ELSEVIER
Journal of Cystic Fibrosis xx (2017) xxx – xxx
Journal of Cystic Fibrosis
www.elsevier.com/locate/jcf

Original Article

Variability of monthly nitrogen multiple-breath washout during one year in children with cystic fibrosis

Kent Green [a,b,*], Thomas Kongstad [a,b], Marianne Skov [a], Frederik Buchvald [a], Susanne Rosthøj [c], Jacob Louis Marott [d], Per Gustafsson [e], Tacjana Pressler [a], Kim Gjerum Nielsen [a]

[a] CF-Centre Copenhagen, Paediatric Pulmonary Service, Department of Paediatrics and Adolescent Medicine, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark
[b] Research Unit on Women's and Children's Health, Copenhagen University Hospital, Rigshospitalet, Tagensvej 20, DK-2100 Copenhagen, Denmark
[c] Section of Biostatistics, Department of Public Health, University of Copenhagen, Øster Farimagsgade 5, Entrance B, 2. floor, Postboks 2099, DK-1014 Copenhagen, Denmark
[d] The Copenhagen City Heart Study, Frederiksberg Hospital, University of Copenhagen, Nordre Fasanvej 57, DK-2000 Frederiksberg, Denmark
[e] Department of Paediatrics, Central Hospital, Lövängsvägen, 541 85 Skövde, Sweden

Received 4 July 2017; revised 17 November 2017; accepted 19 November 2017
Available online xxxx

Abstract

Background: Knowledge of between-session variability of nitrogen multiple-breath washout (N_2MBW) indices is crucial when designing longitudinal interventional studies and in disease monitoring using N_2MBW as end-point. Such information is currently sparse.
Methods: Monthly triplets of N_2MBW were prospectively obtained from 14 children with CF during one year. Linear mixed models were used to analyze variability. Our aim was to assess between-session variability of N_2MBW indices from repeated measurements and compare LCI derived from different software packages currently in use (TestPoint® vs. Spiroware®).
Results: Baseline LCI (median; range) was 9.37 (6.82; 12.08). Between-session differences in LCI measurements were up to 25%. Intra Class Correlation-Coefficient was 0.82. There was no systematic difference between LCI measurements derived from the two software packages ($p = 0.18$); however, variability was significantly higher using Spiroware®.
Conclusions: We report between-session variability of LCI using N_2MBW in school-age children and adolescents with CF. LCI changes exceeding 25% may be considered clinically relevant. TestPoint® and Spiroware® can be used interchangeably in longitudinal studies.

Keywords: Cystic fibrosis; Paediatrics; Lung function; Nitrogen multiple-breath washout; Lung clearance index; LCI

1. Introduction

The nitrogen multiple-breath washout (N_2MBW) test is a re-emerging method for assessing pulmonary impairment in children with obstructive lung disease [1–3] and is increasingly used as primary end-point in paediatric and adult cystic fibrosis (CF) studies [4–7]. Lung clearance index (LCI), the most frequently reported N_2MBW outcome, is a measure of global ventilation distribution inhomogeneity thought to reflect both the non-uniformity of inter-regional ventilation and peripheral airway dysfunction [8].

LCI discriminates between children with CF and healthy controls [9] and correlates closely with structural lung damage assessed using high-resolution computed tomography [10]. LCI is suggested to be more sensitive than spirometry in interventional paediatric CF studies [4]; longitudinally, pre-school LCI may deteriorate with time and during periods with pulmonary

* Corresponding author at: CF-Centre Copenhagen, Paediatric Pulmonary Service, Department of Paediatrics and Adolescent Medicine, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark.
E-mail address: kentgreen@dadlnet.dk (K. Green).

https://doi.org/10.1016/j.jcf.2017.11.007
1569-1993© 2017 European Cystic Fibrosis Society. Published by Elsevier B.V. All rights reserved.

exacerbations [11,12]. Furthermore, LCI may be a good predictor of pulmonary exacerbations in children with CF [13].

Moment ratios (M_1/M_2 and M_2/M_0) are alternative indices of overall ventilation distribution inhomogeneity and appear to have the same sensitivity as LCI in early CF lung disease [14]. They have been sparsely reported in the literature, and their possible additional benefit to LCI in interventional trials and in daily management is unclear [14].

While cross-sectional data on the within-session repeatability of various MBW methods and choices of inert gases is well-known [4,15], studies on long-term (between-session) variability of outcomes from repeated N_2MBW measurements in patients with CF have until recently been lacking [16]. Interpreting the significance of changes when used in clinical monitoring of CF lung disease is therefore difficult. Moreover, knowledge about long-term variability is crucial when designing longitudinal interventional studies [17].

Exhalyzer D® (Eco Medics AG, Duernten, Switzerland) is currently one of the most widespread commercial available equipments for measuring N_2MBW. The analysis software, Spiroware®, delivered with Exhalyzer D® is developed to increase the clinical feasibility from the original TestPoint® based software developed by one of the authors (PG). TestPoint® is considered as Gold Standard analytical software to be used in methodological research studies, while Spiroware® is considered having its advantages in clinical multi-centre studies. Outcomes derived from Spiroware® have in a cross-sectional study previously been shown to significantly differ from those derived from TestPoint® [18].

The primary aim of the present study was to assess the between-session variability of monthly MBW indices from N_2MBW measurements in children with CF over a 1-year period. The secondary aim was to compare data derived from the custom TestPoint® software with data derived from the equipment associated software Spiroware® to assess whether the two software modalities can be used interchangeably in a longitudinal setting. Part of this study has previously been reported in abstract form [19].

2. Materials and methods

2.1. Study design

This is a single-centre, prospective, observational, 1-year study in CF patients attending the outpatient clinic each month as part of scheduled routine clinical visits.

2.2. Subjects

Children (5 to 18 years) with CF were eligible for participation and were continuously recruited from the outpatient clinic at Copenhagen CF-Centre until enrolment of 15 patients. The cohort is part of a larger study, where the 15 CF patients were included as a control group adhering to the ordinary treatment regime, which were compared to an intervention group where a more aggressive treatment regime was guided by LCI. All patients were clinically stable according to modified Fuchs' criteria [20] upon study entrance. In addition, patients had to be clinical stable at last visit; hence, last visit was postponed until clinical stability. N_2MBW measurements were performed at the patient's regular monthly visits at the outpatient clinic regardless of clinical status. Diagnosis was established by typical clinical findings, sweat chloride test > 60 mmol/L, and/or the presence of two disease-causing mutations in the cystic fibrosis transmembrane conductance regulator gene.

2.3. Clinical assessments

Clinical parameters were recorded at each visit: (1) clinical signs of pulmonary exacerbation; (2) current bacterial cultures in mucus obtained by laryngeal suction or by expectoration; and (3) use of antibiotics within 2 weeks prior to visit. A pulmonary exacerbation was defined using a modification of Fuchs' criteria [20] as either a decrease in $FEV_1 \geq 10\%$ relative to the mean value of the previous year, or >2 of the following symptoms: increased quantity or change in sputum colour; increased cough; malaise, fatigue, or lethargy; anorexia or weight loss; increased dyspnoea; or radiographic changes indicative of new or ongoing pulmonary infection. An ongoing exacerbation had to remit before a new event was registered in our clinical database.

Clinicians, patients, and parents were all blinded to the results of the N_2MBW during the study period. Changes in treatment were therefore not guided by LCI; patients were treated according to the standard guidelines at CF-Centre Copenhagen as summarized in the supplemental online material.

2.4. N_2MBW assessment

N_2MBW measurements as well as online and offline calculations of indices were performed by the first author (KG) and by trained and supervised laboratory staff, all in accordance with the recent European Respiratory Society (ERS)/American Thoracic Society (ATS) consensus statement [8]. The Cystic Fibrosis Clinical Trial Network had certified all N_2MBW operators involved in the study. All patients performed N_2MBW prior to spirometry at monthly clinical visits. Tidal breathing N_2MBW was recorded using the Exhalyzer D® (Eco Medics AG, Duernten, Switzerland) and associated software (Spiroware® version 3.1.5 Eco Medics AG) in triplicate, i.e., three tests per session; average of minimum two tests of technically acceptable quality were included at each measurement. LCI and moment ratios were calculated using custom software based on TestPoint® version 7 (Measurement Computing Corporation, Norton, MA, USA). TestPoint® allows in-depth quality control but may be impractical for clinical application (see supplemental online material for explanation of main differences between software packages). However, Spiroware® analysis is currently the standard software for clinics and since comparison between Spiroware® and TestPoint® has scarcely been reported [18], N_2MBW outcomes were calculated using both software modalities. While data obtained with TestPoint® are presented in the main document, LCI calculated from Spiroware® and analysis of agreement to data derived from TestPoint® are provided in the supplemental online material. Furthermore, details on the N_2MBW measurements, quality control assessments and analysis of outcomes are provided in the supplemental online material.

Please cite this article as: Green K, et al, Variability of monthly nitrogen multiple-breath washout during one year in children with cystic fibrosis, J Cyst Fibros (2017), https://doi.org/10.1016/j.jcf.2017.11.007