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Feasibility and clinical applications of multiple breath wash-out (MBW) testing using sulphur hexafluoride in adults with bronchial asthma

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Ventilation heterogeneity is frequent in bronchial asthma and can be assessed using multiple breath wash-out testing (MBW). Most data is available in paediatric patients and using nitrogen as a tracer gas. We aimed to evaluate sulphur hexafluoride (SF₆) MBW in adult asthmatics. Spirometry, whole-body plethysmography, impulse oscillometry and SF₆-MBW were prospectively performed. MBW parameters reflecting global (lung clearance index, LCI), acinar (S_{acin}) and conductive (S_{cond}) ventilation heterogeneity were derived from three consecutive wash-outs. LCI was calculated for the traditional 2.5% and an earlier 5% stopping point that has the potential to reduce wash-out times. 91 asthmatics (66%) and 47 non-asthmatic controls (34%) were included in final analysis. LCI_{2.5} and LCI₅ were higher in asthmatics ($p < 0.001$). Likewise, S_{acin} and S_{cond} were elevated ($p < 0.001$ and $p < 0.01$). Coefficient of variation was 3.4% for LCI_{2.5} and 3.5% for LCI₅ in asthmatics. Forty-one asthmatic patients had normal spirometry. ROC analysis revealed an AUC of 0.906 for the differentiation from non-asthmatic controls exceeding diagnostic performance of individual and conventional parameters (AUC = 0.819, $p < 0.05$). SF₆-MBW is feasible and reproducible in adult asthmatics. Ventilation heterogeneity is increased as compared to non-asthmatic controls persisting in asthmatic patients with normal spirometry. Diagnostic performance is not affected using an earlier LCI stopping point while reducing wash-out duration considerably.

Disease control is the primary goal of asthma therapy being linked to absence of symptoms and exacerbations¹. Regrettably, up to half of the patients are poorly controlled^{2,3}. Despite therapeutic advances, numbers remained fairly unaltered during the last decade.

The clinical and pathophysiological explanations associated with poor disease control are heterogenous. In general, more severe disease is related to more frequent exacerbations, health care contacts³ and symptoms⁴. Lung function is also impaired in severe disease indicated by a lower forced expiratory volume in one second (FEV₁) and lower forced vital capacity (FVC)³. Both parameters represent rather central sites of obstruction. However, involvement of peripheral airways is common in the majority of asthmatic patients⁵. This holds true across the whole spectrum of severity⁶ and may be a consequence of several influencing factors. These include inflammation, wall thickening, smooth muscle hypertrophy, and mucus^{7–10}. However, changes in the lung periphery are still often missed by commonly used techniques such as spirometry.

Impulse oscillometry (IOS) is an inexpensive non-invasive technique to measure airway resistance. It was shown to identify small airway obstruction¹¹, the related characteristics of disease control^{12,13} and response to

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acute bronchodilator therapy¹⁴. Small airway dysfunction was shown to impair quality of life in smokers¹⁵. This even applies in absence of obstructive lung disease.

Other techniques aiming at an early diagnosis or phenotyping have also been investigated. Most recently, Sugawara and co-workers could identify three subtypes of cough variant asthma. They were able to demonstrate a differential therapeutic effect of inhaled corticosteroids (ICS)¹⁶. Eosinophilic airway inflammation is common in asthma and associated with increased corticosteroid responsiveness. Blood eosinophilia is already a widely used parameter in patients with severe disease planned for targeted antibody therapy in personalized medicine¹⁷. Single surrogate markers such as blood eosinophil count, immunoglobulin E, and fractional exhaled nitric oxide (FeNO) have overall moderate diagnostic accuracy¹⁸. However, it was recently demonstrated that FeNO predicts response to ICS in patients with non-specific respiratory symptoms¹⁹. These may represent a distinct phenotype or stage of asthmatic disease not detected using current diagnostic work-up. Ventilation heterogeneity is also frequent in obstructive lung disease and can be assessed using multiple breath wash-out testing (MBW). The technique was shown to be feasible in adult patients with chronic obstructive pulmonary disease (COPD)^{20–22} and pulmonary hypertension²³. Asthmatic patients were found to have increased ventilation heterogeneity as compared to controls^{24,25} that could be improved by therapy^{24,26,27} and is worse during exacerbations²⁸. Moreover, previous investigations also suggest a link to poorer asthma control^{27,29}. An association of ventilation heterogeneity with airway responsiveness was seen in asthma but not in COPD³⁰.

Hence, MBW has great potential to improve phenotyping as well as differential diagnostics. Nevertheless, several metrological issues have still to be overcome. Most MBW data in bronchial asthma has been acquired in paediatric patients using nitrogen (N₂) as tracer gas. The latter potentially suffers from technical issues such as N₂-back diffusion, measurement inaccuracies and vulnerability to leak flows^{31–34}. Mass spectrometry using open wash-in MBW sulphur hexafluoride (SF₆) is considered the gold standard³⁵. However, this has been associated with high costs and effort. Introduction of a photo-magneto-acoustic multi-gas analyser allowed the direct measurement of SF₆ concentrations with high accuracy³⁶. Recently, this led to construction of a closed circuit SF₆-MBW setup considerably facilitating application and reducing costs³⁷. We therefore set out to evaluate the feasibility of SF₆-MBW in adult patients with bronchial asthma and derive potential clinical applications.

Methods

Subjects. We prospectively evaluated patients with known or first diagnosis of bronchial asthma as well as non-asthmatic controls. Classification criteria are given in detail in the *online supplement*. The study protocol was approved by the Medical Ethics Committee II of the Medical Faculty Mannheim (Heidelberg University), compliant with the Declaration of Helsinki and registered at clinicaltrials.gov (NCT03820427). Written informed consent was obtained from all participants and/or the respective legal guardian prior to inclusion.

Study protocol. Spirometry and whole-body plethysmography. All subjects underwent pre-bronchodilator conventional lung function testing including spirometry as well as whole-body plethysmography (MasterScreen Body) and were in stable clinical condition. Existing maintenance therapy was not withheld. Reversibility testing was then performed with doses of 40 µg ipratropium bromide and 100 µg fenoterol hydrobromide administered via soft-mist haler (Berodual Respimat, Boehringer Ingelheim Pharma GmbH & Co. KG, Germany). Indications include presence of either obstruction (FEV₁/FVC < 70% of predicted), hyperinflation (residual volume/total lung capacity (RV/TLC) > 40%), and/or respective flow-volume-curves or flow-pressure curves. In addition to these parameters, maximum expiratory flow (MEF) at 75, 50 and 25% of FVC as well as functional residual capacity (FRC) were determined. Reference values were derived from the revised 1993 version of the European Community for Steel and Coal equations (ECSC)³⁸.

Transfer factor for carbon monoxide (TLCO). TLCO was determined pre-bronchodilator in single breath technique and corrected for ventilated alveolar volume (TLCO/VA). The difference was defined as ΔTLCO.

Multiple breath wash-out (MBW) testing. A commercially available closed-circuit system (Innocor, PulmoTrace ApS, Glamsbjerg, Denmark) was used for MBW measurements as previously described in detail³⁷. The device consists of a 3-liter rebreathing bag filled with a mixture of room air and test gas (94% O₂, 1% SF₆ and 5% N₂O, PulmoTrace ApS) from an on-board gas cylinder. Functional residual capacity (FRC), acinar (S_{acin}) and conductive (S_{cond}) ventilation heterogeneity were derived from three consecutive wash-outs using proprietary software provided by the manufacturer (software version 8.0 beta 1). LCI was calculated for the 2.5% (LCI_{2.5}) and 5% (LCI₅) stopping points, respectively. Subjects were breathing tidally and the test was stopped when end tidal SF₆ had fallen below 1/40 of the starting concentration for three consecutive breaths. Wash-out was always performed until the later LCI_{2.5} stopping point. To show the time saving potential of an earlier LCI₅ stopping point, wash-out times were calculated separately. Only patients with at least two technically acceptable LCI measurements based on slightly modified ATS/ERS criteria (*online supplement*) were included in final analysis. All subjects underwent three consecutive pre-bronchodilator MBW tests in upright position.

Impulse oscillometry (IOS). IOS measurements were performed during tidal breathing (MasterScreen IOS, CareFusion 234 GmbH, Höchberg, Germany). We conducted three consecutive pre-bronchodilator measurements and derived parameters of airway resistance (frequency dependence D5–20) and reactance (resonance frequency F_{res}, reactance area Ax), respectively. In patients undergoing reversibility testing according to above mentioned indications, three consecutive post-bronchodilator measurements were additionally performed.

All lung function tests were independently assessed by two experienced investigators. MBW and IOS were conducted prior to all forced lung function manoeuvres. The difference between FRC as determined by whole-body plethysmography and MBW was defined as ΔFRC_{pleth-MBW}.

	unit	Asthma (n = 91)		Controls (n = 47)		p-value
		value	range	value	range	
age	years	55 ± 18	17–88	47 ± 19	21–85	0.02*
height	cm	173 ± 10	152–198	170 ± 9	145–188	0.02*
weight	kg	79 ± 21	50–132	81 ± 17	45–123	0.54
mMRC		1.1 ± 1.2	0–4	0	0	<0.0001*
smoker						
yes/ex/never	n	18/36/37		4/12/31		0.02*
	%	20/40/40		9/25/66		

Table 1. Baseline characteristics. mMRC: modified Medical Research Council dyspnoea scale. *Statistically significant $p < 0.05$.

Statistical analysis. Mean values are given \pm standard deviation (SD) unless stated otherwise. Differences between groups were assessed by Student's t-test for continuous variables or Chi-squared test for categorical variables. The coefficient of variation (CV) was calculated as SD/mean from two or three valid MBW measurements, respectively. Sample size calculation was based on previously published data³⁹. An overall cohort of 60 subjects would provide 95% power to detect a 1.8 ± 0.4 difference in LCI with a 2:1 allocation of patients and non-asthmatic controls, respectively. An alpha error of less than 5% in two-sided testing was considered statistically significant. R Statistical Software (v3.4.2, Foundation for Statistical Computing, Vienna, Austria) was used for all data analysis⁴⁰. A subgroup of asthma patients with normal lung function in conventional testing was prespecified and defined as having normal FEV₁ ($>80\%$ of predicted) and no obstruction in spirometry (FEV₁/FVC $> 70\%$). All lung function parameters differing between asthma patients with normal lung function and non-asthmatic controls in univariate analysis ($p \leq 0.05$) were included in an elastic-net generalized linear model corrected for age. L1 regularization was used for variable selection based on a k-fold cross validation approach to find optimal hyper-parameters. Diagnostic performance was evaluated using receiver operating curve (ROC) analysis and calculation of area under the curve (AUC).

Results

Final analysis was performed in 91 patients with bronchial asthma (66%) and 47 non-asthmatic controls (34%) with valid data sets. Only two valid MBW measurements could be obtained in 11 non-asthmatic controls (23%) and 32 asthmatics (35%, $p = 0.2$). Five asthmatic patients (3.4%) had to be excluded due to the prespecified acceptability criteria for MBW testing whereas in another 4 patients (2.7%) only one valid MBW measurement could be obtained. Baseline characteristics are given in Table 1. Reversibility testing was performed in 63 patients (69% of asthmatic patients) with details given in Supplementary Table S1. Positive rates were 38% for FEV₁ and Ax, 21% for RV and 29% for D5–20, respectively.

All lung function parameters differed between asthmatic patients and non-asthmatic controls except for total lung capacity (TLC), functional residual capacity as determined by whole-body plethysmography (FRC_{pleth}) and Δ TLCO (Table 2). Forty-one asthma patients had normal lung function in spirometry with details of differences given in Supplementary Table S2. LCI_{2.5} and LCI₅ were both significantly higher in asthmatic patients as compared to non-asthmatic controls (Fig. 1A, $p < 0.001$). Likewise, S_{acin} and S_{cond} were both elevated and significantly different (Fig. 1B, $p < 0.001$ and $p < 0.01$). CV was 3.4% for LCI_{2.5} and 3.5% for LCI₅ in patients with asthma. No significant differences were found as compared to 3.0% for LCI_{2.5} ($p = 0.28$) and 3.2% for LCI₅ ($p = 0.37$) in non-asthmatic controls. Parameters of local ventilation heterogeneity showed considerably larger variation. CVs were 42% for S_{acin} and 82% for S_{cond} in asthma as compared to 39% ($p = 0.74$) and 127% ($p = 0.17$) in non-asthmatic controls, respectively. Δ FRC_{pleth-MBW} was 0.04 ± 0.52 L in non-asthmatic controls as compared to 0.61 ± 0.75 L in asthmatic patients (Fig. 1C, $p < 0.001$). Asthmatic patients with normal spirometry also had an elevated Δ FRC_{pleth-MBW} of 0.46 ± 0.62 as compared to non-asthmatic controls ($p < 0.001$).

In the regularized generalized linear model used for variable selection, FEV₁/FVC, maximum expiratory flow at 25% of FVC (MEF₂₅), LCI_{2.5}, FRC_{MBW}, area under the reactance curve (Ax), resonance frequency (F_{res}), TLCO/VA and Δ FRC_{pleth-MBW} remained as predictors for asthma after adjustment for age and smoking status. ROC analysis revealed an AUC of 0.906 for the differentiation from non-asthmatic controls that exceeded diagnostic performance of the individual parameters (Fig. 2A). Diagnostic accuracy was significantly lower when only including parameters of conventional lung function testing (AUC = 0.819, $p < 0.05$, Fig. 2B). A model only consisting of conventional lung function testing and MBW but without IOS parameters yielded an improved AUC of 0.863 ($p = 0.2$, Fig. 2C). No differences were found between LCI₅ (AUC = 0.683) and LCI_{2.5} (AUC = 0.697, $p = 0.27$) when used as distinct parameters. S_{acin} and S_{cond} had lower diagnostic accuracy (AUC = 0.615 and 0.593).

Mean total wash-out time was 102 ± 37 s in non-asthmatic controls and 102 ± 39 s in patients with asthma for LCI_{2.5}. When using the earlier LCI₅ stopping point, wash-out times were significantly reduced by 24 s ($p < 0.001$) and 28 s ($p < 0.001$), respectively.

Discussion

We were able to demonstrate that MBW measurements are feasible in patients with bronchial asthma. Global and local ventilation heterogeneity is increased as compared to non-asthmatic controls. These differences persist when comparing asthmatic patients with normal conventional lung function parameters to non-asthmatic controls. MBW parameters therefore may contain additional information that can be used to identify asthmatic patients

	unit	asthma (n = 91)		non-asthmatic controls (n = 47)		p-value
		value	range	value	range	
spirometry						
FEV ₁ /VC	%pred	84 ± 14	42–112	99 ± 7	84–115	<<0.001*
FEV ₁ /FVC	%	72 ± 10	44–92	83 ± 6	71–99	<<0.001*
FEV ₁	%pred	80 ± 20	22–132	101 ± 13	65–135	<<0.001*
VC	%pred	95 ± 18	42–132	102 ± 13	64–124	0.01*
MEF ₇₅	%pred	61 ± 27	11–122	96 ± 25	48–162	<<0.001*
MEF ₅₀	%pred	48 ± 26	10–127	88 ± 27	35–170	<<0.001*
MEF ₂₅	%pred	36 ± 23	9–107	67 ± 28	13–141	<<0.001*
body plethysmography						
TLC	%pred	109 ± 18	65–153	108 ± 11	87–128	0.60
RV	%pred	143 ± 51	48–451	125 ± 27	79–201	<0.01*
RV/TLC	%	45 ± 11	22–80	37 ± 8	21–57	<<0.001*
FRC _{pleth}	L	3.4 ± 0.9	1.1–6.0	3.1 ± 0.5	2.3–4.2	0.05
TLCO/VA	%pred	88 ± 15	62–122	96 ± 10	80–116	<0.001*
TLCO	%pred	79 ± 16	41–125	87 ± 10	66–108	<0.001*
ΔTLCO	%pt	12 ± 9	0–44	11 ± 8	0–33	0.50
impulse oscillometry						
D5–20	%	40 ± 41	0–265	14 ± 11	0–47	<0.001*
Ax	—	1.5 ± 1.8	0.0–10.8	0.3 ± 0.2	0.0–1.1	<0.001*
F _{res}	Hz	19 ± 8	6–44	11 ± 4	3–22	<0.001*
multiple breath wash-out						
LCI _{2.5}	—	8.6 ± 1.8	5.5–13.6	7.0 ± 0.9	5.7–8.9	<0.001*
LCI ₅	—	6.6 ± 1.3	4.5–10.4	5.6 ± 0.6	4.5–7.0	<0.001*
FRC _{MBW}	L	2.7 ± 0.9	1.0–6.1	3.1 ± 0.8	1.8–4.6	0.01*
S _{acin}	L ⁻¹	0.17 ± 0.15	–0.2–0.65	0.07 ± 0.09	–0.35–0.21	<0.001*
S _{cond}	L ⁻¹	0.06 ± 0.04	–0.03–0.18	0.04 ± 0.04	–0.07–0.13	<0.01*

Table 2. Lung function testing (whole cohort). FEV₁: forced expiratory volume in one second, (F)VC: (forced) vital capacity, MEF: maximum expiratory flow at 75, 50 and 25% of FVC, TLC: total lung capacity, RV: residual volume, TLCO(/VA): transfer factor (corrected for ventilated alveolar volume), FRC: functional residual capacity, D5–20: frequency dependence of resistance, AX: area under reactance curve, Fres: resonance frequency, LCI: lung clearance index at 2.5% and 5% stopping points, S_{acin}: acinar ventilation heterogeneity, S_{cond}: conductive ventilation heterogeneity. %pred: percent of predicted, %pt: percentage points, *statistically significant p < 0.05.

with abnormal ventilation missed by current tests. Including parameters of ventilation heterogeneity and small airway disease significantly improves diagnostic accuracy of our prediction model. Using an earlier stopping point does not affect diagnostic performance of LCI while considerably reducing wash-out duration.

Our findings are in accordance with previously published data in asthmatic children. Residual global ventilation heterogeneity could be identified despite well-controlled disease and normal FEV₁. We also found significant differences between adults with asthma and non-asthmatic in acinar but not conductive ventilation heterogeneity. In contrast, parameters of regional inhomogeneity did not differ significantly between asthmatic and healthy children²⁵. LCI was moderately, but statistically significantly elevated in a smaller cohort of asthmatic children while effect of acute bronchodilator therapy with salbutamol was detected. However, a very small subgroup of four patients with large improvement of airway obstruction were identified to show a decreased ventilation heterogeneity⁴¹. MBW indices were found not to be ideal for assessing bronchodilator reversibility in younger children with stable wheeze⁴². Although measurements using our setup themselves were demonstrated to be rather time effective, an additional interval should have been introduced after the forced breathing manoeuvres required during spirometry and plethysmography. We therefore decided to focus on the pre-bronchodilator in our investigation acknowledging the potential value of additional post-bronchodilator measurements to be further evaluated in adults. Abnormalities identified visually using magnetic resonance imaging (MRI) were shown to significantly correspond to poor asthma control⁴³. In adult respiratory care, application of MBW comprises numerous potential scenarios. Kjellberg and co-workers were able to identify a “small airway subtype” in asthma patients. It was linked to reduced FEV₁, smoking and blood eosinophilia and may potentially improve phenotyping. IOS and N₂-MBW were found to give complementary information about peripheral airway dysfunction. These are attributable to different domains of small airway disease addressed by either test as recently demonstrated⁵. Altered values of D5–20 and LCI were found in 23% and 45% of asthmatic patients with normal FEV₁⁴⁴. This favourably corresponds to our findings at hand in asthma and also with previous reports in COPD using IOS and MBW, respectively. Small airway disease was detected with IOS even in early stages and linked to typical symptoms such as dyspnoea⁴⁵. In early stages, IOS parameters outperformed conventional spirometry when differentiating heavy smokers with normal lung function as well as early-stage COPD⁴⁶. Likewise, LCI was shown to be elevated in

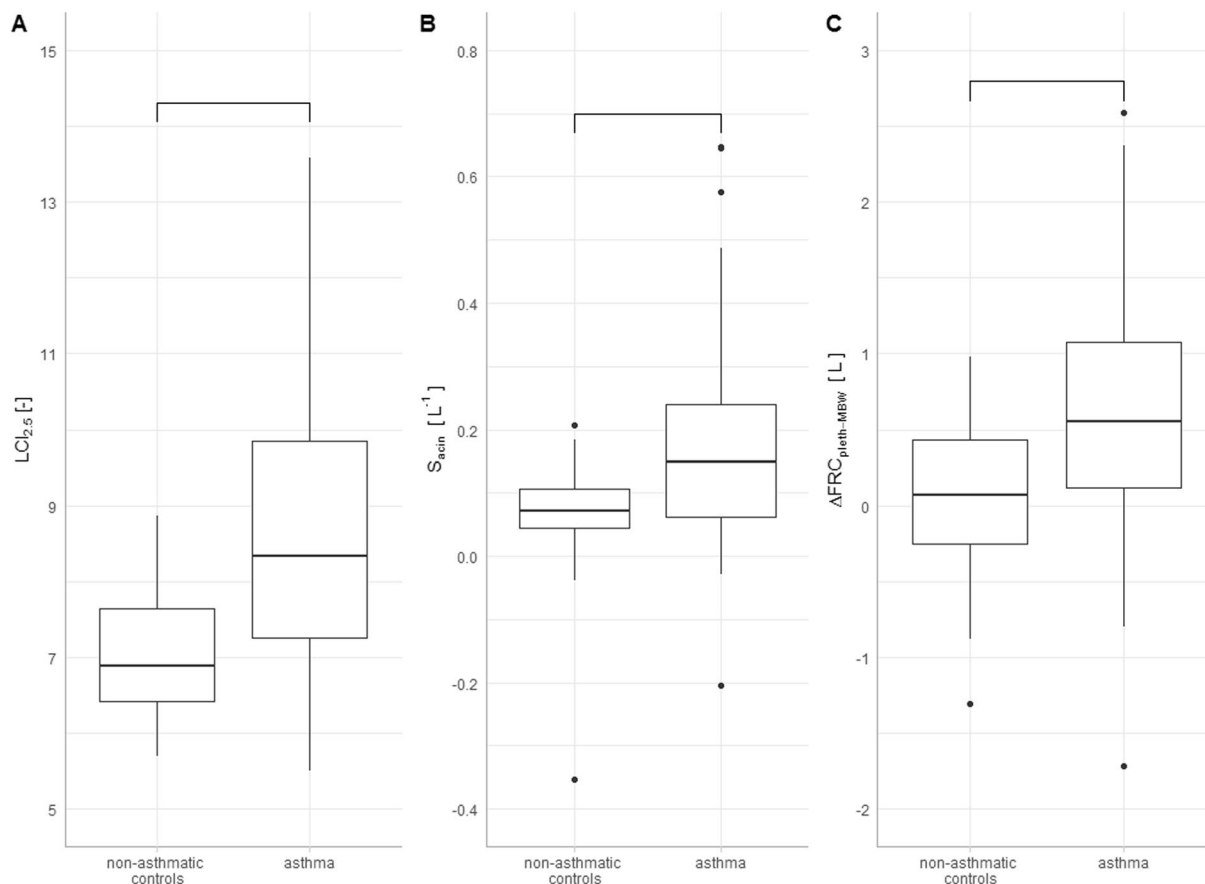


Figure 1. MBW parameters. Box-and-whisker-plots for (A) LCI_{2.5} ($p < 0.001$), (B) S_{acin} ($p < 0.001$) and (C) $\Delta\text{FRC}_{\text{pleth-MBW}}$ ($p < 0.001$) separated for asthma patients and non-asthmatic controls. Connectors indicate statistically significant ($p < 0.05$) differences.

COPD in general and increases with GOLD stage²⁰. Even in absence of spirometric obstruction, LCI was already pathologically altered²². Differences in FRC as measured by plethysmography and MBW were described previously in patients with obstructive lung disease^{39,47,48}. When using an exogenous tracer gas such as SF₆, these can be easily explained as only ventilated areas will contribute to FRC determination. In contrast, all compressible gas volumes are measured in body plethysmography⁴⁹. Correspondingly, we found an increased $\Delta\text{FRC}_{\text{pleth-MBW}}$ in asthmatic patients even in absence of spirometric changes. Inclusion of this MBW parameter increases diagnostic accuracy already considerably. A model based on all objectively selected parameters including MBW and IOS further improves diagnostic accuracy. This outperforms both conventional tests and as well as distinct parameters from novel tests alone. Therefore, $\Delta\text{FRC}_{\text{pleth-MBW}}$ itself may yield diagnostic information due to tracer gas not reaching non-ventilated areas when obstruction is present. Taken together, evidence exists that novel parameters of small airway disease improve diagnostic accuracy and have therapeutic implications.

In clinical and scientific routine, several metrological aspects should be considered. Recently, it was demonstrated that duplicate LCI measurements are sufficient in adults³⁹ and preschool children⁵⁰. Intra-test repeatability is not affected while total test time is reduced significantly. These findings could be replicated in pre-school children suffering from cystic fibrosis using an N₂-based setup⁵¹ with all three studies opposing current general recommendations³⁵. Although we were able to acquire at least two successful runs in at least 90% of asthmatic patients and all non-asthmatic controls, using an earlier stopping point may eventually contribute to even higher success rates. In accordance with our findings, LCI₅ was shown to be reliable in childhood and adolescence⁵² with equal diagnostic performance to the traditional stopping point⁵³. However, this approach requires separate normal values that may be overcome using predictive modelling. An algorithm was demonstrated to reliably extrapolate LCI_{2.5} from earlier stopping points with reasonable accuracy. Additionally, this has the potential to further reduce wash-out time by up to 41% when using a 10% cut-off for prediction⁵⁴. A similar 43% reduction in wash-out time can be potentially achieved when estimating LCI using Bayesian modelling⁵⁵. Meaningful differences in MBW outcome measures depending on the test gases have been described^{20,56}. In general, nitrogen-based systems reproducibly yield higher absolute LCI readings than SF₆-MBW^{49,57,58}. N₂ has a higher diffusion rate and smaller molar mass as compared to SF₆ resulting in a more proximal diffusion-convection front³⁵. While SF₆ may not reach very poorly ventilated regions during wash-in, endogenous N₂ may prolong wash-out from these regions resulting in higher LCI values. Hence, attention has to be paid to test gas choice when interpreting MBW results⁵⁹. Despite the above-mentioned potential advantages of SF₆-MBW, it should be noted that tracer gas still

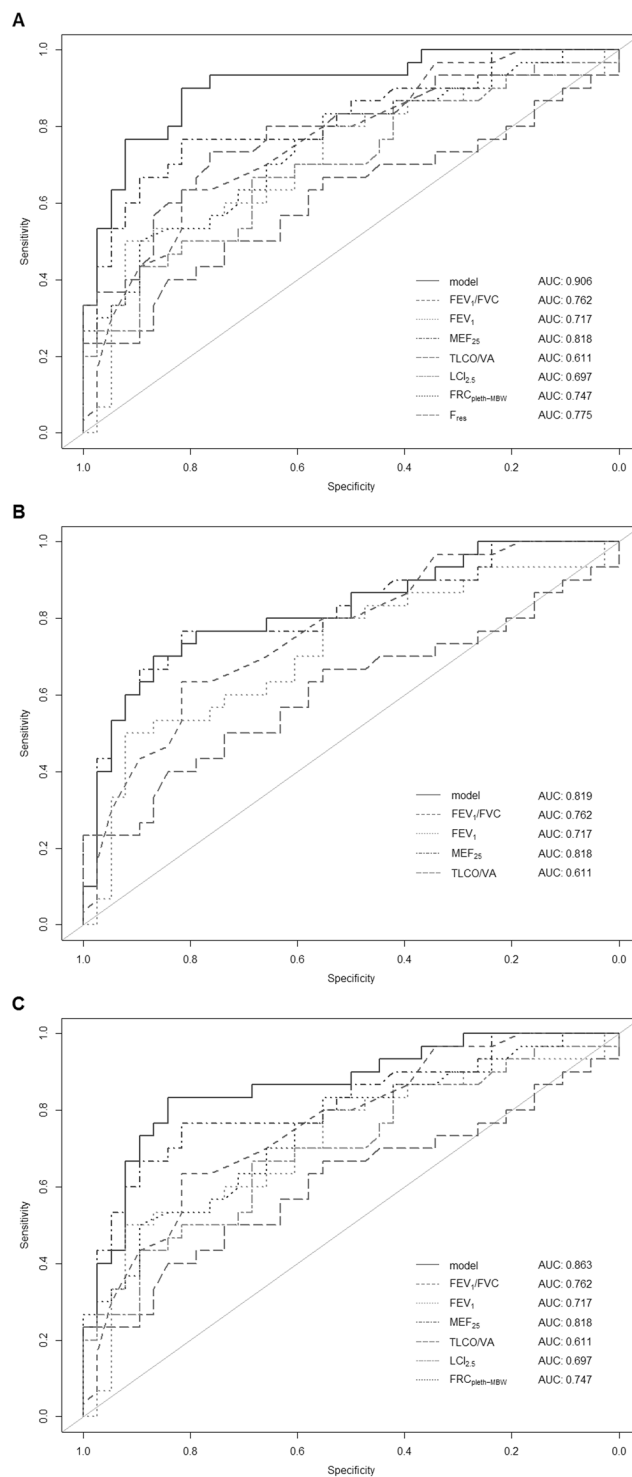


Figure 2. Diagnostic performance. ROC analysis for differentiation of asthmatic patients with normal conventional lung function testing ($n = 41$, $FEV_1 \geq 80\%$ predicted, $FEV_1/FVC \geq 70\%$) and non-asthmatic controls ($n = 47$). **(A)** Good diagnostic performance ($AUC = 0.906$) of the model when including predictors identified during regularization. **(B)** Significantly lower accuracy ($AUC = 0.819$, $p < 0.05$) when including only parameters of conventional lung function testing. **(C)** Addition of MBW without IOS parameters also improves diagnostic performance ($AUC = 0.863$, $p = 0.2$).

is associated with considerable costs. The system we used is commercially available and has regulatory approval (FDA and CE mark). Nevertheless, SF_6 is not allowed for medical use in several countries. While no solid reference values are available for closed-circuit SF_6 -MBW in adults to date, age was identified the major factor

influencing factor for nitrogen-based LCI measurements in adults and therefore prespecified as a control variable in our model⁶⁰. The influence of height seems to be negligible in patients older than six years while a nonlinear decrease pattern was described when using SF₆ as tracer gas⁶¹. Single breath N₂-wash-out can be seen as a potentially time efficient alternative to MBW testing. However, sensitivity was found to be lower in adult asthmatic patients as compared to MBW and may therefore be a marker of more severe disease⁶². Within-test repeatability found in our study is comparable to previously published data in stable adults showing CVs between 2.5 and 4.5% for LCI using SF₆ as tracer gas^{37,39,63,64}. When paediatric populations are investigated, CV tends to be slightly higher ranging from 3.2 to 8.5%^{50,54,65}. Likewise, considerably larger CVs have been shown for S_{cond} and S_{acin} with more variability in non-asthmatic controls than in COPD ranging from 17 to 73%⁶⁶. This corresponds favourably to our findings. We found similar CV ranges in both groups except for S_{cond} in non-asthmatic controls showing a higher repeatability of 127%. We can reasonably exclude poor quality control as all lung function tests were independently assessed by two experienced investigators. Rather this may be attributable to the overall lower values of S_{cond} making it more vulnerable to variation in non-asthmatic controls. The fact that variation was largest in non-asthmatic controls lets us conclude that this does not negatively affect diagnostic performance in disease. In summary, our findings add well to previous reports in paediatric cohorts and different test gases and may further facilitate the routine use of MBW. Results obtained with different tracer gases should not be compared directly.

When interpreting our results, several points should be taken into consideration. First, we did not obtain structured information on asthma control, symptoms or medication. Moreover, diagnosis relied on a respiratory specialist evaluation according to Global Initiative for Asthma (GINA) criteria¹. Although this clinical information would have been valuable, we do not consider this a major drawback of our study as we primarily set out for feasibility evaluation. The same holds for biomarkers such as laboratory parameters or FeNO. The latter did not show differences between asthmatic children and controls whereas LCI was significantly elevated²⁵. Second, our cross-sectional design does not allow to provide estimates of the minimal clinically important difference for SF₆-MBW. Due to the high intra-test repeatability, it should be possible to detect small longitudinal changes while further research is required. Nevertheless, our findings contribute to closing another knowledge gap in adult MBW testing. Personalized medicine cannot be reduced to a single biomarker or functional test. Assessment of ventilation heterogeneity using MBW may be one brick in the wall for improving phenotyping of asthmatic patients that warrants further investigation. Third, reference values were derived from the revised 1993 version of European Community for Steel and Coal (ECSC) equations³⁸. This was mainly as the current Global Lung Function Initiative (GLI) reference values are restricted to spirometry. Requiring separate reference calculations for whole-body plethysmography, we aimed to avoid any mixing of the two statistically differing concepts.

Conclusions

SF₆-MBW measurements are feasible in adult patients with bronchial asthma. Indices of global (LCI) and local ventilation heterogeneity (S_{acin}, S_{cond}) both are elevated as compared to non-asthmatic controls. Differences persist in asthmatic patients without obstruction in spirometry. MBW parameters therefore may contain additional information that can be used to identify asthmatic patients with abnormal ventilation missed by current tests. For LCI as the most important MBW outcome measure, using an earlier stopping point does not affect diagnostic performance while considerably reducing the duration of the wash-out procedure. Reproducibility was high for both LCI stopping points. S_{acin} and S_{cond} both showed larger variability.

Data availability

The datasets generated during and analysed during the current study are available from the corresponding author on reasonable request.

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Author contributions

F.T. writing first draft of manuscript, study design, data management, data analysis. S.L. data collection, data management, data analysis. J.Sch. data management, data analysis. J.G. data analysis, revision of manuscript, data management. M.S. data collection, data management. T.Gr. data analysis, data management. I.A. study design, revision of manuscript. M.B. study design, revision of manuscript. T.Ga. data analysis, data management, revision of manuscript. J.Sa. study design, data analysis, revision of first draft of the manuscript.

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Additional information

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