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Changes in breathing pattern upon 100% oxygen in children at early school age

K. Jost[a,b], N. Lenherr[b], F. Singer[c], S.M. Schulzke[b], U. Frey[b], P. Latzin[b,*], S. Yammine[d]

[a] Department of Biomedical Engineering (DBE), University of Basel, Basel, Switzerland
[b] Department of Pediatrics,University of Basel Children's Hospital, Basel, Switzerland
[c] Division of Respiratory Medicine, University Children's Hospital Zurich, Zurich, Switzerland
[d] Department of Pediatrics, Inselspital, Bern University Hospital, University of Bern, Switzerland

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ABSTRACT

Nitrogen multiple-breath washout (N_2MBW) is an increasingly used tidal breathing test in young children to assess ventilation inhomogeneity. However, the test requires 100% oxygen to perform. We aimed to examine the potential influence of pure oxygen on breathing pattern in school-aged children.

We performed tidal breathing measurements under room air followed by N_2MBW in 16 former preterm children and 24 healthy controls. We compared tidal volume (VT), coefficient of variation of VT (CV_{VT}), respiratory rate (RR), and minute ventilation (V_E) between tidal breathing and N_2MBW, and between the start and end of tidal breathing. Mean (range) age was 6.8 (5.9, 9.0) years. VT, RR and V_E showed no significant change upon oxygen-exposure, while CV_{VT} significantly decreased by 5% (95% CI: 1.2, 9.0; $p = 0.012$). However CV_{VT} was also the only parameter which significantly decreased during tidal breathing. Overall, pure oxygen has no systematic effect on breathing pattern in young school-aged children. N_2MBW can reliably be used as tracer gas in this age group.

1. Introduction

Multiple breath gas washout (MBW) measurements, which are used to estimate overall ventilation inhomogeneity, are being increasingly used in clinical practice (Singer et al., 2013; Yammine et al., 2013). MBW is a tidal breathing test, that can be performed in all age groups including children (Lum et al., 2007; Stahl et al., 2014). The resulting lung clearance index (LCI) has proven to help in the detection of early lung disease in children with cystic fibrosis (CF) (Gustafsson et al., 2003; Kieninger et al., 2011), and closely correlates to structural airway abnormalities (Ellemunter et al., 2010; Gustafsson et al., 2008; Owens et al., 2011). In the presence of a natural, regular breathing pattern, the calculation of LCI is robust and replicable (Gappa et al., 1993; Robinson et al., 2013; Singer et al., 2013). The application of 1 L tidal volume significantly increases LCI by an average of one unit in healthy children, forcing them to breath at a lower end-expiratory volume (functional residual capacity (FRC)) (Yammine et al., 2014). Given that LCI is calculated as a ratio of cumulative expired volume divided by FRC (calculated during tidal breathing), reliability of its measurements requires natural breathing pattern (Stanojevic et al., 2015).

While MBW tests can be performed using sulphur hexafluoride (SF_6) as tracer gas, nitrogen (N_2) MBW using 100% oxygen (O_2) as washout gas is regaining importance. The technical advantages of N_2MBW include the broad availability and low cost of O_2, as well as the avoidance of SF_6 as potential greenhouse gas. Pure O_2 can, however, influence breathing pattern in young children (Bates et al., 2013; Cross and Warner, 1951; Schibler et al., 2000; Singer et al., 2014). Singer et al. assessed tidal breathing measurements using ambient air, 40% O_2 and N_2MBW with pure O_2 in healthy infants and infants with CF. They were able to demonstrate an initial hypoventilation and increase in variability of breathing pattern upon O_2 administration, independent of disease state. Additionally, Bates et al. (Bates et al., 2014) demonstrated depressed minute ventilation in 21-year-old, who had been term born, after 60 s of pure O_2 administration. In contrast, adults who had been born premature showed a substantially reduced reaction of minute ventilation to hyperoxia.

Until now it is not known whether O_2 influences breathing pattern in early school age children. This would be an important determination, given the frequent us of N_2MBW in that age group. If it were determined that 100% O_2 alters breathing pattern, this would disrupt the stable, natural tidal breathing required

* Corresponding author at: University of Basel Children's Hospital (UKBB), Spitalstrasse 33, 4031 Basel, Switzerland.
E-mail address: philipp.latzin@ukbb.ch (P. Latzin).

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for accurate test results and would affect measurements significantly. A more comprehensive understanding of the effects of pure O_2 administration is necessary in order to accurately discriminate between the presence of true ventilation inhomogeneity, due to airway pathology, and erroneously measured ventilation inhomogeneity, due to O_2 administration.

1.1. Aims and hypothesis

Our aim was to systematically compare breathing patterns with and without exposure to 100% O_2 in children at early school age. We hypothesized that (i) pure O_2 alters breathing pattern in children, and (ii) changes in breathing pattern are less pronounced in former preterm children as compared to healthy term children. In order to investigate this, we compared tidal breathing measurement (ambient air) with two consecutive N_2MBW measurements (pure O_2). Differences between the two measurement types were compared with physiological variability, which was assessed by comparing the start and the end of the tidal breathing measurement.

Our primary outcome parameter was tidal volume (VT). Secondary outcomes were coefficient of variation of VT (CV_{VT}), respiratory rate (RR), and minute ventilation (V_E). As exploratory outcomes, we assessed if possible changes in breathing pattern influence LCI and FRC.

2. Methods

Between May 2012 and February 2014 we performed lung function measurements in healthy term-born and in former preterm children at early school age. This study represents a nested cross-sectional study and is part of a large cohort follow up (BILD) (Fuchs et al., 2012; Proietti et al., 2014). Patients were recruited consecutively, according to test validity comprising one valid tidal breathing measurement under room air, and at least two valid N_2MBW measurements. A further inclusion criterion was white ethnicity. Exclusion criteria were the presence of congenital bronchopulmonary malformations, asthma, or other chronic respiratory diseases, and respiratory infections within the 3 weeks preceding their lung function measurements. The study was approved by the Ethics Committee of the Canton Bern, and written parental informed consent was obtained prior to measurements. All tests were conducted at the University Children's Hospital in Bern, Switzerland.

2.1. Measurements

Measurements were performed in a previously described N_2MBW setup (Singer et al., 2012, 2013) using the Exhalyzer D and Spiroware 3.1.6. (Eco Medics AG, Duernten, Switzerland), following current consensus (Robinson et al., 2013). Prior to each measurement day flow and gas sensor of the equipment were calibrated. Children were sitting upright, watching a movie, wearing a nose clip, and breathing through a bacterial filter with a snorkel mouthpiece attached. Constant flow rate was monitored by the software, indicating flows below 950 mL/s of either the air or oxygen, both applied via wall outlets. We first performed 3 min tidal breathing measurements using medical air applied through an open by-pass system at 1 L/s. After a short break we moved into the second phase, which consisted of N_2MBW measurements using 100% O_2. Administration of O_2 was only started after regular breathing pattern was established, as determined by superimposed flow-volume loops. That period of adaptation took up to 10 breaths. Washout measurement was repeated after a pause consisting of the measurement time plus one minute to obtain at least two N_2MWB measurements that met quality criteria according to ERS/ATS guidelines (Robinson et al., 2013). Significant changes in breathing pattern

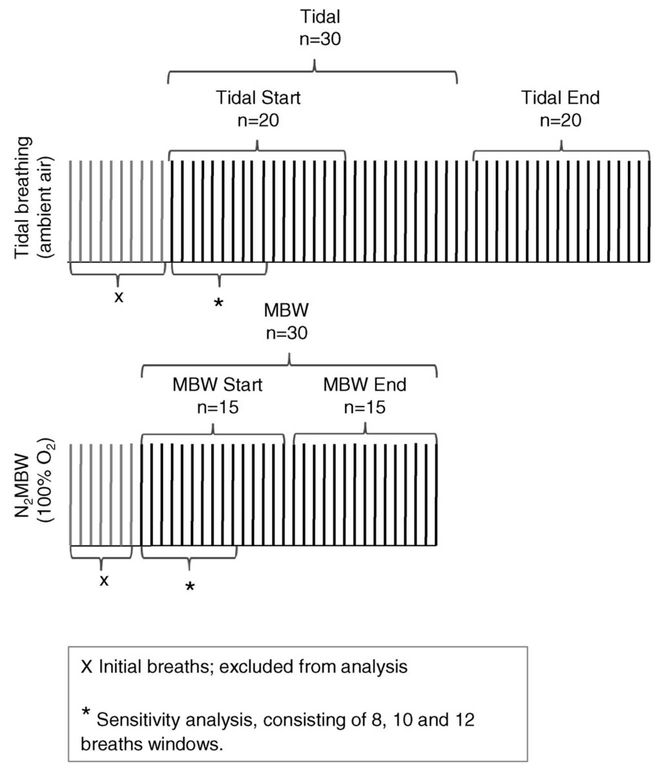

Fig. 1. Breathing pattern analysis; windows of interest.
Illustration of observation windows (in parentheses) for tidal breathing measurements (top) and nitrogen multiple breath washout (N_2MBW, bottom). Tidal breathing measurement under ambient air, divided into 3 windows of interest: Start n = 20 breaths; Tidal n = 30 breaths; End n = 20 breaths. First 10 breaths of tidal breathing measurement were systematically excluded from analysis to allow for a child's adaptation to the setup (marked with x). Breaths just prior to the start of pure O_2 exposure for N_2MBW, excluded as adaptation phase (marked with x). N_2MBW measurement under pure O_2, divided into 3 windows of interest: Start n = 15 breaths; MBW n = 30 breaths; End n = 15 breaths. Sensitivity analysis was done using smaller breath sample sizes (observation windows) are denoted with asterisks (*).

possibly resulting in changes in CO_2 could be excluded as stable CO_2 signal was observed and used as quality control.

2.2. Data processing and analysis

The first 5–10 measured breaths are considered an adaptation phase, during which the child adjusts to breathing into a machine (Hutten et al., 2010). For the analysis, therefore, we systematically excluded the first 10 breaths of every tidal breathing measurement and the breaths before start of O_2 wash-in during N_2MBW. Recorded raw data were analysed for tidal breathing parameters using Lungsim 4.8.1. (NM Modeling, Thalwil, Switzerland).

Primary and secondary outcomes (VT, CV_{VT}, RR and V_E) were assessed during predefined time windows (see Fig. 1) and derived from tidal breathing measurements, the first and the second N_2MBW tests. For primary analysis, only the first N_2MBW test was compared to tidal breathing; for the sensitivity analysis (see Section 2.2.4), analyses were repeated using the second N_2MBW test.

Comparison of the primary and secondary outcome variables included the following calculations (Fig. 1).

2.2.1. Ambient air versus N_2MBW measurements (30 breaths vs 30 breaths)

Comparison of a long continuous measurement period (30 consecutive breaths during tidal breathing measurements (Tidal 30), and 30 during N_2MBW (N_2MBW 30)).