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Journal of Cystic Fibrosis 12 (2013) 567 – 574

Journal of Cystic Fibrosis

www.elsevier.com/locate/jcf

Original Article

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

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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 (N_2) SBW and spirometry were applied. We analyzed the gasses' phase III slope (SnIII — normalized for tidal volume) and FEV_1 from spirometry.
Results: SnIII from tidal DTG-SBW, SnIII from vital capacity N_2-SBW, and FEV_1 improved significantly after airway clearance. From these tests, individual change of SnIII from tidal DTG-SBW and FEV_1 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.

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 (SF_6) 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 SF_6 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 (CO_2 — capnography) or the SnIII from nitrogen (N_2) 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

Abbreviations: CF, cystic fibrosis; CO_2, carbon dioxide; CR, coefficient of repeatability (between-test repeatability); DTG, double-tracer gas: 26.3% helium and 5% sulfur hexafluoride; FEV_1, forced expiratory volume in one second; He, helium; LCI, lung clearance index; ICC, intra-class correlation coefficient (intra-test repeatability); $MEF_{25–75}$, mean expiratory flow between 25 and 75% of expired volume; MBW, multiple-breath washout test; N_2, nitrogen; PFT, pulmonary function test; PT, chest physiotherapy; SIII, slope of alveolar phase III from gas washout curves; SnIII, tidal volume normalized phase III slope from gas washout curves; SBW, single-breath washout; SF_6, sulfur hexafluoride.

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1569-1993/$ -see front matter © 2013 European Cystic Fibrosis Society. Published by Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jcf.2013.05.010

inhalation and chest PT. We analyzed SnIII of DTG, CO_2, and N_2 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 (FEV_1) and mean expiratory flow between 25% and 75% of expired volume ($MEF_{25–75}$) 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 N_2-SBW, (iv) vital capacity N_2-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. N_2 measured indirectly via side-stream oxygen (O_2) and main-stream CO_2 sensors is used for the N_2-SBW tests. CO_2 measured directly is used for capnography. The DTG mixture contains 26.3% He and 5% SF_6, 21% O_2 and balance N_2 (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 SF_6 [16,17]. The principle of this new tidal DTG-SBW test is that the molar mass signal aggregates the He and SF_6 washout behavior, i.e. phase III slopes of He and SF_6 [16]. These inert gasses distribute similarly by convection in the large central airways. Due to the differing molecular weight of He and SF_6, 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% O_2 was applied for N_2-SBW during tidal breathing. Maneuvers for vital capacity N_2-SBW were guided by visual incentives. CO_2 was measured prior to tidal SBW tests and used for capnography.

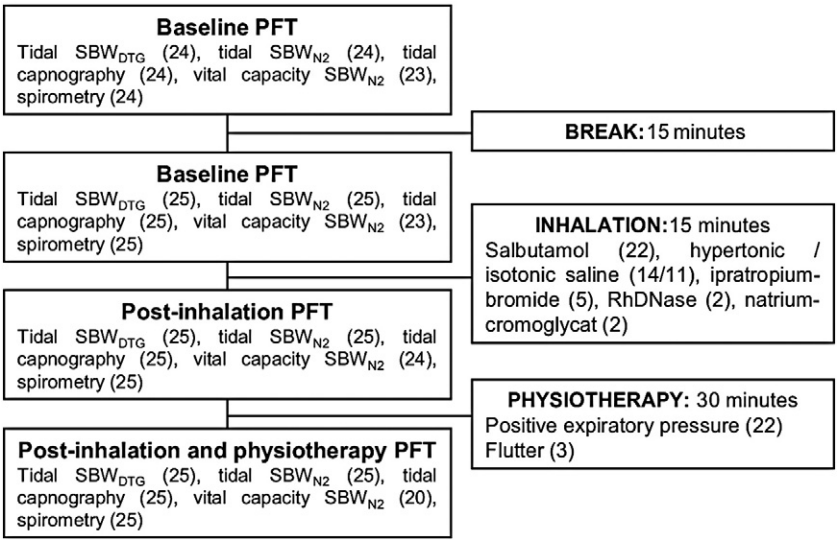

Fig. 1. Flow chart of the study design.