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Original Article

Agreement between multiple-breath nitrogen washout systems in children and adults

William Poncin [a,1], Florian Singer [b,1], Anne-Sophie Aubriot [a], Patrick Lebecque [a,*]

[a] Cystic Fibrosis Unit, Cliniques Universitaires St Luc, Université de Louvain, Avenue Hippocrate 10, 1200 Brussels, Belgium
[b] Division of Pediatric Pulmonology, University Children's Hospital Zurich, Steinwiesstrasse 75, 8032 Zurich, Switzerland

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Abstract

Background: Comparability of multiple breath washout (MBW) systems has been little explored. We assessed agreement in lung clearance index (LCI) from two similar, commercial nitrogen MBW setups in patients with Cystic Fibrosis (CF) and controls.
Methods: The EasyOne Pro (NDD) and Exhalyzer D (EM) were randomly applied in 85 adults (34 with CF) and 97 children (47 with CF and normal forced expiratory volume in one second). We assessed differences between setups in LCI, lung volumes and breathing pattern and diagnostic performance for detecting abnormal lung function.
Results: Compared to NDD, EM measured higher LCI, functional residual capacity and cumulative expired volume while respiratory rate was lower. Mean difference (limits of agreement) in LCI was 1.30 (−2.34 to 4.94). In CF, prevalence of abnormal LCI was greater in children and similar in adults using EM compared to NDD.
Conclusions: Agreement of MBW outcomes between setups is poor and explained by nitrogen measurement techniques and breathing pattern.

Keywords: Cystic fibrosis; Respiratory function tests; Lung volume measurement; Child; Data accuracy

1. Introduction

Nitrogen multiple breath inert gas washout (MBW) is increasingly adopted within both clinical and research settings [1]. Ease of testing, favourable diagnostic performance in mild lung disease, and increasing availability of setups running on oxygen (O_2) led to renaissance of MBW [2–4]. The derived lung clearance index (LCI) is an established lung function outcome of both central and peripheral airways where early cystic fibrosis (CF) lung disease originates [5]. LCI is a volume ratio, i.e. cumulative expired volume over functional residual capacity (lung turnovers), estimating ventilation distribution efficiency [3]. Compared to forced expiratory volume of the first second (FEV_1) from spirometry, LCI is more specific and sensitive for structural and functional pathology detected in computed tomography scans and treatment response in mild CF lung disease [6–8]. Accordingly, LCI from different setups is reported from studies targeting early origins of mild CF [4,7,9–11]. Though, agreement between systems is largely unknown. The extent to which MBW outcomes of different devices are interchangeable has been little explored.

We assessed agreement of LCI measurement between two commercially available MBW setups with comparable design, the EasyOne Pro; ndd (NDD) and the Exhalyzer D; Eco Medics AG (EM) [3]. Both apply 100% O_2 via open bypass, indirectly measure nitrogen concentration, have similar sensors, and *in vitro* validation data are available [12–14]. The objective of this study was to establish comparability of setups in children with mild

Abbreviations: BMI, Body mass index; CO_2, carbon dioxide; CF, Cystic Fibrosis; CEV, cumulative expired volume; NDD, EasyOne Pro; EM, Exhalyzer D; FEV_1, forced expiratory volume of the first second; FRC, functional residual capacity; $FEF_{25–75}$, forced expiratory flow between 25% and 75% of forced vital capacity; LCI, lung clearance index; MBW, multiple breath washout; O_2, oxygen; SD, standard deviation.

* Corresponding author at: Pediatric Pulmonology, & Cliniques Universitaires St Luc, Université de Louvain, Brussels, Belgium.
E-mail address: Patrick.Lebecque@uclouvain.be (P. Lebecque).
[1] These authors contributed equally to this work.

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CF lung disease, adults with CF and healthy controls. Primary outcome was agreement of LCI. We hypothesized that there was no clinically relevant difference between setups, i.e. LCI differences would not exceed 10%, corresponding to the magnitude of LCI between-test variability [3,12].

2. Methods

2.1. Study design

We conducted a prospective, cross-sectional study in the CF outpatient setting of the University Hospital Saint-Luc (Brussels, Belgium). From May 2013 to March 2015 healthy adults, adults with CF, healthy children and children with CF were enrolled. Prior to the study manufacturers installed the equipment, provided training in calibration and measurements, and approved operational readiness of the setup. For LCI measurements, all participants were randomly assigned to NDD or EM followed each with the other device. Randomization was established by alternate allocation using the participant's identification number. 5 min for instruction and training followed by maximum 25 min for MBW were allocated for each device. This time frame was considered sufficiently long to allow for at least two high quality tests and to increase protocol adherence in children with short attention spans and adults with advanced lung disease in whom MBW may be time consuming [15]. A single investigator (W.P.) applied MBW in all participants. Following MBW patients with CF performed spirometry. The study was approved by the local Ethics Committee. Written informed consent was obtained from caregivers and participants.

2.2. Participants

All participants were naïve to MBW and studied at least three weeks apart from any symptom suggesting upper respiratory tract infection (i.e. nasal congestion, rhinorrhea or sore throat). Patients with CF were enrolled when clinically stable, i.e. not fulfilling criteria of pulmonary exacerbation [16], within the last two months as judged by a single clinician (P.L.) and without previous infection with methicillin-resistant *Staphylococcus aureus* or *Burkholderia cepacia*. CF adults with mild to moderate lung disease were enrolled consecutively while all children (6.0 to 17.9 years) with classic CF (sweat chloride concentration >60 mmol/L) were approached. Age-matched healthy controls were recruited by advertisement and selected on the basis of a questionnaire to exclude past or current smoking, history of wheezing, asthma or chronic cough, prematurity (<34 weeks of gestation), and orthopaedic, neuromuscular or cardiac diseases likely to affect the respiratory system.

2.3. Study assessments

2.3.1. Nitrogen multiple-breath washout

We used two commercially available, unmodified, stand-alone MBW setups including hard- and software: the EasyOne Pro and WBreath software (version 3.37; ndd Medical Technologies, Zurich, Switzerland), and the Exhalyzer D and Spiroware software (version 3.1; Eco Medics AG, Duernten, Switzerland) [12,15,17]. Both setups include an open bypass delivering pure O_2 (via demand valve in NDD) for nitrogen washout, two ultra-sonic flowmeters for tidal flow and molar mass measurement, and O_2 and carbon dioxide (CO_2) sensors. Both setups measure nitrogen indirectly. NDD estimates nitrogen from molar mass, EM from the remainder gas fraction after subtracting the O_2 and CO_2 fractions (Dalton's law of partial pressures) [12,18]. Linearity of sensors and accuracy of algorithms to measure lung volumes in EM have been tested against the current reference standard [12]. Similar but preliminary data exist for NDD [14].

All recommended acceptability criteria for inert gas washout testing were applied [3]. However we performed two instead of three MBW runs and accepted FRC variability ≤15% instead of 10%. We have chosen the more liberal cut-off from two technically acceptable tests because (i) 15% is well below the 25% cut-off beyond which measurements should be discarded, (ii) to decrease testing time and increase success rate, and (iii) since two technically acceptable tests do not significantly influence mean LCI values or its sensitivity to detect abnormal ventilation distribution efficiency [19–21]. Three or more runs were conducted whenever quality standards were not met (two children). Testing conditions were akin: MBW measurements were performed in a sitting position, breathing through a snorkel mouth piece and wearing a nose clip. Subjects watched the same video for distraction facilitating regular breathing. The operator manually ended the washout if end-tidal nitrogen concentration of at least three consecutive breaths fell below 1/40th of initial end-tidal nitrogen concentration. Software automatically calculated all MBW outcomes as recommended [3]. Functional residual capacity (FRC) is the ratio of net volume of exhaled nitrogen over the difference between initial and final end-tidal nitrogen concentration. Cumulative expired volume is the net cumulative volume required to washout nitrogen to 1/40th of its initial concentration. Wait time between tests were determined by the setups` lockout time, i.e. at least 1.5 times the previous measurement duration. The primary outcome LCI is the ratio of cumulative expired volume over FRC, units are lung turnover. Secondary outcomes were diagnostic performance, repeatability, tidal volume, tidal volume over functional residual capacity (VT/FRC), respiratory rate, minute ventilation, and measurement duration per test. Immediate success rate determined in children was defined as proportion of those children in whom acceptable MBW tests were obtained from the first two attempts compared to those requiring more attempts. We also assessed CO_2 drift due to changes in breathing pattern. Data were however only available from NDD. Central overread of MBW quality was provided at the University Children's Hospital Zurich.

2.3.2. Spirometry

Patients with CF performed spirometry using the Jaeger MasterScreen (CareFusion, Germany) according to guidelines [22]. Outcomes were FEV_1 and forced expiratory flow between