

New time-saving predictor algorithm for multiple breath washout in adolescents

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BACKGROUND: Multiple breath washout (MBW) is an informative but time-consuming test. This study evaluates the uncertainty of a time-saving predictor algorithm in adolescents.

METHODS: Adolescents were recruited from the Copenhagen Prospective Study on Asthma in Childhood (COPSAC₂₀₀₀) birth cohort. MBW trials were performed at 13 y of age with Innocor model Inn00400 using sulfur hexafluoride (SF₆) as tracer gas. Measurements were analyzed using a mixed model focusing on two prediction points doubling (t5%) and quadrupling (t10%) the standard end point (t2.5%).

RESULTS: One hundred and seventy-two MBW trials conducted in 78 adolescents with and without asthma from COPSAC₂₀₀₀ were included. At t10%, the washout time (WoT) was reduced by 41%, and an uncertainty of 0.159 lung clearance index (LCI) units was introduced (± 2 SD), ± 1.27). At t5%, the WoT was reduced by 25%, with an uncertainty of 0.083 LCI units (± 0.558). The optimal prediction point, which led to most saved time and least uncertainty was t5%.

CONCLUSION: The predictor algorithm is capable of shortening the MBW test time but introduces an increasing uncertainty with earlier prediction points. This first-of-a-kind prediction algorithm holds promise in shortening the MBW test in children but should be used with caution in subjects with normal LCI values.

Multiple breath washout (MBW) is a promising tool for measuring lung function (1,2) requiring less cooperation, but longer measuring time than other methods, which highlights the need for time-saving procedures. The test investigates ventilation inhomogeneity of the lungs, which is currently measured as a lung clearance index (LCI). The MBW method used in this study measures LCI utilizing the nonresident tracer gas sulfur hexafluoride (SF₆) requiring a wash-in phase prior to the washout phase. One such MBW trial lasts ~5 minutes, dependent on the age, body size, and lung status of the subject. According to Consensus guidelines, three trials are needed to complete a test making MBW testing rather time consuming (3).

MBW has been shown to be more sensitive than spirometry in detecting structural lung disease accompanying, e.g., cystic fibrosis (1). While spirometry requires active patient collaboration, MBW is measured during tidal breathing and may therefore be more feasible for children (4,5). However, some of the trials are typically interrupted due to impatience of the child. Additionally, changes in breathing pattern often occur at the end of the trial due to saliva production, dryness in the mouth, or lack of concentration, which can alter or even invalidate the test result. A reduction of test time therefore has the potential to increase success rate of the test by saving otherwise discarded trials, which could enable testing young children.

For historical reasons, the washout phase is proceeded until the end-tidal concentration of the tracer gas is 1/40 of the starting concentration (6). In this study, we used MBW data from adolescents participating in the Copenhagen Prospective Study on Asthma in Childhood (COPSAC₂₀₀₀) birth cohort to investigate the ability of a predictor algorithm to extrapolate LCI from higher end-tidal tracer gas concentrations. The aim was to evaluate the decrease in washout time (WoT) in relation to the introduced LCI uncertainty (LCI error (LCIe)) at different points of prediction.

RESULTS

Baseline

Seventy-eight (46% boys) of the 411 adolescents in the COPSAC₂₀₀₀ cohort were included in the study at mean (SD) age 13 y (0.64) and performed 216 trials. Fifty-four tests did not meet the predefined acceptability criteria and were excluded. Eighteen (21%) subjects had asthma at the time of measurement. Mean (SD) forced expiratory volume in 1 s (FEV1) / forced vital capacity (FVC) was 0.88 (0.07), mean (SD) functional residual capacity (FRC) was 1.93 l (0.45), and mean (SD) LCI was 6.22 units (0.51). Demographics, patient characteristics, and MBW baseline data are displayed in [Table 1](#). Number of individuals and included trials at each prediction point are displayed in [Table 2](#).

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Error and Saved Time

In **Figure 1**, the LCIE are shown with prediction limits and SDs. The lowest mean LCIE is found at t4% and the highest LCIE is found at t10%. At all prediction points, the mean error is positive, and the SD is increasing from t4% to t10%.

In **Table 3**, the decrease in WoT is shown at the different prediction points as saved time (ST). The lowest ST is found at t4% and the highest ST is found at t10%. In **Table 1**, MBW

Table 1. Baseline

No. of subjects	<i>n</i> = 78
Antropometrics	
Gender (%male)	46
	Mean (SD)
Age (years)	13 (0.64)
Height (cm)	161.8 (8.4)
Weight (kg)	52.0 (10.6)
Spirometry	
FEV ₁ /FVC	0.88 (0.07)
MBW	
FRC (l.)	1.93 (0.45)
LCI	6.22 (0.51)
WoT (s)	93.2 (22.9)
	Median (IQR)
CV _{LCI} (%)	3.2 (2.0;4.5)
CV _{NewLCI5} (%)	4.7 (2.1;6.3)
CV _{NewLCI10} (%)	5.3 (2.3;9.5)
CV _{FRC} (%)	2.7 (1.7;4.4)

Demographics, patient characteristics, and MBW baseline data. CV,coefficient of variation; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; FRC, functional residual capacity; IQR, interquartile range; LCI, lung clearance index; MBW, multiple breath washout; WoT, washout time.

data are shown with the coefficient of variation (CV) of FRC, original LCI (LCI_{Org}), LCI at t5% (LCI_{New5}), and LCI at t10% (LCI_{New10}). Median (interquartile range (IQR)) CV of LCI_{Org} is 3.2% (2.0;4.5), where median (IQR) CV for prediction point t5% and t10% is 4.7% (2.1;6.3) and 5.3% (2.3;9.5), respectively.

Prediction

The ST/highest prediction limit (HPL) ratio is highest at t5% indicating that this is the optimal extrapolation point (**Table 3**).

In **Figure 2**, the difference between LCI_{New} and LCI_{Org} is plotted against LCI_{Org} to examine for systematic errors in the algorithm. At t10%, the differences are distributed over a larger range than at t5%. At t5%, the distribution is not associated with the magnitude of the mean LCI_{Org}, whereas at t10%, the distribution seems more scattered in the higher values of LCI (7 to 8), with fewer observations near zero. However, logarithmic transformation of the differences did not improve the distribution (data not shown).

When extrapolating from t10%, we found a mean LCIE (±2 SD) of 0.159 (±1.27) and a mean ST of 38.6 s. In comparison, when extrapolating from t5%, we found a mean LCIE of 0.083

Table 2. Number of tests

Time point	Individuals	Total trials
t10%	77	162
t9%	77	156
t8%	77	153
t7%	78	154
t6%	76	149
t5%	74	144
t4%	67	134

Amount of tests included at different time points.

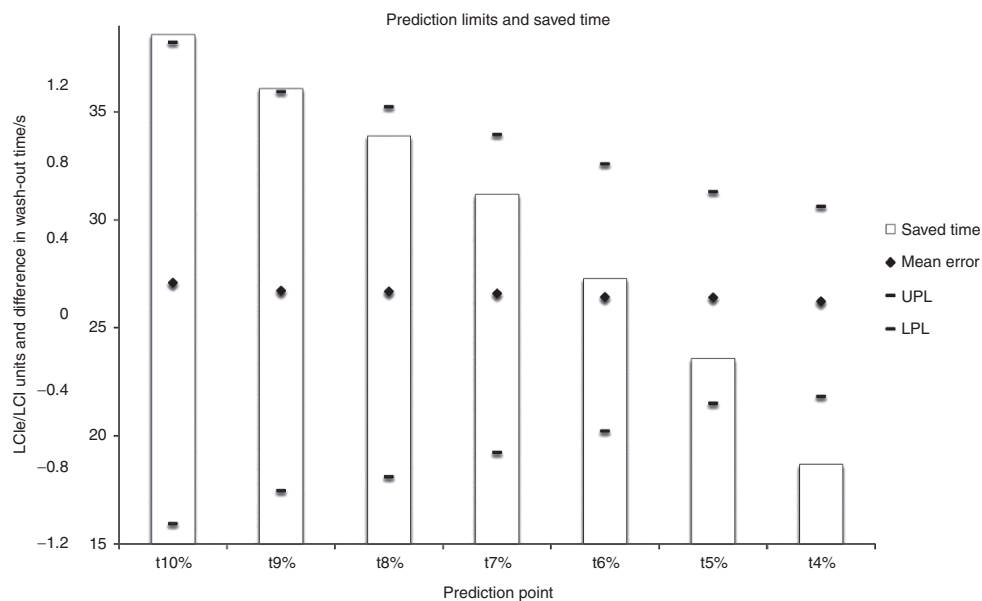


Figure 1. Mean prediction error (new – original) with 95% prediction limits in LCI units (left axis) at different prediction points. The column is decrease in washout time in seconds (right axis). LCI, lung clearance index; LPL,lower prediction limit; UPL,upper prediction limit.

(± 0.558) and a mean ST of 23.6 s. At t5% where ST/HPL is highest, the LCIE ($\pm 2SD$) equals 1.3% ($\pm 9\%$) of the mean LCI and the WoT is reduced with 25.3%.

DISCUSSION

The proposed predictor algorithm is capable of shortening the MBW test procedure and provides an estimate of the LCI with a mean LCIE ($\pm 2SD$) of 1.3% ($\pm 9\%$) and a reduction in mean WoT of 25.3% at the optimal prediction point.

At all prediction points the mean LCIE is positive, and the SD is increasing from t4% to t10%. This implies that the algorithm is overestimating LCI and indicates that earlier prediction points increase the uncertainty. To determine the optimal prediction point to use for extrapolation, it is relevant to evaluate the amount of saved time in relation to the LCIE and the SD of this. HPL gives an idea of the most extreme error the algorithm introduces, and from our data, a direct correlation

of the saved time and HPL suggests that the optimal point of prediction is t5%. At this prediction point, the HPL is 0.64 LCI units, which is considered a high inaccuracy in subjects with normal LCI values.

The median CV for LCI_{Org} in our study was 3.2%, which is comparable to other studies reporting CV for LCI_{Org} from 4 to 9% (7–10). This implies that the MBW measurement itself is affected by some uncertainty, which should be taken into account when evaluating the algorithm. The CV is higher for extrapolated LCI values compared to the CV of LCI_{Org} , underlining the uncertainty introduced by the algorithm.

Lung function measurements are commonly used in a clinical setting to distinguish between normal and abnormal subjects and to monitor disease progressing. Our study was cross-sectional, why we cannot evaluate how the algorithm performs over time in the same subject.

Shortening of the MBW test time has been the topic of interest of other studies. Yammine *et al.* (11) examined sensitivity and specificity in children with cystic fibrosis when stopping the washout at 5% of the starting concentration. They found a similar or improved sensitivity and specificity with this prediction point compared with the traditional end point of 2.5% and proposed this as a way of shortening test time. The average of saved measuring time in cystic fibrosis patients was 30 vs. 21% in controls (11), which is comparable to our findings of a 25% reduction of WoT in a mixed cohort of asthmatics and healthy adolescents.

The predictor algorithm is capable of shortening the washout phase in each trial by 20–30 s when extrapolating from t5%. This may be considered negligible but actually accounts for at least a 25% reduction of the washout phase and 10–15%

Table 3. Prediction

Stop point	LCIE, mean (SD) (LCI units)	ST, mean (SEM) (s)	ST/HPL
t4%	0.062 (0.250)	18.7 (0.85)	33.6
t5%	0.083 (0.279)	23.6 (1.13)	37.2
t6%	0.085 (0.352)	27.3 (1.28)	35.0
t7%	0.105 (0.419)	31.3 (1.44)	33.6
t8%	0.115 (0.488)	33.9 (1.56)	31.5
t9%	0.228 (0.526)	36.1 (1.69)	31.2
t10%	0.159 (0.635)	38.6 (1.82)	27.3

HPL, highest prediction limit; LCI, lung clearance index; LCIE, LCI error; ST, saved time.

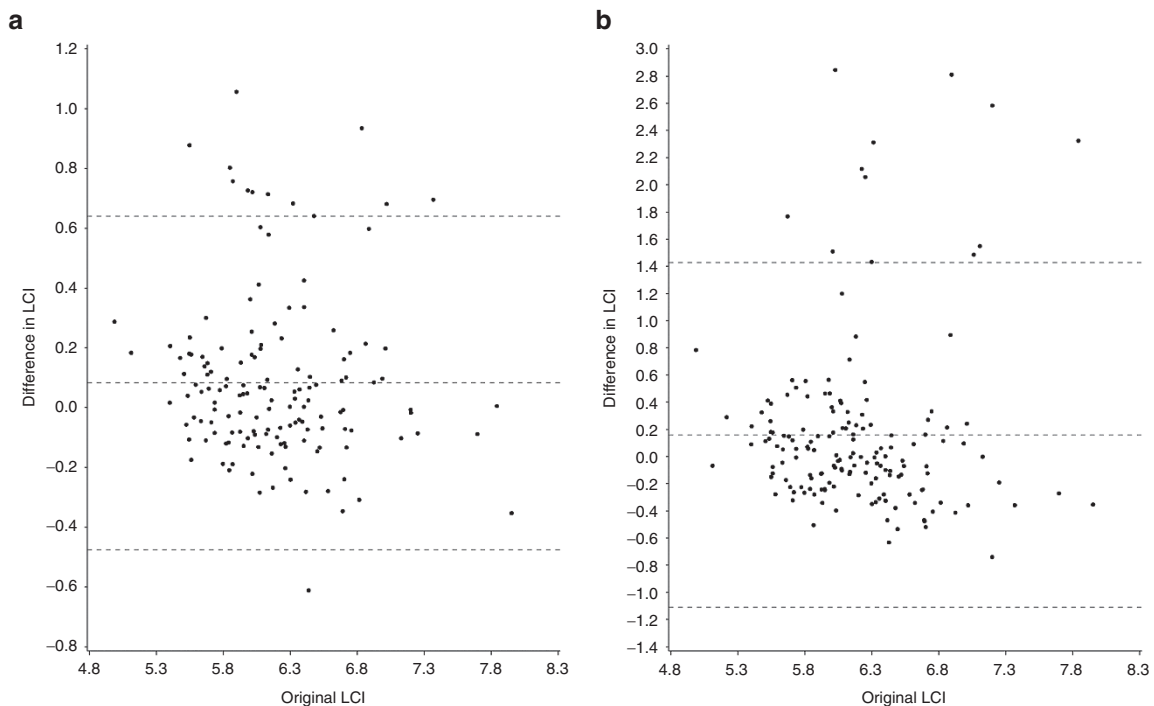


Figure 2. Bland–Altman plot for prediction points (a) t5% and (b) t10%, doubling and quadrupling the standard prediction point of t2.5%, i.e., 1/40 of the starting concentration. The difference between predicted (new) and original (org) data is plotted against original result.

reduction of the entire test time, which may facilitate and ease testing of young children. Moreover, the wash-in phase will also be shortened, as the concentration of tracer gas at the beginning of the wash-in will be higher.

The algorithm, which is based on washout of SF₆ tracer gas, approved for use with Innocor (Innovision ApS, Glamsbjerg, Denmark) in the European Union and the United States, could be modified to include washout of other tracer gases such as N₂.

In conclusion, this study investigates a new approach to the MBW method using a novel predictor algorithm with the potential to save test time and avoid discarded tests in impatient children. The algorithm is capable of shortening the test with at least 10–15% with a mean LCIE (± 2 SD) of 1.3% ($\pm 9\%$) but introduces a potential uncertainty of around 0.6 LCI units.

METHODS

Study Population

Participants in this study were recruited from the COPSAC₂₀₀₀ cohort (12), which is a prospective, longitudinal, birth-cohort study of 411 infants born to asthmatic mothers in 1998–2001. The children were enrolled at 1 mo of age excluding children with severe congenital abnormality, gestational age <36 wk, and any lung symptoms prior to enrolment. The children were followed closely from birth with scheduled clinic visits every half-year until age 7 y and again at age 13 y. All the MBW measurements utilized in this study were conducted routinely during the scheduled 13-y visit at the COPSAC clinic. The 78 included participants were the ones who had completed MBW measurements by the time of data analysis.

Lung symptoms were recorded in daily diaries fulfilled from birth by the parents. Asthma was defined according to a strict predefined algorithm based on these lung symptom recordings and response to treatment and was exclusively diagnosed by the pediatricians working at the COPSAC clinic. Adolescents without asthma were defined as healthy in this study.

MBW Measurements

The Innocor model Inn00400, (Innovision ApS), which was used to perform MBW assessments in this study, was validated as described by Gønem *et al.* (13). It was calibrated on a daily basis according to manufacturer's guidelines and used an almost fully automatic software that ensured an equal measuring technique independent of the observer. The device has a re-breathing valve unit with connections to a re-breathing bag for the wash-in phase of the tracer gas SF₆, a flow meter connected to a mouthpiece via a bacterial filter, and room air. MiniValve with a pre-capillary dead space of 62.3 ml was inserted in the re-breathing valve unit. The mean (SD) weight of the participants was 52.0 kg (10.6) giving a mean pre-capillary dead space per kg body weight (SD) of 1.25 ml/kg (0.24).

For the wash-in phase, the device supplied a gas mixture containing 0.2% SF₆ and 35.5% oxygen (O₂) among others and used a scrubber to clear the produced carbon dioxide (CO₂). Participants wore noseclips and breathed through mouthpieces (small, 22 mm, Hans Rudolph, Shawnee, KS) attached to a flow meter (4719 series Hans Rudolph) until gas equilibrium was reached, i.e., the variation of the SF₆ concentration between inspiration and expiration was below 2%. The connections switched from re-breathing bag to room air at the first exhalation of the washout phase. The participants breathed room air until the end tidal concentration of SF₆ had reached a level below 1/40th of the starting concentration in three consecutive breaths. Only successfully finished trials were included. The outcomes that were used in the analysis were LCI, FRC, and WoT.

The collected data were sent to Innovision ApS, where the algorithm was used to extrapolate LCI values. Thereafter, raw data and the extrapolated values were sent to the COPSAC clinic, where the statistical analysis was performed, and the results were interpreted. Analysis was focused on two prediction points doubling (t5%) and

quadrupling (t10%) the standard finish point of the trial (2.5% of the initial tracer gas concentration).

Predictor Algorithm

The algorithm was designed to predict the LCI and FRC at 2.5% (1/40) of the starting concentration at prediction points between 10 and 4% of the starting concentration. The washout part of SF₆ was first normalized to an even breathing tidal volume using the phase three slope of the SF₆. Then, a best-fit-curve through the last nine end-tidal values was extrapolated to the normal 2.5%, and the estimated expired cumulated volume (VCE) was found. A similar best-fit-curve was done on the SF₆ volume of each breath and by extrapolating to the estimated VCE the total volume of expired SF₆ was estimated, and the FRC was determined. Finally, the predicted LCI was calculated as the estimated VCE divided by the estimated FRC.

Statistics

A predefined acceptability criterion was made for MBW trials in the same subject: $(FRC_x - FRC_{mean})/FRC_{mean} < 4.8\%$, which is in agreement with the most narrow acceptability criterion of ERS/ATS consensus statement (3). If all trials from an individual varied $>4.8\%$, the individual was excluded.

LCIE is defined as the difference between LCI_{New} and LCI_{Org} ($LCI_{New} - LCI_{Org}$). ST is defined by the difference between the original WoT and the time at prediction. The HPL is the numerical value of LCIE plus 2 SD. The ratio ST/HPL is calculated by dividing saved time with HPL. It is used to find the optimal prediction point regarding the amount of saved time in relation to the size of the error obtained when using the algorithm.

Individual CV was calculated by the SD of all trials of the individual divided by the mean. A median CV and IQR were calculated for LCI_{Org}, FRC, LCI_{New5}, and LCI_{New10}, as the values were not normally distributed.

Measurements of LCIE and ST were analyzed using a mixed model with the individual as a random effect in order to take account of the repeated measurements on the same individual. Mean values for LCIE and ST were calculated as the overall estimate of the intercept in this model. These were compared to the mean LCI and mean WoT to calculate the percentage deviation and reduction. For the LCIE, SDs of the individual observations were calculated by summing up between- and within-individual variance using mixed model estimates. Prediction limits were defined as the 95% confidence limits on the individual observations calculated using the SD for individual observations. For saved time, SE of the mean saved time is provided by estimating the SE of the intercept in the mixed model.

Prediction at t5% and t10% were chosen for further analyses as the concentrations are two and four times the concentration at the end of a conventional test (1/40 of the starting concentration), respectively.

Prediction point-dependent LCIE was assessed using plots showing mean and upper and lower prediction limits. Prediction point-dependent saved time was compared to LCIE. Agreement between LCI_{Org} and LCI_{New}, thus the LCIE, was assessed using Bland–Altman plots in t5% and t10% with limits of agreement (mean ± 2 SD) shown as dotted lines (14).

All statistics on algorithm data were carried out using SAS version 9.3 and SAS Enterprise Guide 5.1 version 5.100.0.12019 (SAS, Cary, NC) at the COPSAC clinic.

Ethics

The Copenhagen Ethics Committee (KF 01-289/96) and The Danish Data Protection Agency (2008-41-2434) approved the study, and informed consent was obtained from both parents at enrollment.

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