Treatment response of airway clearance assessed by single-breath washout in children with cystic fibrosis

Chiara Abbas 1, Florian Singer 1, Sophie Yammime, Carmen Casaulta, Philipp Latzin *

Division of Respiratory Medicine, Department of Pediatrics, University Hospital of Bern, 3010 Bern, Switzerland

Received 18 December 2012; received in revised form 30 March 2013; accepted 26 May 2013
Available online 19 June 2013

Abstract

Background: We studied the ability of 4 single-breath gas washout (SBW) tests to measure immediate effects of airway clearance in children with CF.

Methods: 25 children aged 4–16 years with CF performed pulmonary function tests to assess short-term variability at baseline and response to routine airway clearance. Tidal helium and sulfur hexafluoride (double-tracer gas: DTG) SBW, tidal capnography, tidal and vital capacity nitrogen (N2) SBW and spirometry were applied. We analyzed the gasess’ phase III slope (SnIII — normalized for tidal volume) and FEV1 from spirometry.

Results: SnIII from tidal DTG-SBW, SnIII from vital capacity N2-SBW, and FEV1 improved significantly after airway clearance. From these tests, individual change of SnIII from tidal DTG-SBW and FEV1 exceeded short-term variability in 10 and 6 children.

Conclusions: With the tidal DTG-SBW, an easy and promising test for peripheral gas mixing efficiency, immediate pulmonary function response to airway clearance can be assessed in CF children.

© 2013 European Cystic Fibrosis Society. Published by Elsevier B.V. All rights reserved.

Keywords: Children; Cystic fibrosis; Respiratory function test; Physical therapy modalities; Pulmonary ventilation

1. Introduction

Airway clearance regimens, e.g. short-acting bronchodilator inhalation followed by chest physiotherapy (PT), are standard of current routine care in cystic fibrosis (CF). Few studies have attempted to measure treatment response in pulmonary function [1–4]. The currently most promising pulmonary function tests (PFTs) are the gas washout tests. These tests quantify the efficiency of gas mixing (ventilation distribution homogeneity) which may improve upon airway clearance [5–9]. The sulfur hexafluoride (SF6) multiple-breath washout (MBW) technique demonstrates changes in pulmonary function following four weeks of hypertonic saline or dornase alpha inhalation in mild CF lung disease [2,10]. However, immediate pulmonary function changes seem more difficult to assess [11–15].

We have recently developed and validated a new tidal single-breath washout (SBW) technique [16,17]. This SBW is based on a tidal in- and exhalation of a double-tracer gas (DTG) mixture containing helium (He) and SF6 during normal quiet breathing. An increased (steeper) phase III slope, i.e. the slope of phase III normalized for tidal volume (SnIII DTG), implies increased ventilation inhomogeneity near the acinar lung regions [17]. Alternatively, the SnIII from carbon dioxide (CO2 — capnography) or the SnIII from nitrogen (N2) SBW tests may contain information on global ventilation inhomogeneity [18,19]. Our objective was to study the ability of these gas washout tests to detect immediate pulmonary function changes upon routine
inhalation and chest PT. We analyzed SnIII of DTG, CO₂, and N₂ washout tests performed at baseline and after airway clearance. The primary end point was the change in SnIII upon intervention. We assessed these changes in the whole study population based on statistical thresholds (p < 0.05) and in individuals based on clinical thresholds (>95% short-term variability). Secondary aims were to compare SnIII changes with changes in forced expiratory volume in one second (FEV₁) and mean expiratory flow between 25% and 75% of expired volume (MEF₂₅–₇₅) from spirometry.

2. Methods

2.1. Study design

Twenty-five children aged 4–16 years attending the CF outpatient clinic at the Children’s University Hospital of Bern, Switzerland, were recruited. CF was diagnosed clinically in infancy. We conducted a pragmatic trial to study the ability of gas washout tests in measuring response to every-day airway clearance regimens (Fig. 1, Table 1). Children used their standard inhalation and PT regimen as performed at home. First, all children inhaled salbutamol or ipratropium bromide in saline solution for 15 min. Second, children performed chest PT under the guidance of pediatric CF physiotherapists for 25 min. Pulmonary function tests (PFT) consisted of two repeats at baseline (PFT #1), one PFT (#2) following inhalation and one PFT (#3) following both inhalation and PT. The first two baseline tests were performed 15 min apart to assess short-term repeatability between tests. The order of assessments within each PFT occasion was (i) tidal DTG-SBW, (ii) tidal capnography, (iii) tidal N₂-SBW, (iv) vital capacity N₂-SBW, and (v) spirometry. In total, 590 SBWs were successfully performed. To avoid possible training effects, baseline tests were averaged for comparison with PFT following interventions. The study (018/1) was approved by the Ethics Committee of the Canton of Bern, Switzerland. The children’s assent was obtained and all parents or caregivers provided full written informed consent for this study.

### Table 1

Characteristics of patients and interventions.

| Age (years) | 11.3 ± 3.5 |
| Females/males (n) | 15/10 |
| ΔF508 homozygous (n) | 12 |

### Inhalation medication and chest physiotherapy

- Hypertonic saline solution (3% or 6% NaCl): 14
- Isotonic saline solution (0.9% NaCl): 11
- Salbutamol: 22
- Ipratropium bromide/rhDNase/natriumcromoglycat: 2/2/5
- Positive end-expiratory pressure technique (PEP)/flutter: 22/3

Data are given as absolute counts, age is given as mean ± SD.

2.2. Pulmonary function tests

All tests were done by a single investigator (CA). We used available hard- and software (Exhalyzer D®, Eco Medics AG, Duernten, Switzerland) for all SBW tests as described previously [16,17,20–22]. In brief, side- and main-stream ultrasonic flowmeters measure molar mass and tidal flow. The molar mass signal is used for the DTG-SBW. N₂ measured indirectly via side-stream oxygen (O₂) and main-stream CO₂ sensors is used for the N₂-SBW tests. CO₂ measured directly is used for capnography. The DTG mixture contains 26.3% He and 5% SF₆, 21% O₂ and balance N₂ (Carbagas, Bern, Switzerland). This DTG mixture has the same molar mass as air, such that the shape of the washout curve can be attributed to He and SF₆ [16,17]. The principle of this new tidal DTG-SBW test is that the molar mass signal aggregates He and SF₆ washout behavior, i.e. phase III slopes of He and SF₆ [16]. These inert gasses distribute similarly by convection in the large central airways. Due to the differing molecular weight of He and SF₆, they distribute differently in the small peripheral airways. DTG was applied for a single tidal inhalation prior to exhalation back to functional residual capacity. Similarly, 100% O₂ was applied for N₂-SBW during tidal breathing. Maneuvers for vital capacity N₂-SBW were guided by visual incentives. CO₂ was measured prior to tidal SBW tests and used for capnography.

![Fig. 1. Flow chart of the study design.](image-url)
Between every gas washout test, children relaxed at least for two minutes.

Phase III slope (SIII) analysis was done by a single investigator (FS) using available software (LungSim, Numerical Modelling, Thalwil, Switzerland) according to the recent consensus document on inert gas washout testing and as previously described [17,23]. Tidal SBW tests were selected if tidal volumes were sufficiently large, i.e. phase III of the washout curve reflected at least 50% of expired tidal volume. SIII was calculated automatically by linear fit between 65 and 95% of expired volume from tidal tests [24], and between 25 and 75% of expired volume from the vital capacity N2-SBW [25,26]. The fit was manually adjusted if necessary. SIII was multiplied (normalized) with tidal volume (SnIII) to account for physiological differences in breaths within and between subjects [25]. SnIII from DTG, N2, and CO2 washout curves was the primary measure (Fig. 2a and b). SnIII_{DTG} mainly reflects acinar (diffusion–convection dependent) ventilation inhomogeneity [27]. SnIII_{DTG} z-scores were derived from a previous study in 52 healthy school-aged children from the same population [17]. SnIII_{N2} and SnIII_{CO2} are measures of global ventilation inhomogeneity and gas exchange efficiency. In general, a smaller, less steep slope (SnIII) upon airway clearance reflects improved gas mixing efficiency [25]. Thus a decrease in absolute SnIII_{N2} or SnIII_{CO2} values would suggest improved pulmonary function. Change of SnIII_{DTG} z-scores towards the normal range (within two z-scores) also reflects improved pulmonary function and gas mixing efficiency of both He and SF6 [16,25].

Spirometry was performed using a handheld device (EasyOne, ndd Medical Technologies, Zurich, Switzerland) according to current standards [28]. Outcomes were FEV₁ and MEF_{25–75}.

z-Scores were derived from published reference data [29].

2.3. Statistics

All analyses were done using Stata™ (StataCorp. 2009. Release 11. College Station, TX). We calculated sample size using the airway clearance regimen as the main exposure and SnIII_{DTG} as the primary outcome. We based our estimate on published SnIII_{DTG} variability of 20.8% within a comparable population. We estimated a treatment response of twice the variability (41.6%). Assuming a two-sided significance level of 5% and a power of 80%, 23 study participants would be needed to complete this study. We aimed to recruit 25 patients. To assess intra-test repeatability at baseline, the intraclass correlation coefficient (ICC) was calculated from a simple multilevel model from baseline data. The ICC relates between-subject variance to total variance, an ICC > 0.8 suggests good repeatability. We chose the ICC as we aimed to compare repeatability on untransformed data measured on different scales, and to account the within-subject variance to the varying degrees of variance between subjects [30]. As PFT data were not normally distributed, we described data by median (inter-quartile range — IQR) and compared data by Wilcoxon matched-pairs signed-rank tests on the group level. p-Values < 0.05 were considered statistically significant. On the individuals’ level we estimated the significance of observed changes in pulmonary function using the coefficient of repeatability (CR). The CR estimates the range of short-term variability between tests explained by technical or physiological factors which normally affect all physiological tests [31,32].

We calculated the CR of SnIII, FEV₁ and MEF_{25–75} from the first two baseline PFTs, i.e. 1.96 * standard deviations of differences between measurements. Following the airway clearance interventions, we considered any observed change in SnIII, FEV₁ and MEF_{25–75} greater than their CR as clinically significant.

3. Results

Ten boys and fifteen girls with CF were enrolled (Table 1). Mean (SD) age was 11.3 (3.5) years. Tidal gas washout tests and spirometry were obtained in all children except for one boy at baseline. The vital capacity N2-SBW was achieved by 20 children during all PFTs (Fig. 1). Thus, complete tidal SBW and spirometry data were available in 24 children and vital capacity of repeatable.
N\textsubscript{2}-SBW in 20 children. Intra-test repeatability was excellent for FEV\textsubscript{1} (ICC = 0.96), MEF\textsubscript{25–75} (ICC = 0.97) and SnIII\textsubscript{DTG} (ICC = 0.97), and good for tidal SnIII\textsubscript{N2} (ICC = 0.85). Tidal SnIII\textsubscript{CO2} (ICC = 0.69) and vital capacity SnIII\textsubscript{N2} (ICC = 0.67) were more variable in children. At baseline, twelve children had abnormal FEV\textsubscript{1} (<−2 z-scores) and 22 children had abnormal SnIII\textsubscript{DTG}. In those 13 children with normal FEV\textsubscript{1}, SnIII\textsubscript{DTG} was abnormal in ten.

On the group level, the tidal DTG-SBW and the vital capacity N\textsubscript{2}-SBW were the only gas washout tests detecting statistically significant pulmonary function response (Table 2). Similarly FEV\textsubscript{1} and MEF\textsubscript{25–75} improved (Fig. 3). Regarding the timing of response, SnIII\textsubscript{N2} from vital capacity N\textsubscript{2}-SBW, and FEV\textsubscript{1} and MEF\textsubscript{25–75} improved already after inhalation (2nd PFT). These measures kept their level without further improvement following chest PT (3rd PFT). Interestingly, the SnIII\textsubscript{DTG} marginally decreased (improved) after inhalation but significantly improved following chest PT. Baseline SnIII\textsubscript{DTG} median (IQR) was −66.0 (−168.5; −46.2) compared to −22.4 (−105.1; 57.2) mg/mol at the 3rd PFT (p = 0.017). Measures of ventilation heterogeneity were weakly or not interrelated, and FEV\textsubscript{1} and MEF\textsubscript{25–75} were consistently correlated.

On the individuals’ level, the size and direction of pulmonary function response in relation to the short-term variability (CR) were assessed. Pulmonary function responses were heterogeneous (Fig. 4). We observed both, smaller, less steep (improved) and steeper (worsened) SnIII as well as increased (improved) and decreased (worsened) FEV\textsubscript{1} or MEF\textsubscript{25–75} (Table 3). Clinical significant response (change > CR) was evident in 13 children: SnIII\textsubscript{DTG} (n = 10), SnIII\textsubscript{N2} from tidal SBWN\textsubscript{N2} (n = 4), SnIII\textsubscript{CO2} from tidal capnography (n = 1), MEF\textsubscript{25–75} (n = 8), and FEV\textsubscript{1} (n = 6). Change in pulmonary function was demonstrated by more than one PFT in 6/13 children. Relevant change of SnIII\textsubscript{DTG}, FEV\textsubscript{1} and MEF\textsubscript{25–75} was present in six children. In the other seven children, SnIII\textsubscript{DTG} exclusively changed in four children, and both FEV\textsubscript{1} and MEF\textsubscript{25–75} in three children. Individual response in SnIII\textsubscript{N2} from vital capacity SBWN\textsubscript{N2} did not exceed the CR.

![Image]

Fig. 3. Pulmonary function response on the group level. The normalized phase III slope (SnIII) from the tidal double-tracer gas single-breath washout (DTG-SBW), mean expiratory flow between 25% and 75% of expired volume (MEF\textsubscript{25–75}), and forced expiratory volume in one second (FEV\textsubscript{1}) improved comparing baseline pulmonary function (left box) and pulmonary function following routine airway clearance regimes (right box) in 24 children. z-Scores were derived from previous data [29]. p-Values were derived from Wilcoxon matched-pairs signed-rank tests.

To assess if the gas washout tests prove of higher value in a sub-set of patients, we stratified children into those with mild (normal baseline FEV\textsubscript{1}) and moderate CF lung disease (decreased baseline FEV\textsubscript{1} <−2 z-scores). In children with mild CF, SnIII\textsubscript{DTG} decrease was slightly greater compared to children with abnormal FEV\textsubscript{1} in whom SnIII\textsubscript{DTG} tended to increase (p = 0.042). Interestingly in the latter children with moderate CF lung disease, pulmonary function response was better detected by the vital capacity N\textsubscript{2}-SBW and spirometry: vital capacity SnIII\textsubscript{N2} decreased (p = 0.034) and FEV\textsubscript{1} improved (p = 0.002) while it did not change significantly in children with mild CF. This was confirmed by multivariable regression analysis (data not shown) adjusting for age, gender, and hypertonic vs. isotonic saline solution inhalation.

### Table 2

<table>
<thead>
<tr>
<th>Pulmonary function tests</th>
<th>Unit</th>
<th>n</th>
<th>Baseline</th>
<th>CR</th>
<th>Post-inhalation</th>
<th>p-Value</th>
<th>Post-inhalation &amp; physiotherapy</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tidal breathing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DTG-SBW</td>
<td>SnIII mg/mol</td>
<td>24</td>
<td>−66.0 (−168.5; −46.2)</td>
<td>65.3</td>
<td>−45.2 (−151.7; 89.1)</td>
<td>0.378</td>
<td>−22.4 (−105.1; 57.2)</td>
<td>0.017</td>
</tr>
<tr>
<td></td>
<td>SnIII z-Score</td>
<td>24</td>
<td>−3.3 (−5.4; −2.9)</td>
<td>1.3</td>
<td>−2.9 (−5.0; −0.2)</td>
<td>0.378</td>
<td>−2.5 (−4.1; −0.9)</td>
<td>0.018</td>
</tr>
<tr>
<td></td>
<td>Capnography</td>
<td>SnIII % CO\textsubscript{2}</td>
<td>24</td>
<td>0.8 (0.6; 1.0)</td>
<td>0.5</td>
<td>0.8 (0.6; 1.0)</td>
<td>0.946</td>
<td>0.7 (0.6; 1.1)</td>
</tr>
<tr>
<td></td>
<td>N\textsubscript{2}-SBW</td>
<td>SnIII % N\textsubscript{2}</td>
<td>24</td>
<td>6.5 (4.0; 8.9)</td>
<td>4.1</td>
<td>5.4 (3.8; 8.5)</td>
<td>0.382</td>
<td>6.8 (4.2; 9.5)</td>
</tr>
<tr>
<td><strong>Vital capacity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N\textsubscript{2}-SBW</td>
<td>SnIII % N\textsubscript{2}</td>
<td>20</td>
<td>8.7 (5.5; 12.5)</td>
<td>9.3</td>
<td>7.0 (4.7; 12.0)</td>
<td>0.019</td>
<td>6.3 (4.4; 11.9)</td>
<td>0.009</td>
</tr>
<tr>
<td>Spirometry</td>
<td>FEV\textsubscript{1} L</td>
<td>24</td>
<td>1.5 (1.3; 1.9)</td>
<td>0.3</td>
<td>1.7 (1.2; 2.0)</td>
<td>0.021</td>
<td>1.7 (1.2; 1.9)</td>
<td>0.033</td>
</tr>
<tr>
<td></td>
<td>FEV\textsubscript{1} z-Score</td>
<td>24</td>
<td>−2.15 (−3.3; −1.1)</td>
<td>0.8</td>
<td>−1.8 (−2.8; −0.9)</td>
<td>0.015</td>
<td>−2.0 (−3.0; −0.9)</td>
<td>0.051</td>
</tr>
<tr>
<td></td>
<td>MEF\textsubscript{25–75} L/s</td>
<td>24</td>
<td>1.3 (0.9; 1.8)</td>
<td>0.4</td>
<td>1.2 (0.9; 1.9)</td>
<td>0.011</td>
<td>1.2 (1.0; 2.0)</td>
<td>0.027</td>
</tr>
<tr>
<td></td>
<td>MEF\textsubscript{25–75} z-Score</td>
<td>24</td>
<td>−2.4 (−4.0; −1.6)</td>
<td>0.9</td>
<td>−2.4 (−3.6; −1.0)</td>
<td>0.017</td>
<td>−2.4 (−3.6; −0.8)</td>
<td>0.031</td>
</tr>
</tbody>
</table>

Pulmonary function data are given as median (IQR) and compared between baseline and post-intervention using the Wilcoxon matched-pairs signed-rank test. The coefficient of repeatability (CR) reflects the 95% range of short-term variability between tests. SBW: single-breath washout; SnIII: phase III slope normalized (multiplied) by tidal volume; DTG: double-tracer gas (5% helium and 26.3% sulfur hexafluoride); FEV\textsubscript{1}: forced expiratory volume in one second; and MEF\textsubscript{25–75}: mean expiratory flow between 25% and 75% of expired volume. Spirometry and DTG-SBW z-scores were calculated from published data [17,29].
4. Discussion

4.1. Summary

This study shows that the new tidal DTG-SBW test can be used to assess changes in gas mixing efficiency upon chest PT. This test seems especially attractive in patients with mild CF lung disease. The shape of the last third of the washout curve, the SnIIIDTG, is repeatable and sensitive outcome of the DTG-SBW. SnIIIDTG statistically significantly decreased comparing baseline and post-airway clearance values. In ten of 24 children, this change in SnIIIDTG clearly exceeded the predefined clinical threshold (short-term variability). The classical tests, spirometry and the vital capacity N2-SBW, rather reflect improvement of ventilatory capacity after bronchodilator inhalation. The latter pulmonary function response was more evident in children with advanced CF lung disease.

4.2. Clinical relevance

Easy and sensitive pulmonary function measures gain increasing interest in early interventional research to maintain respiratory health in CF [2,10]. We found that routine airway clearance improves pulmonary function which is measurable within the time frame of a single breath. The tidal DTG-SBW was easily applicable, highly repeatable within tests, and detected

Table 3

<table>
<thead>
<tr>
<th>Pulmonary function tests</th>
<th>Unit</th>
<th>n</th>
<th>CR</th>
<th>Median (IQR) response</th>
<th>Individual (n) response &gt; CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tidal DTG-SBW</td>
<td>SnIII mg/mol</td>
<td>24</td>
<td>65.3</td>
<td>−31.7 (−83.1; 3.2)</td>
<td>Flatter</td>
</tr>
<tr>
<td>Tidal DTG-SBW</td>
<td>z-Score</td>
<td>24</td>
<td>1.3</td>
<td>−0.6 (−1.6; 0.1)</td>
<td>Steeper</td>
</tr>
<tr>
<td>Tidal capnography</td>
<td>% CO2</td>
<td>24</td>
<td>0.5</td>
<td>0.1 (−0.2; 0.2)</td>
<td></td>
</tr>
<tr>
<td>Tidal N2-SBW</td>
<td>% N2</td>
<td>24</td>
<td>4.1</td>
<td>−0.1 (−1.6; 0.6)</td>
<td></td>
</tr>
<tr>
<td>Vital capacity N2-SBW</td>
<td>% N2</td>
<td>20</td>
<td>9.3</td>
<td>0.8 (0.5; 3)</td>
<td></td>
</tr>
<tr>
<td>Spirometry</td>
<td>FEV1 L</td>
<td>24</td>
<td>0.3</td>
<td>−0.1 (−0.2; 0.0)</td>
<td>Increase</td>
</tr>
<tr>
<td></td>
<td>z-Score</td>
<td>24</td>
<td>0.8</td>
<td>−0.2 (−0.6; 0.1)</td>
<td>Decrease</td>
</tr>
<tr>
<td></td>
<td>MEF25−75 L/s</td>
<td>24</td>
<td>0.4</td>
<td>−0.2 (−0.4; 0.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>z-Score</td>
<td>24</td>
<td>0.9</td>
<td>−0.4 (−0.8; 0)</td>
<td></td>
</tr>
</tbody>
</table>

Response in pulmonary function calculated as difference between baseline — post-inhalation and physiotherapy pulmonary function test (#3) are given as median and inter-quartile range (IQR). The number of children in which individual PFT differences were greater than the PFT’s coefficient of repeatability (CR = 1.96 * SD of differences between the two baseline PFTs). Flatter normalized phase III slopes (SnIII) and increased spirometry indices reflect pulmonary function improvement.

SBW: single-breath washout; DTG: double-tracer gas (5% helium and 26.3% sulfur hexafluoride); FEV1: forced expiratory volume in one second; and MEF25−75: mean expiratory flow between 25 and 75% of expired volume.
significant changes in gas mixing following routine airway clearance regimens in children. The effect size was significant with respect to both predefined statistical (on the group level) and clinical (on the individual level) thresholds (p- and CR-values). SnIII from vital capacity N2-SBW and spirometry indices also improved reassuring the clinical relevance. Statistically significant changes in gas mixing following standardized interventions, e.g. inhalation of hypertonic saline solution, have been shown previously [2,10]. The current study adds that treatment response can be measured easily in a single breath and may exceed short-term variability of gas mixing efficiency, i.e. the CR from repeated baseline tests, in individuals.

Most previous studies failed to detect effects of airway clearance on pulmonary function [15,33]. Fuchs et al. [15] did not find consistent changes in the lung clearance index (LCI), a measure of global ventilation inhomogeneity, following PT. Similarly, spirometry indices did not change. However, inhalation prior to PT was not applied and 14 patients may have provided less statistical power.

4.3. Physiological relevance

The DTG-SBW test differentiates specific ventilation inhomogeneity arising in pre-acinar lung regions where the diffusion–convection front of He arises, and the proximal acinar airways where the diffusion–convection front of SF6 arises. Secretions, airway inflammation, remodeling and other factors may impair the homogeneity and efficiency of ventilation distribution. Those mechanisms may have influenced He and SF6 wash-in, ventilation distribution, and subsequent washout of He and SF6 during the tidal DTG-SBW test.

Our data suggest that the combination of bronchodilator and chest PT can immediately improve gas mixing. SnIII\textsubscript{DTG} z-scores significantly decreased. Poorly ventilated lung spaces may have been recruited by the interventions and subsequently altered gas mixing. We hypothesize that the observed dynamics in gas mixing were mediated by the two major airway spaces which can be characterized by gas transport mechanisms: (i) convection dependent ventilation inhomogeneity in the central airways, and (ii) diffusion–convection dependent ventilation inhomogeneity near the acinar entrance [34]. Both convection and diffusion–convection dependent ventilation inhomogeneities give rise to the SnIII\textsubscript{N2} from vital capacity N2-SBW. SnIII\textsubscript{N2} from vital capacity N2-SBW, FEV\textsubscript{1} and MEF\textsubscript{25–75} systemically improved after bronchodilation but did not further improve after chest PT. Inhalation therapy may have primarily affected large airways via bronchodilation leading to decreased convection dependent ventilation inhomogeneity as well as increased ventilatory capacity. However, SnIII\textsubscript{N2} from tidal N2-SBW and SnIII\textsubscript{CO2} from capnography as previously described [19] were less able to measure immediate changes in gas mixing. The improvement of SnIII\textsubscript{DTG} following bronchodilator and chest PT suggests that sputum mobilization improved gas mixing in more peripheral air spaces where the convection–diffusion fronts of SF6 and He arise.

Measures of specific ventilation heterogeneity, such as the tidal DTG-SBW test, may be especially attractive to assess pulmonary function response in children with rather mild CF lung disease. Airway clearance regimens may improve regional ventilation heterogeneity in pre-acinar and acinar airways in these children. These specific changes in gas mixing efficiency can only be tracked by gases of similar conductive but highly differing diffusive properties, e.g. He and SF6 [35,36]. Given the progression of CF lung disease with increasing involvement of the central airways over time, the DTG-SBW could lose sensitivity in more advanced lung disease as it measures only regional ventilation heterogeneity. We found that in children with more pronounced CF lung disease (decreased FEV\textsubscript{1}), classical vital capacity N2-SBW and spirometry may detect pulmonary function response better than DTG-SBW. However, the numbers in the subgroups are small. The latter findings should thus be interpreted cautiously and require further study.

4.4. Strengths and limitations

The high intra-test repeatability (ICC) of the tidal SnIII\textsubscript{DTG} and tidal SnIII\textsubscript{N2} shows, that these measures are reliable in children whereas e.g. vital capacity SnIII\textsubscript{N2} is more variable despite the standardized breathing maneuver. Compared to the low variability between tests (CR) in FEV\textsubscript{1} in our study and previous reports [32], higher variability of SnIII from both tidal and vital capacity SBW tests was observed. The range of SnIII variability was well in line from multiple SnIII indices (Scond, Sacin) derived from MBW [22,24,37]. The current SnIII variability is likely to be physiological as measurement noise has been shown to be low [16,22].

The current pragmatic study incorporated airway clearance regimens as done regularly at home. We did not aim to compare any intervention but to assess the ability of four gas washout tests to measure immediate pulmonary function response to routine airway clearance. Further, chest PT is difficult to control, largely depends on the patients’ effort, and few studies exist showing immediate efficacy [11,12,14]. The study rather demonstrated real-world efficacy of routine airway clearance in children with CF. Treatment response seems to be frequently heterogeneous and may not exceed clinical thresholds [38]. The drawbacks of the current and other pragmatic designs are that interventions are not allocated randomly. However, pragmatic studies provide data from less selected populations and findings are considered to be clinically relevant [39]. We related observed treatment response in individuals to what can be expected solely due to short-term variability (CR). The CR provides 95% probability that the observed changes in pulmonary function following intervention were not due to chance. Changes greater than the CR were evident in half of the children. However, it is less clear, if change in gas mixing efficiency is predictive for sustained improvement of pulmonary function in CF.

Singer et al. [16,17] developed an easy SBW protocol that is especially attractive for measurements in children. This tidal DTG-SBW requires a few normal tidal breaths. Previous SBW protocols usually required exhalation to residual lung volume, inhalation to vital capacity, and then exhalation back to residual volume with predefined tidal flows. The LCI, the classical index derived from standard MBW, reflects efficiency of tracer gas
clearance, a robust measure of overall ventilation heterogeneity. However, standard MBW may take up to 40 min in children [40].

The current setup is currently the first which has been validated according to the ERS/ATS consensus on inert gas washout testing [23]. The software enables online visual control of signals and flow-volume curves as currently recommended. A limitation of the DTG-SBW test is that SF6 is required, a potential green house gas which is prohibited in some countries.

5. Conclusion

Gas mixing efficiency improves upon routine airway clearance regimens in children with CF. The tidal DTG-SBW is a promising test to assess gas mixing efficiency within the timeframe of a single breath. The treatment response measured by the DTG-SBW was significant based on both statistical and clinical thresholds. The DTG-SBW seems especially sensitive to measure pulmonary function response to chest PT in children with normal FEV1. In children with more advanced CF lung disease and decreased FEV1, spirometry and the classical vital capacity N2-SBW may demonstrate bronchodilator effects. The tidal DTG-SBW allows for easy and repeated assessments of gas mixing efficiency, an outcome of growing interest in CF care.

Disclosures

Dr. Abbas has no conflicts of interest to disclose. Dr. Singer has no conflicts of interest to disclose. Dr. Yammie has no conflicts of interest to disclose. Dr. Casaulta has no conflicts of interest to disclose. Dr. Latzin has no conflicts of interest to disclose.

Funding sources

The work for this report was funded by the Julia Bangerter-Rhyner Foundation and the Swiss Society for Cystic Fibrosis (http://www.cfch.ch). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgments

The authors would like to thank all the children and their families for their participation in the study. The authors thank Ruth Lacorcia Stauffer, Nicole Martin Santschi, and Sarah Clausen for their input and valuable care, and Per Gustafsson, Markus Roos, Urs Frey, Cindy Thamrin, and Georgette Stern for their scientific support. The authors would also like to express their gratitude to Martin Schoeni and Nicolas Regamey for their patient care.

References


