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Original Article

Lung clearance index during hospital admission in school-age children with cystic fibrosis

Liam Welsh [a,b,*], Christopher Nesci [a], Haily Tran [a], Marisol Tomai [a], Sarath Ranganathan [a,b,c]

[a] Department of Respiratory Medicine, Royal Children's Hospital, Melbourne, Australia
[b] Murdoch Children's Research Institute, Melbourne, Australia
[c] Department of Paediatrics, University of Melbourne, Australia

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Abstract

Background: There is currently limited information regarding lung clearance index (LCI) and its response to treatment of pulmonary exacerbations in CF. We aimed to examine the utility of LCI for assessing short term clinical response to IV antibiotic therapy in school-age children with CF.
Methods: Subjects experiencing exacerbations and hospitalised for IV antibiotics performed both multiple breath nitrogen washout (MBNW) and spirometry on admission to hospital and prior to discharge.
Results: 27 patients (aged 6–20 years) had paired data for MBNW and spirometry. Mean LCI reduced from 12.18 to 11.65 (4.4%) by time of discharge and FEV_1 *z*-score improved from −3.05 to −2.86 (6.2%). Overall, LCI improved in n = 15 (55%) patients compared with n = 18 (67%) where FEV_1 improved.
Conclusions: In summary, these findings do not support the use of LCI (or indeed, FEV_1) to gauge the short term clinical response to IV antibiotic therapy in school-age children with cystic fibrosis.

Keywords: Cystic fibrosis; Lung function; Multiple breath washout; Pulmonary exacerbation

1. Introduction

Pulmonary disease in children with cystic fibrosis (CF) begins early in life with lung function abnormalities and bronchiectasis detected as soon as 3 months [1,2]. Traditional measures of lung function such as spirometry are often insensitive to the inhomogeneous nature of primary lung disease, with forced expiratory volume in 1 s (FEV_1) commonly preserved in the normal range for the first decade [3]. Despite this, spirometry is still used as the mainstay of lung function testing to monitor disease progression and response to therapy in outpatient and inpatient settings.

Multiple breath washout is now regarded as a more suitable method to gauge the subtle changes seen in early lung disease [4] and has the advantage of being applicable to all age-groups. Though it is well established that lung clearance index (LCI) is often abnormal in CF, it remains unclear what constitutes a clinically significant change. This is certainly an important question for those in the early stages of the disease process, which may be the optimal time to intervene, but it is also pertinent for those with established disease.

There is currently limited information regarding LCI and its response to treatment. To date, just three studies have examined the usefulness of LCI to gauge clinical improvement during hospital admission following a course of intravenous (IV) antibiotic therapy [5–7] and a heterogeneous response has been reported in each. Importantly, only one of these studies has reported on alveolar phase III indices. Evidently, further data are

* Corresponding author at: Respiratory Medicine, Royal Children's Hospital, Melbourne, Flemington Road, Parkville 3052, Australia. Tel.: +61 3 9345 5842; fax: +61 3 9345 9154.
E-mail address: Liam.welsh@rch.org.au (L. Welsh).

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required to better define the role of LCI and its concomitant indices in monitoring acute response to treatment.

The primary aim of this study was to examine the utility of LCI for assessing short term clinical response to IV antibiotic therapy in school-age children with CF. Firstly, we hypothesized that LCI would improve during the admission and secondly, that LCI would be a clinically useful tool for assessing the therapeutic benefit of IV antibiotics. Preliminary results of this study have previously been reported in the form of an abstract [8].

2. Methods

Between January and December 2013, consecutive patients with CF who were admitted to the Royal Children's Hospital (RCH), Melbourne requiring IV therapy were invited to participate. A pulmonary exacerbation was defined as any change in symptoms from baseline such as increase or development of cough, increase in purulent sputum production, or decrease in exercise tolerance, not responding to outpatient therapy. A clinical determination was made by the treating physician to administer IV antibiotics. Patients performed multiple breath nitrogen washout (MBNW) and spirometry on admission and prior to discharge. This study was approved by our local human research ethics committee. Informed consent was obtained from all patients and/or their parents.

Prior to testing, height was recorded without shoes to the nearest 0.1 cm using a fixed stadiometer (Harpenden Stadiometer, Holtain Ltd, Dyfed, UK) and weight was measured in minimal clothing, without shoes, to the nearest 0.1 kg using digital scales (Tanita BWB 600, Tanita Corporation, Tokyo). Height, weight and body mass index (BMI, i.e. weight/height^2), were reported in both raw form and as *z*-scores [9].

MBNW was performed using an Exhalyzer D (EcoMedics AG, Switzerland) running Spiroware version 3.1 software with the child sitting upright and wearing a nose clip. In brief, each test consisted of two phases. Following a period of tidal breathing of ambient air, participants were instructed to maintain their respiratory rate while breathing 100% oxygen. Each MBNW test finished when there were three consecutive breaths < 1/40th of the starting nitrogen concentration. A minimum of two satisfactory LCI results were obtained for each patient. A satisfactory trial was defined as a regular breathing pattern throughout the test, with no signs of mouth leak, and functional residual capacity (FRC) values within 10%. The minimum interval between tests was equal to washout time. Tests were performed before or at least 2 h after physiotherapy to avoid any confounding effects on FRC and thereby LCI. This methodology adheres to the most recently published consensus statement [10]. LCI was calculated as the cumulative expired volume required to dilute the end-tidal nitrogen concentration to 1/40th of the starting concentration divided by FRC. LCI results were expressed in absolute terms and also as *z*-scores [11].

Spirometry was performed using an MS Pneumo spirometer (Care Fusion, Germany) running SentrySuite version 2.7 software according to ATS/ERS standards [12] with results expressed as percent predicted and *z*-scores [13].

The Australian Cystic Fibrosis Data Registry was used to collect clinical information regarding genotype, newborn screening status, pancreatic insufficiency, CF related diabetes mellitus, and *Pseudomonas aeruginosa* (*PsA*) infection. Hospital records were used to determine the length of stay in hospital.

3. Statistics

Statistical analysis was performed using Stata Version 12.0 (Stata Corporation, Texas, USA). Paired *t*-tests were used to assess the change in lung function parameters over the course of the hospital admission. To determine whether changes in lung function outcomes during admission could be explained by factors other than IV antibiotic therapy, a stepwise regression model was developed to determine the influence of: sex, age, genotype (categorized as homozygous ΔF508 versus other/unknown), newborn screening, body mass index, pancreatic insufficiency, and *PsA* infection. Pearson's correlation was used to measure the magnitude and statistical significance of the relationship between change in LCI and FEV1 *z*-scores between admission and discharge. Significance levels were set at $p < 0.05$. LCI *z*-scores were generated using healthy control data (n = 57) from Vermeulen et al. [11] which used the same equipment and included children of a similar age range to our study (i.e. 4–18 years). The mean (SD) for LCI in their control group was 7.30 (0.50).

4. Results

Throughout 2013, we invited 48 children to participate in this study (4 declined). We collected paired MBNW and spirometry data from 27 patients (age 6–20 years) with CF on admission and prior to discharge during their hospital admission. Seventeen children completed baseline measurements only and were therefore not included in the analysis, however, they were similar in terms of sex (59% female), age (14.8 years), LCI *z*-score (8.7) and FEV_1 *z*-score (−3.16) when compared to the study group. Clinical demographics are shown in Table 1 and lung function results are shown in Table 2. Plots of spirometry and lung clearance index on admission and discharge are shown in Figs. 1 and 2.

The mean (SD) time to test on admission was 1.2 (0.9) days and mean time of test before discharge was 1.7 (2.5) days. The

Table 1
Clinical demographics of patients.

Subjects	27
Female (%)	15 (56%)
Age (years)	14.7 (6.2; 19.9)
ΔF508 homozygous (%)	13 (48%)
Pseudomonas aeruginosa colonised (%)	9 (33%)
Pancreatic insufficiency (%)	22 (81%)
Diagnosis by newborn screening (%)	17 (63%)
Height *z*-score	−0.05 (0.97)
Weight *z*-score	−0.31 (0.91)
BMI *z*-score	−0.25 (0.83)

Data presented as n, n (%), mean (range) or mean (SD).