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Evaluation of a multiple breath nitrogen washout system in children

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Abstract

Introduction: The multiple breath nitrogen washout (MBW) test offers a sensitive measure of airway function. In this study we aim to (a) assess the validity of the EasyOne Pro LAB (MBW_{ndd}) in an in vitro lung model, (b) assess the feasibility, repeatability, and reproducibility of MBW_{ndd} and (c) compare outcomes with the Exhalyzer D (MBW_{EM}) and body plethysmography.

Methods: In vitro, functional residual capacity (FRC) measurements were assessed using a lung model under quasi-physiological conditions and compared to measured FRC. In vivo plethysmography and MBW were performed in a prospective study of children at two visits (n = 45 healthy; n = 41 cystic fibrosis [CF]). Bland-Altman plots were used to compare agreement between FRC and lung clearance index (LCI) measurements.

Results: In vitro FRC_{ndd} measurements were repeatable but lung volumes were underestimated (mean relative difference -5.4% (limits of agreement [LA] -9.6%; -1.1%), 95% confidence interval (CI) -6.27; -4.45). In vivo, compared to plethysmography, FRC_{ndd} was consistently lower (-19.3% [-40.5; 1.9], 95% CI [-23.9; -14.7]), and showed a volume dependency. LCI_{ndd} values were also higher in children with smaller lung volumes. The within-test coefficient of variation of the FRC_{ndd} and LCI_{ndd} were 4.9% in health, and 5.6% and 6.9% in CF respectively. LCI_{ndd} was reproducible between-visits (mean relative difference [LA] -3.7% [-14.8; -7.5; 95% CI -6.6; -0.73] in health [n = 17] and 0.34% [-13.2, 22.8; 95% CI -5.0; 5.69] in CF [n = 23]). When calculated using the same algorithm, LCI_{ndd} was similar to LCI_{EM} in health.

Conclusions: MBW_{ndd} measurements are feasible, repeatable, and reproducible, however, MBW-derived outcomes are not interchangeable with MBW_{EM}.

KEYWORDS

function pulmonary testing

1 | INTRODUCTION

The ndd EasyOne Pro LAB (ndd Medical Technologies, Zurich, Switzerland) is a commercially available and Federal Drug Administration (FDA) approved multiple breath washout (MBW) device, which measures lung volumes and ventilation inhomogeneity. The availability of an FDA approved device is an important step towards the use of MBW as a routine clinical test. Accurate functional residual capacity (FRC) measurements are essential for accurate calculation of the primary ventilation inhomogeneity outcome of the MBW test, the lung clearance index (LCI). Therefore, international consensus recommends the validation of MBW devices such that FRC is within 5% of measured volume from a realistic lung model.¹ Previously, Raaijmakers et al² confirmed accurate measurement of FRC with the EasyOne Pro LAB device to be within 5% compared to a lung model; however, when compared to plethysmographic measurements of FRC in healthy children and adults, the EasyOne Pro LAB underestimated FRC by more than 20%. Subsequently, the software associated with the EasyOne Pro LAB underwent fundamental changes to the algorithms used to compute the nitrogen gas concentration (software version V2.1.0.8/9 released in March 2016).³ Retrospective analysis of previously collected data showed improved FRC agreement compared to plethysmography in adults.⁴

Using the updated EasyOne Pro LAB software we aimed to (a) validate FRC measurements over a range of volumes in vitro using a lung model, (b) prospectively evaluate the feasibility, repeatability, and reproducibility of FRC and LCI in children and (c) compare the outcomes and breathing pattern between the EasyOne Pro LAB and the Exhalyzer D device (Ecomedics AG, Duernten, Switzerland), as well as with lung volumes measured using body plethysmography. We hypothesized that the updated EasyOne Pro LAB software improves the feasibility, repeatability, and reproducibility of the test, and improves the agreement between the two commercially available devices.

2 | METHODS

2.1 | In vitro lung model experiments

To systematically assess the technical repeatability and accuracy of FRC measured by the EasyOne Pro LAB device we used a previously described lung model^{5,6} and quasi-physiological conditions. In brief, the custom-built Plexiglas lung model consisted of one lung compartment partly filled with water, room air and 5% CO₂, and one communicating compartment that enabled mechanical ventilation through the water column, surrounded by an outer water tank heating the inner compartments to 37°C. The lung compartment was filled with water such that the gas volume above the water surface determined resting lung volume (ie, FRC). A ventilator (Fabian Plus Acutronic Medical Systems AG, Hirzel, Switzerland) with a fixed respiratory rate (15 breaths/min) ventilated the lung model to reflect the lung volume ranges observed in a pediatric population.

To minimize the possible sources of error from varying respiratory rates, we restricted the model to this quasi-physiological, fixed respiratory rate. We consecutively tested eight-volume settings in triplicate (tidal volumes ranging from 250-900 mL and FRC volumes ranging from 600-3000 mL).

2.2 | In vivo measurements

In the prospective observational study, children between 4 and 18 years of age (>18 kg) were enrolled from July 2016 to December 2017 at four participating sites; The Hospital for Sick Children (Toronto, Canada), The Royal Brompton Hospital (London, UK), Inselspital (Bern, Switzerland), and Marien hospital (Wesel, Germany) in collaboration with Beatrix Children's Hospital University Medical Centre Groningen. The study sample size (approximately 20/site) was a convenient sample balanced across study sites. Healthy controls (without a history of chronic bronchodilator or controller medication use for asthma symptoms, nor chronic lung disease), and a group of children with cystic fibrosis (CF) were recruited. Exclusion criteria for the CF group included the use of supplemental oxygen and previous organ transplant. All participants underwent a clinical assessment to determine if they were free of acute respiratory tract symptoms; testing was rescheduled at least 4 weeks later if children were symptomatic. The study was approved by the local research ethics board at each participating site. Informed written consent was obtained from the parents or guardians. Assent was obtained from subjects when appropriate.

All participants performed plethysmographic lung volume (FRC) measurements using commercial equipment available at each site. Plethysmographic lung volume measurements were performed according to American thoracic society standards⁷ and reported as a volume in liters. Before data collection, the manufacturer installed the EasyOne Pro LAB device (MBW_{nda}) equipment, provided training, and approved operational readiness of the setup new to the device. All MBW_{nda} measurements were performed according to the manufacturer's operator manual on the same software version (V2.2.0.14/15) at two study visits separated by 1 to 4 months. Over the course of the study there were further updates made to the software that affected the calculation of FRC values but did not affect data acquisition. Therefore, MBW_{nda} results were recalculated using version (v3.02.00.06). All MBW trials were evaluated for evidence of leaks, reequilibration of baseline gases, and end of test criteria on software version (v3.02.00.06) by independent reviewers from two sites using published recommendations.^{1,8} Each trial was also evaluated for breathing pattern to ensure it was representative of relaxed tidal breathing with no evidence of hyperventilation. A successful MBW test occasion had a minimum of two acceptable trials.⁹ Results are reported for tests where two independent reviewers agreed on trial acceptability.

A subset of participants (from three sites) also performed MBW on the Exhalyzer D (MBW_{EM}; Duernten, Switzerland, software version 3.1.6). The Exhalyzer D was chosen as the comparator as it

the other commercially available device that also measures multiple breath nitrogen washout. The order of testing (MBW_{EM}: MBW_{ndd}) was randomized 1:1 using a random number generator. The same testing order was used at the follow-up visit. MBW_{EM} measurements were performed according to the International Standard Operating Procedure,¹⁰ and reviewed for quality by two independent reviewers using the same criteria as for MBW_{ndd}. Results are reported for tests where two independent reviewers agreed on trial acceptability. In addition to the comparison of the primary outcomes (LCI and FRC), breathing pattern indices (tidal volume (V_T), respiratory rate, and minute ventilation) were compared between the two devices.

One fundamental difference observed between the two commercial devices was the algorithm used to calculate LCI. The EasyOne Pro Lab calculated the FRC at the airway opening but the cumulative expired volume (CEV) from the gas sampling point, whereas the Exhalyzer D calculated both FRC and CEV at the airway opening. Therefore, LCI_{ndd} was recalculated to the airway opening (LCI_{ndd-ao}), instead of the gas sampling point, to match the LCI_{EM} algorithm and American Thoracic Society/European Respiratory Society consensus statement.¹

2.3 | Statistical analysis

Agreement between FRC measurements (in vitro and in vivo), and between devices (MBW_{ndd} and MBW_{EM}) was compared using a Bland-Altman plot.¹¹ Limits of agreement (LA) were calculated as the mean difference $\pm$ 1.96 times the standard deviation (SD) of the difference. Repeatability was determined by the coefficient of variation (CV) of trials within the same test. Absolute and relative differences of MBW outcomes between test-occasions within the same subject were compared using paired *t*-tests. A *P*-value $< .05$ was regarded as statistically significant. The analysis was done in Stata 14 (College Station, TX).

3 | RESULTS

3.1 | In vitro FRC measurements

Within-test agreement of FRC_{ndd} was approximately 5% of measured FRC under body temperature and pressure saturated conditions with CO₂ added. The mean difference between lung model and measured FRC was -5.4% (limits of agreement -9.6% ; -1.1% , 95% confidence interval (CI) -6.27 ; -4.45) (Figure 1). The repeatability of the test was also high (mean CV 1.2% (SD [0.9])). However, there was a systematic underestimation of lung volumes generated by the model, whereby large volumes had a larger offset (Figure 1).

3.2 | In vivo MBW measurements

A total of 86 subjects (45 healthy and 41 CF) were enrolled (Table 1; Figure S1). Feasibility for EasyOne was high and similar between

FIGURE 1 Agreement between FRC measured by MBW_{ndd} FRC generated by the lung model under BTPS conditions and CO₂ added. Mean difference FRC_{ndd} measured – FRC model (-5.4% (Limits of agreement -9.6% ; -1.1%). BTPS, body temperature and pressure saturated; FRC, functional residual capacity, MBW, multiple breath nitrogen washout

TABLE 1 Characteristics of participants with an acceptable MBW_{ndd} measurement at the first visit

	Health (n = 24)	CF (n = 34)
n (%) Female	12 (50%)	21 (62%)
Age (years) mean (range)	12.7 (6-17.8)	11.8 (6.7-17.6)
Weight (kg) centile-for-age	64.4 (25.8)	55.3 (28.1)
BMI centile-for-age	50.7 (28.9)	46.6 (21.9)
Height (cm) centile-for-age	58.5 (23.0)	48.8 (24.4)
FEV ₁ (% predicted) n = 22	102.2 (11.0)	92.1 (17.9)
FEV ₁ z-scores n = 22	0.19 (0.9)	-0.66 (1.5)
FRC pleth (L)	2.3 (0.85)	2.0 (0.7)
LCI mean (SD)	7.5 (0.8)	9.9 (2.7)
FRC (L) mean (SD)	1.9 (0.9)	1.51 (0.7)
CEV (L) mean (SD)	13.6 (5.5)	16.0 (11.3)
Within-test repeatability		
CV% LCI (median, IQR)	4.9 (2.5, 7.3)	6.9 (3.6, 10.0)
CV% FRC (median, IQR)	4.9 (2.7, 10.5)	5.6 (3.2, 9.0)
Between-test reproducibility (n = 17 HC; n = 23 CF)		
% Difference LCI (mean, LA)	-3.7 (-14.8, 7.5)	0.34 (-13.2, 22.8)
% Difference FRC (mean, LA)	4.8 (-19.4, 31.8)	0.15 (-20.0, 20.3)

Notes: An acceptable MBW visit consisted of at least two technically acceptable trials, which were deemed accepted by two independent reviewers. Data presented as mean (SD) unless otherwise indicated. Anthropometric centiles calculated using CDC growth charts,¹² percent predicted FEV and z-scores calculated using Global Lung Function Initiative reference equations.¹³

Abbreviations: BMI, body mass index; CEV, cumulative expired volume; CF, cystic fibrosis; CV, coefficient of variation; FEV₁, forced expiratory volume in 1 s; FRC, functional residual capacity; HC, healthy control; LA, limits of agreement; LCI, lung clearance index pleth, plethysmography.

reviewers at three sites (Figure S1). On average participants attempted a test four times (range 2-12) at each test occasion. Overall, 80% and 83% of the individual trials were confirmed to be acceptable by two reviewers at the first and second visits respectively; however, this translated to 67% of test occasions accepted by two reviewers at the first visit and 59% at the second visit. The main reason for unsuccessful tests was an irregular breathing pattern or evidence of leaks. The disagreement between reviewers was often due to irregular breathing patterns. Feasibility varied by site (Table S1). There were no adverse events observed during testing.

Compared to FRC measured by plethysmography, FRC_{ndd} was consistently lower in healthy children (mean difference -19.3% (LA -40.5 , 1.9), 95% Confidence Interval -23.9 ; -14.7) and showed a lung volume dependency with the largest differences observed in children with the smallest FRC (Figure 2A). Similar results were observed in the CF group (Figure S2). For the Ecomedics, overall the findings were similar, with FRC_{EM} lower than plethysmography (Figure 2B).

MBW_{ndd} outcomes were repeatable. CV was within 10% for LCI_{ndd} and FRC_{ndd} for both health (LCI CV IQR 2.5-7.3%; FRC CV IQR 2.7-10.5) and CF (LCI CV IQR 3.6%-10%, FRC CV IQR 3.2-9.0%) for the majority of tests (Table 1). MBW_{ndd} measurements were measured successfully at two visits in 17 healthy and 23 CF subjects. The average time between repeated visits was 2.3 months (range 1-4 months). The mean difference between sequential LCI_{ndd} measurements was -3.7% (LA; -14.8 , 7.5 , 95% CI -6.6 ; -0.73) in health and 0.34% (LA -13.2 , 22.8 ; 95% CI -5.0 ; 5.69) in CF (Table 1).

3.3 | Comparisons between MBW_{ndd} and MBW_{EM}

There were paired MBW_{ndd} and MBW_{EM} data for 10 healthy (mean [SD] age 10.3 [4.1]) and 15 CF subjects (mean [SD] age 11.9 [3.1]) from three sites. Feasibility for MBW_{EM} also differed by site and reviewer (Figure S1; Table S1). The subset with measurements on both devices was similar but slightly younger (Table S2). The average LCI_{EM} was 6.95 (SD 0.48) in health and 9.58 (3.16) in CF. The average FRC_{EM} was 1.56 L (SD 0.97) in health and 1.73 L (0.71) in CF. The lung volume-dependent bias was also observed for FRC_{EM} compared with plethysmography (Figure 2B). LCI_{ndd} was 1.1 (SD 0.2) units higher than LCI_{EM} in health, and 0.4 (SD 0.3) units lower in CF (Figure S4). Breathing pattern indices did not differ between the healthy controls and subjects with CF. In the pooled data (healthy and CF subjects) respiratory rate and minute ventilation were significantly higher for MBW_{ndd} than MBW_{EM} (Table 2).

The differences observed between the two devices were further investigated. LCI_{ndd} decreased with age (Figure 3A), whereas LCI_{EM} did not (Figure S3). The differences were thought to be attributed to differences of algorithms in analysis software between devices; therefore, LCI_{ndd} was re-calculated to the airway opening (LCI_{ndd-ao}), instead of the gas sampling point, to match the LCI_{EM} algorithm. The LCI_{ndd-ao} was lower than LCI_{ndd} by an average of -0.9 (LA -0.1 , 1.8 , 95% CI -1.81 ; 0.10) units in health and 1.2 (LA 0.2 , 2.1 , 95% CI -1.32 ; -1.0) units in CF; the age dependency was no longer observed

(Figure 3B). After recalculation, the differences between the devices were minimal in healthy subjects; LCI_{ndd-ao} was -0.1 (SD 0.5) units lower in health (Figure S5) but 1.4 (SD 1.5) units lower in CF (Figure S6).

4 | DISCUSSION

MBW testing with the EasyOne Pro LAB device was feasible, repeatable, and reproducible. MBW_{ndd} outcomes showed a bias for smaller lung volumes, suggesting that the current hardware (ie, dead space) and/or software version may not be ideally suited for children less than 10 years of age.

In vitro experiments confirmed that measurement precision of the MBW_{ndd} device is high, however, accuracy was fair. This suggests that both generated lung model volumes and measurements were repeatable as shown for other setups.^{5,14,15} However, a negative lung

FIGURE 2 A, Agreement between FRC_{pleth} and FRC_{ndd} in healthy children at the first visit. Mean difference -19.3% (limits of agreement -40.5% ; 1.9%). B, Agreement between FRC_{pleth} and FRC_{EM} in healthy children the first visit ($n = 10$). Mean difference -10.9% (95% limits of agreement -42.1% ; 20.3%). FRC, functional residual capacity

TABLE 2 Comparison of breathing pattern indices between MBW_{ndd} and MBW_{EM} within the same subject

	NDD N = 25	Ecomedics N = 25	Mean difference between devices (95% CI)
Vt, mL	438.0 ± 174	459.3 ± 185	-21.3 (-50, 8)
Vt/kg	11.3 ± 2.8	11.8 ± 2.9	-0.5 (-1.3, 0.2)
RR (/min)	25.2 ± 5.5	18.0 ± 4.1	7.2 (5.7, 8.8)
MV, L/min	10.5 ± 3.1	7.7 ± 2.4	2.8 (1.8, 3.8)

Notes: Bold differences indicate the observed difference between devices within the same subject was statistically significant at $P < .0001$. Data were pooled for health and CF ($n = 10$ HC; $n = 15$ CF).

Abbreviations: CF, cystic fibrosis; CI, confidence interval; HC, healthy control; MV, minute ventilation; RR, respiratory rate; Vt, tidal volume; Vt/kg, tidal volume divided by weight in kg.

volume-dependent bias was observed in vivo which was smaller than the positive bias in vitro. Although the in vitro data are an important aspect of validation, the lung model is not a biological model and may not represent the human lung during dynamic breathing.⁵ We chose to use a fixed respiratory rate (15 breaths/min) to minimize

possible sources of error from a varying respiratory rate,^{5,14,15} but acknowledge this may not reflect normal in vivo breathing patterns. Temperature fluctuations in the model may differ from in vivo conditions, and we did not modulate the lungs' CO₂ fraction or the normal variability in breathing patterns. However, FRC measurement from other systems was apparently less affected by in vitro temperature fluctuations.^{5,14} In a retrospective analysis Tonga et al found the original differences observed in adults between FRC_{ndd} and plethysmography were corrected with the updated software. Our results suggest that the bias still exists in children with small lung volumes. Although FRC measured by plethysmography is not a gold standard, it is the most established and feasible measurement of lung volumes in children.

MBW_{ndd} measurements were feasible in children naïve to the device, with success rates consistent with previous studies.^{16,17} In this study all results were presented based on a consensus agreement between two independent reviewers, and therefore the feasibility does not reflect a single-center experience. Although there was good agreement between reviewers for acceptable trials, agreement for acceptable test occasions was lower and reflects the need for further standardization of over-reading protocols and practice. The main study findings were similar when analyses were repeated using quality control decisions made by a single reviewer (Table S4). In addition, the success rates varied between the sites. Although the same testing protocol was followed at each site, feasibility was affected at some sites where the protocol was combined with complementary protocols. In addition, the experience of these four sites may not necessarily represent naïve sites that will likely require training and support. Furthermore, the data acquisition user interface (software version V2.2.0.14/15) had limited visualization of the washout curve and washout data, which may have led to missed leaks during testing, and affected measurement at all sites. Over the course of the study, the user interface was improved to allow for a closer inspection of gas and flow tracings to assess for leaks or abnormal breathing patterns (software version v3.02.00.06). The improved software version was used for the qualitative review of study data and for reporting of values and may have led to exclusion of results originally accepted by the operators during data acquisition. The two devices (MBW_{ndd} and MBW_{EM}) were chosen for comparison because of their similarities, but they do differ in several ways

FIGURE 3 A, Relationship between LCI_{nda} and age in healthy subjects ($n = 24$). B, Relationship between LCI_{nda} and age in healthy subjects. ($n = 24$) LCI_{nda} was recalculated at the airway opening (ie, when the dead space was removed from the CEV for each breath). CEV, cumulative expired volume; LCI, lung clearance index

including that the MBW_{ndd} devices deliver O₂ using a demand value compared with a passive bias-flow on the MBW_{EM} device. Some participants reported discomfort with the demand valve and noise generated by the MBW_{ndd} system, which may also affect feasibility and changes in respiratory rate. The observed difference in breathing patterns may explain some of the differences in MBW outcomes. The respiratory rate on both devices is within the expected range of 18 to 30 breaths/min typically observed in normal children. Similarly, the tidal volumes were within the expected range. The comparison is limited to a small number of subjects and requires further study.

FRC_{ndd} and LCI_{ndd} measurements were also repeatable and reproducible (2-3 months), which is comparable to previously published studies.^{16,18,19} The timing of the repeated measurements was chosen specifically to reflect routine clinical follow-up in children with CF and may not represent the reproducibility for other intervals.

Consistent with previous studies^{2,16} MBW_{ndd} outcomes were not interchangeable with the MBW_{EM}. This may be partially explained by the difference in algorithms between the devices used to calculate LCI. The age-dependent LCI inverse relationship initially observed for LCI_{ndd} was no longer observed when LCI_{ndd} was recalculated at the airway opening (ie, when the dead space was subtracted from the CEV for each breath).¹ Of note, the size-dependent bias observed for FRC_{ndd} compared with FRC_{pleth}, was also observed for the FRC_{EM}, which is consistent with previous studies in healthy children²⁰ and may partially reflect size-dependent effects of tissue nitrogen on the FRC measurement.²¹ The observed association of lung volume measurement (FRC) with lung size requires further study. Interpretation of the results of the comparison between the two devices are limited because of the low number of subjects successfully completing the entire study protocol. This may have been due to the fact that the present protocol was added at the end of another long protocol in one out of three centers. The primary aim of this study was to evaluate the EasyOne Pro LAB device therefore direct comparisons with the Exhalyzer D, a secondary aim, were only performed at three of the participating sites and thus limits direct comparison of feasibility. Although the magnitude of the differences in FRC and LCI were smaller than previously reported,^{2,16} the observed differences highlight the need for systematic validation following both hardware and software updates to equipment. The observed differences between devices also mean that further standardization of the MBW test is necessary before either device is introduced into routine clinical care notwithstanding algorithm alignment, it is essential that manufacturers are transparent in describing the algorithms used and calculations applied in their software.

5 | CONCLUSION

MBW measurements on the EasyOne Pro LAB are feasible, repeatable, and reproducible. Measurements with the EasyOne Pro Lab and Exhalyzer D are not interchangeable. Further work is needed on standardizing algorithms used and calculations applied.

CONFLICT OF INTERESTS

Dr. Latzin reports personal fees from Vertex, personal fees from Novartis, Roche, Polyphor, Vifor, Gilead, Schwabe, Zambon, Santhera and grants from Vertex, outside the submitted work. Dr. Zwitterloot reports nonfinancial support from NDD medical technologies, during the conduct of the study; other from Advisory board GSK, other from Advisory board Vertex Pharmaceuticals, other from Part of faculty MBNW LEAD meeting Bern, Vertex Pharmaceuticals, outside the submitted work; Dr. Stanojevic reports grants from Vertex Pharmaceuticals, during the conduct of the study; Ms. Jensen reports grants from Vertex Pharmaceuticals, during the conduct of the study. Dr. Singer reports personal fees from Novartis, Vertex, outside the submitted work; Dr. Ratjen reports grants and personal fees from Vertex and personal fees from Novartis, Bayer, Roche, Genetech, outside the submitted work. Dr. Davies reports others from Algiapharma AS, Bayer AG, Boehringer Ingelheim Pharma GmbH & Co. KG, Galapagos NV, ImevaX GmbH, Nivalis Therapeutics, Inc., ProQR Therapeutics III B.V., Proteostasis Therapeutics, INC., Raptor Pharmaceuticals, Inc, Vertex Pharmaceuticals (Europe) Limited, Enterprise, Novartis, Pulmocide and Flatley, grants from CF Trust, other from Teva, outside the submitted work; Dr. Anagnostopoulou, Dr. Gappa Ms, Isaac, Mr. Short, Ms. Saunders have nothing to disclose.

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REFERENCES

- Robinson PD, Latzin P, Verbanck S, et al. Consensus statement for inert gas washout measurement using multiple- and single-breath tests. *Eur Respir J*. 2013;41(3):507-522.
- Raaijmakers L, Jensen R, Stanojevic S, Ratjen F. Validation of multiple breath washout devices. *J Cyst Fibros*. 2017;16:e22-e23.
- Buess C. Improved MBW Algorithm. (Application Note – Improved MBW V03R). 2017. <https://www.ndd.ch/en/support/download/application-notes.html#downloads-easyoneprolab>. Accessed May 25, 2020.
- Tonga KO, Robinson PD, Farah CS, King GG, Thamrin C. In vitro and in vivo functional residual capacity comparisons between multiple-breath nitrogen washout devices. *ERJ Open Res*. 2017;3(4):00011-2017.
- Singer F, Houlitz B, Latzin P, Robinson P, Gustafsson P. A realistic validation study of a new nitrogen multiple-breath washout system. *PLoS One*. 2012;7(4):e36083.
- Anagnostopoulou P, Vomsattel S, Kentgens AC, et al. An innovative lung model for multiple breath washout testing in health and disease. *Clin Biomech*. 2019;66:74-80.
- Wanger J, Clausen JL, Coates A, et al. Standardisation of the measurement of lung volumes. *Eur Respir J*. 2005;26(3):511-522.
- Jensen R, Stanojevic S, Klingel M, et al. A systematic approach to multiple breath nitrogen washout test quality. *PLoS One*. 2016;11(6):e0157523.
- Robinson PD, Latzin P, Ramsey KA, et al. Preschool multiple-breath washout testing. An official American Thoracic Society technical statement. *Am J Respir Crit Care Med*. 2018;197(5):e1-e19.

10. Jensen R, Green K, Gustafsson P, et al. *Standard Operating Procedure: Multiple Breath Nitrogen Washout Exhalizer® D*. Ecomedics AG. 2013. http://www.mbwtraining.com/ECFS_MBW_SOP.pdf. Accessed May 25, 2020.
11. Bland JM, Altman DG. Measurement error. *BMJ*. 1996;312(7047):1654.
12. Kuczmarski R, Ogden CL, Guo S, et al. *CDC Growth Charts*. National Center for Health Statistics. 2000.
13. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J*. 2012;40(6):1324-1343.
14. Gonem S, Singer F, Corkill S, Singapuri A, Siddiqui S, Gustafsson P. Validation of a photoacoustic gas analyser for the measurement of functional residual capacity using multiple-breath inert gas washout. *Respiration*. 2014;87(6):462-468.
15. Schmidt A, Yammine S, Proietti E, et al. Validation of multiple-breath washout equipment for infants and young children. *Pediatr Pulmonol*. 2015;50(6):607-614.
16. Poncin W, Singer F, Aubriot AS, Lebecque P. Agreement between multiple-breath nitrogen washout systems in children and adults. *J Cyst Fibros*. 2016;16:258-266.
17. Fuchs SI, Schwerk N, Pittschieler K, et al. Lung clearance index for monitoring early lung disease in alpha-1-antitrypsin deficiency. *Respir Med*. 2016;116:93-99.
18. Fuchs SI, Eder J, Ellemunter H, Gappa M. Lung clearance index: normal values, repeatability, and reproducibility in healthy children and adolescents. *Pediatr Pulmonol*. 2009;44(12):1180-1185.
19. Fuchs SI, Ellemunter H, Eder J, et al. Feasibility and variability of measuring the lung clearance index in a multi-center setting. *Pediatr Pulmonol*. 2012;47(7):649-657.
20. Jensen R, Stanojevic S, Gibney K, et al. Multiple breath nitrogen washout: a feasible alternative to mass spectrometry. *PLoS One*. 2013; 8(2):e56868.
21. Kane M, Rayment JH, Jensen R, McDonald R, Stanojevic S, Ratjen F. Correcting for tissue nitrogen excretion in multiple breath washout measurements. *PLoS One*. 2017;12(10): e0185553.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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