocentric study in PCD and pancreatic insufficient CF children showed that 1) unlike we hypothesized, PaO_2 could be measured low as early as 10

years of age and significantly decreased over time in all studied children, irrespectively of the disease; 2) as expected, if gas exchange could reflect ventilation-perfusion ratio mismatch, CF children worsened their gas exchange with age to a greater extent than PCD children, but exhibited (usually) no hypercapnia or PaO_2-$PaCO_2$ ratios dissimilar to that of PCD children 3) in line with previous studies, lung spirometry did not differ according to disease during childhood and was associated to PaO_2 impairment.

4.1. PaO_2 and $PaCO_2$ measurements

No study has so far reported PaO_2 and $PaCO_2$ measurements in a large population of PCD patients and no previous authors have compared PaO_2 or $PaCO_2$ between PCD and CF patients. In the two diseases, PaO_2 decrease progresses with ventilation-to-perfusion inequality, mostly because of ventilation inhomogeneity. The initial location of lung impairment (basal in PCD and apical in CF) (Cohen-Cymberknoh et al., 2014) but also the possible poor lung perfusion due to low level of NO (lower in PCD) (Lundberg et al., 1996b, Walker et al., 2013) could involve differences between PCD and CF children's gas exchange.

While the decrease in PaO_2 can initially easily be compensated by an increase in ventilation in both groups, the steeper increase in $PaCO_2$ in CF children could reflect the impairment of new territories with better ventilation-perfusion ratio (lower lobes) while upper lesions persist, preventing effective hyperventilation to keep steady the $PaCO_2$ level. We do not know much of the progression with age of lung levels of NO except that the lower NO output measured in PCD compared to CF patients persisted from childhood to adulthood (Walker et al., 2013, Horvàth et al., 2003) in favour of a stable effect.

As previously shown (Kraemer et al., 2009), we measured a progressive increase in

$PaCO_2$ in CF children with nearly no measurement outside the range of normal while PCD children significantly less increased their $PaCO_2$ (Magnin at al., 2012). In accordance with predicted changes in PaO_2 and $PaCO_2$ when ventilation-perfusion ratio decreases because of increasing ventilation inhomogeneity and in the absence of compensation from other lung territories (West, 2005), we measured a decrease in PaO_2 much larger than the increase in $PaCO_2$ (3.5 times more) resulting in no clear difference in the PaO_2-$PaCO_2$ ratio progression with age (Figure 2c) between the two groups.

Kraemer et al. measured different courses of $PaCO_2$ values in a large cohort of CF children (Kraemer et al., 2009) according to the children's *CFTR* genotypes. We did not replicate this result, but the analysis of small groups probably lacked power. Moreover, the exclusion in our study of pancreatic sufficient patients may not totally explain this difference and Kraemer et al. might have included children with more severe phenotypes.

In our study children, only PaO_2 could reach values lower than the lower limit of normal in patients as young as 10 years of age, and this decrease was associated with the decrease in forced expiratory volumes. The assessment of gas mixing demonstrated that ventilation inhomogeneity can occur with or without central airway obstruction in PCD and CF children (Aurora et al., 2005, Boon et al., 2015, Green et al., 2012, Gustafsson et al., 2003, Kraemer et al., 2005). The complexity of the relationships between infections, inflammation, and peripheral airway impairment in PCD and CF (Ratjen et al., 2016, Simpson et al., 2015) cannot be addressed from our retrospective study, but we acknowledge that despite possible more peripheral lung impairment in PCD children at inclusion (more lung hyperinflation with similar spirometry), no difference in PaO_2 or $PaCO_2$ values between the two groups of

children was evidenced in our study. The magnitude of the recorded PaO_2 decline (mean -0.21 z-score per year) was slightly higher than the one we previously found in PCD children (mean -0.17 z-score) (Magnin et al., 2012) or than that measured in a population of CF children (-0.83 mmHg/year) (Kraemer et al., 2009).

4.2. Spirometry measurements

The scarce studies that compared spirometry between PCD and CF children focused on FEV1, neglecting expiratory flows. FEV_1 was similar in PCD and CF children and adults tested during routine assessment (Cohen-Cymberknoh et al., 2014) or in PCD and CF children tested during a respiratory exacerbation (with a similar FEV_1 decrease from baseline) (Ratjen et al., 2016). However, the general acceptation that respiratory prognosis is worse in CF patients seems to be contradicted by the absence of difference in spirometry during childhood, unless a slower decline with age were demonstrated in PCD patients which we did not find (Figures 2d, E1). Conversely, Cohen-Cymberknoh and colleagues (Cohen-Cymberknoh et al., 2014) were able to measure a large and significant decline in FEV_1 over time in children and adults CF patients with or without pancreatic insufficiency, but not in PCD patients. The inclusion of adult patients might be responsible for the dissimilar relationships between disease and FEV_1 decrease. Moreover, the indisputable improvement in FEV_1 in CF French children during the study (+ 15% predicted at 10-14 years of age between 1995 and 2015) might have lessened the difference with PCD children (Vaincre la Mucoviscidose, 2017).

4.3. Clinical differences between PCD and CF children

The earlier age at bronchiectasis diagnosis in PCD compared to CF was unexpected. The age of bronchiectasis was reliable in CF children followed up since birth with a Computed Tomography no later than in the fifth years of age, i.e. before

the median age at bronchiectasis diagnosis (Table 1). In PCD children, the delay between PCD and bronchiectasis diagnoses was shorter, probably because most of children diagnosed at a young age with PCD displayed unusual severe respiratory symptoms which required full work-up including lung imaging. Moreover, the finding of bronchiectasis in a child with a sino-pulmonary syndrome is highly suggestive of PCD after the exclusion of CF or other rare diseases. This procedure favours the diagnosis of young PCD children with bronchiectasis compared to PCD patients with no or less pulmonary symptoms (no early bronchiectasis), who are usually diagnosed later (except for subjects with *situs inversus*).

Despite similar proportions of bronchiectasis, *P. aeruginosa* was scarcely detected in PCD compared to CF children's sputum. The frequency of *P. aeruginosa* in PCD children (14.6%) was comparable (11.1 to 14.2%) (Green et al., 2012, Ratjen et al., 2016) or less (27% and 37%) (Maglione et al., 2014, Pifferi et al., 2012) than previously reported. In children and adults with PCD or CF, it was evidenced that *P. aeruginosa* in sputum was related to pulmonary hyperinflation and ventilation inhomogeneity (Kraemer et al., 2005, Pifferi et al., 2012), which was not confirmed for ventilation inhomogeneity in a study that included PCD patients, 89.9% of whom did not have *P. aeruginosa* in sputum (Green et al., 2012). Differences in airway inflammation responses after bronchial infection between PCD and CF patients (Ratjen et al., 2016) may result in different impacts of infection on LF, but our study did not encompass enough PCD children with *P. aeruginosa* in sputum to look for this effect.

4.4. Limits of the method

Our study presents limitations mostly due to its retrospective design which in return allowed the analysis of repeated PaO_2 and $PaCO_2$ measurements during a long period.

We did not compare arterial and capillary PaO_2. A good correlation was found between arterial and capillary PaO_2 in 70 sick children breathing air room (mean (SD) difference of 1.5 (0.5) mmHg) (Gaultier et al., 1979), and a meta-analysis including 664 individuals also measured a small difference between arterial and earlobe capillary PaO_2 (mean [95%CI] 2.40 [1.90;2.80] mmHg) (Zavorsky et al., 2007).

We did not calculate the alveolar-arterial PO_2 difference; however, to take into account $PaCO_2$ progression with respect to PO_2 changes (Kraemer et al., 2009) we considered the PaO_2-$PaCO_2$ ratio which was not different between the two groups. The main limitation was the lack of direct evaluation of the ventilation to perfusion ratio which was not routine in the follow-up of children. Now days, ventilation inhomogeneity can non-invasively be tracked from early childhood using techniques such as the multiple breath washout, but routine evaluation of perfusion remains an issue in children.

Other factors influencing lung function were not taken into account (clinical status and treatment). However, except for age at bronchiectasis diagnosis (see comment in paragraph 4.3), most of clinical factors that significantly differed between groups (Table 1) were disease-specific (age at diagnosis, neonatal respiratory distress, otorhinolaryngological surgery) (De Boeck et al., 2017, Noone et al., 2004, Pruliere-Escabasse et al., 2010), and had, therefore, a potential effect on gas exchange included in disease status. Other factors were not mentioned such as the onset of allergic broncho-pulmonary aspergillosis (ABPA) which may have happened in some CF children but in none of the PCD children, leaving this infection also disease-related. Finally, treatments were not mentioned but they are also disease-related in France. For example, rhDNase would only be used in CF patients, topical steroids only in some PCD children and all children would perform physiotherapy. Therefore, looking at

differences between PCD and CF children regarding these factors would be close to compare the single effect of the diseases.

Conclusion

This is the first study aimed at deciphering the potential differences in lung impairment between PCD and CF children using gas exchanges characteristics as an indirect reflect of ventilation/perfusion mismatch. Despite differences in pathophysiology, PaO_2 was similarly impaired in both groups, but CF children may alter more their gas exchanges with time. Consequently, PCD children who deteriorate less with age might truly benefit from an early diagnosis to prevent early lung impairment. Further prospective studies including older patients and more direct measurements of ventilation-perfusion ratio might give insight into the different courses of these two diseases.

Conflicts of interest: none

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Figures legends

Figure 1 – Number of children with PaO_2 measurements at different age groups

Closed bars represent PCD children and open bars CF children

Figure 2 – Gas exchanges and spirometry trends over time in children with Primary Ciliary Dyskinesia or Cystic Fibrosis

2a: PaO_2 in children with Primary Ciliary Dyskinesia (PCD) (closed circles) and Cystic Fibrosis (CF) (open circles)

2b: $PaCO_2$ in PCD (closed circles) and CF (open circles) children

2c: PaO_2-$PaCO_2$ ratio in PCD (closed circles) and CF (open circles) children

2d: FEV_1/ FVC in PCD (closed circles) and CF (open circles) children

Solid lines are linear regressions over time in PCD children, dotted lines are linear regressions over time in CF children. Each child contributed for more than one point.

PaO_2: partial pressure of Oxygen; $PaCO_2$: partial pressure of Carbon Dioxide; FVC: Forced Vital Capacity; FEV_1: Forced Expiratory Volume in 1 second

Tables

Table 1 – Characteristics of children at inclusion

	PCD n=42 unless specified	**CF n=73 unless specified**	***P* value**
Female	22 *(52.4)*	34 *(46.6)*	=0.55
Geographical origin Europe Sub-Saharan Africa Others	 37 *(88.1)* 3 *(7.1)* 2 *(4.8)*	n=72 66 *(91.6)* 2 *(2.8)* 4 *(5.6)*	=0.62
Neonatal respiratory distress	n=33 23 *(69.7)*	n=66 1 *(1.5)*	**<0.0001**
Age at diagnosis (years)	6.7 [3.1; 10.1]	n=57 0.4 [0.1; 2.0]	**<0.0001**
Age at inclusion (years)	8.9 [6.4; 13.5]	11.0 [7.3; 14.2]	=0.23
BMI (z-score)	-0.38 [-1.07 ;0. 41]	-0.48 [-1.15;0.27]	=0.99
Otorhinolaryngology surgery	n=40 14 *(35)*	n=71 5 *(7.0)*	**=0.0002**
Type of surgery Adeno and/or tonsillectomy Myringotomy Other	n=14 5 *(35.7)* 8 *(57.1)* 1 *(7.1)*	n=5 2 *(40.0)* 0 *(0.0)* 3 *(60.0)*	
Bronchiectasis	26 *(61.9)*	43 *(58.9)*	=0.75
Age at bronchiectasis diagnosis (years)	n=19 8.0 [5.0; 10.8]	n=38 10.2 [8.0; 12.0]	**=0.01**
Pseudomonas aeruginosa in sputum (ever)	n=41 6 *(14.6)*	48 *(59.3)*	**<0.0001**

Results are expressed as number *(percentage)* or as median [Interquartile Range; IQR]
PCD: Primary Ciliary Dyskinesia; CF: Cystic Fibrosis; BMI: Body Mass Index;

Table 2 - Lung function of the study children at inclusion

Indexes median [IQR]	**PCD**	**CF**	*P* value
PaO_2 (z-score)	n=42 -1.80 [-3.40 ; -0.40]	n=73 -1.80 [-4.20 ; 0.60]	=0.72
$PaCO_2$ (z-score)	n=42 0.20 [-0.20 ; 0.60]	n=73 0.40 [0.00 ; 0.60]	=0.15
FEV_1 (z-score)	n=27 -1.21 [-1.82 ; -0.39]	n=59 -1.82 [-3.05 ; -0.29]	=0.12
FEV_1/FVC (z-score)	n=27 -1.33 [-1.60 ; -0.25]	n=59 -1.38 [-2.13 ; -0.64]	=0.14
RV (% predicted)	n=16 132.9 [110.1 ; 162.1]	n=25 118.6 [101.7 ; 158.9]	=0.10
RV/TLC (% predicted)	n=16 130.1[112.8 ; 141.2]	n=25 116.6 [97.3 ; 145.9]	**=0.01**
TLC (% predicted)	n=18 105.0 [92.51;116.2]	n=31 107.1 [99.7;113.7]	=0.25

PaO_2: partial pressure of O_2; PaO_2: partial pressure of CO_2; FVC: Forced Vital Capacity; FEV_1: Forced Expiratory Volume in 1 second; RV: Residual Volume; TLC: Total Lung Capacity; IQR: interquartile range

Table 3 Association between covariates and PaO_2 in crude models: Age adjusted bivariate mixed model constructed with 278 observations in 110 children for group disease, sex and BMI, and with 241 observations in 99 children for lung function indexes

Covariates	Unit	β [95%CI]	*P* value
Age	year	-0.22 [-0.30 ; -0.15]	**<0.0001**
Groups			
PCD		0.03 [-0.45 ; 1.05]	=0.43
CF (reference)		Ref	
Age	*year*	*-0.21 [-0.29 ; -0.13]*	***<0.0001***
Sex			
Female		-0.32 [-1.02 ; 0.39]	=0.38
Male (reference)		Ref	
Age	*year*	*-0.22 [-0.29 ; -0.14]*	***<0.0001***
BMI			=0.52
BMI>2 z-score		0.66 [-1.07 ; 2.39]	
-2<BMI<+2 z-score		0.59 [-0.44 ; 1.61]	
<-2 z-score (reference)		Ref	
Age	*year*	*-0.22 [-0.29 ; -0.14]*	***<0.0001***
FEV_1	z-score	0.77 [0.61 ; 0.93]	**<0.0001**
Age	*year*	*-0.11 [-0.19 ; -0.04]*	***0.004***
FVC	z-score	0.71 [0.53 ; 0.89]	**<0.0001**
Age	*year*	*-0.16 [-0.24 ; -0.08]*	***=0.0002***
FEV_1/FVC	z-score	0.85 [0.61 ; 1.09]	**<0.0001**
Age	*year*	*-0.16 [-0.24 ; -0.08]*	***=0.0001***
$FEF_{25\%-75\%}$	z-score	0.62 [0.46 ; 0.78]	**<0.0001**
Age	*year*	*-0.16 [-0.23 ; -0.08]*	***=0.0001***

95%CI: 95% confidence interval; BMI: Body Mass Index; FEV_1: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; $FEF_{25\%-75\%}$: Mean Forced Expiratory Flows between 25% and 75% of FVC

The beta coefficient indicates the amount of PaO_2 z-score increase or decrease (positive or negative beta coefficient, respectively) compared to the reference group (=0) for categorical factors and for each 1 unit (1 year or 1 z-score) increase in continuous covariates.

Table 4 –Association between covariates and PaO_2 in multivariate models adjusted on group disease for 241 observations in 99 children

Covariates	Unit	Model including FVC		Model including FEV_1	
		β [95%CI]	**P value**	**β [95%CI]**	***P* value**
Age	1 year	-0.11 [-0.19 ; -0.04]	**0.003**	-0.11 [-0.19 ; -0.04]	**0.004**
FEV_1	1 z-score	-		0.71 [0.44 ; 0.97]	**<0.0001**
FVC	1 z-score	0.65 [0.44 ; 0.85]	**<0.0001**	-	
FEV_1/FVC	1 z-score	0.82 [0.43 ; 1.21]	**<0.0001**	0.29 [-0.08 ; 0.65]	0.13
$FEF_{25\%-75\%}$	1 z-score	-0.14 [-0.44 ; 0.16]	0.36	-0.08 [-0.40 ; 0.22]	0.58

Multivariate models are adjusted for age and group. Two models were given because of colinearity of FVC and FEV_1.

95%CI: 95% confidence interval. FVC: Forced Vital Capacity; FEV_1: Forced Expiratory Volume in 1 second; $FEF_{25\%-75\%}$: Mean Forced Expiratory Flows between 25% and 75% of FVC.

The beta coefficient indicates the amount of PaO_2 z-score increase or decrease (positive or negative beta coefficient, respectively) for each 1 unit (1 year or 1 z-score) increase of the covariate