



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 PaO₂, PaCO₂, or PaO₂:PaCO₂ 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 (PaO₂ median [IQR] PCD $-1.80 [-3.40; -0.40]$; CF $-1.80 [-4.20; 0.60]$ z-scores; $P = 0.72$). PaO₂ and PaO₂:PaCO₂ ratio similarly and significantly decreased with age in both groups ($P < 0.01$) whereas PaCO₂ 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.

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 (FEV₁) in CF but not in PCD

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). FEV₁ 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, FEV₁ 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 FEV₁ 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

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vasodilator effect increasing PaO₂ 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 and Nielsen, 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-Cymerberknoh 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 (PaO₂) steeply decreased in parallel to (but earlier than) FEV₁ reaching low level in school age children while PaCO₂ slightly increased from low to normal level (Kraemer et al., 2009). In PCD children, PaO₂ also significantly decreased with age and could be altered in school age children but PaCO₂ 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. PaO₂, PaCO₂ and PaO₂-PaCO₂ 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 PaO₂ (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 1 cm of pleural surface.

We looked for all LFTs including PaO₂ 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 PaO₂ 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 PaO₂ 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

PaO₂ 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 2–4 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 PaO₂ 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 PaO₂ and PaCO₂, were expressed as absolute values, percentages of predicted or as z-scores (standard deviations from the mean) (Gaultier et al., 1979; Qunjer et al., 2012; Rolland-Cachera et al., 1991; Stocks and Qunjer, 1995). To take into account repeated measures in individuals, the effect of the disease on PaO₂, PaCO₂ and PaCO₂-PaCO₂ ratio was studied using a random-intercept mixed model, adjusted for age. Further bivariate analyses assessed the association of the following covariates with PaO₂ (as, in contrast to PaCO₂, PaO₂ was altered in more than one children): sex, Body Mass Index (BMI), Forced Expiratory Capacity (FVC), FEV₁, FEV₁/FVC and FEF25%-75%; and genotypes. Then, significant covariates at a 20% threshold were retained in two final multivariate models (one including FVC and the second FEV₁ 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 Fig. 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

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