



LETTER TO THE EDITOR

Implementing nitrogen multiple breath washout as a clinical tool – A feasibility study



KEYWORDS

Multiple breath washout;
Lung clearance index;
Cystic fibrosis;
Primary ciliary dyskinesia;
Children

Dear editor,

The multiple-breath inert gas washout (MBW) test involves recording an inert tracer gas being cleared from the lungs during normal tidal breathing. In nitrogen (N_2) MBW resident nitrogen is washed out by inhaling 100% oxygen. MBW allows us to calculate the lung clearance index (LCI), defined as the number of lung turnovers required to washout an inert gas to 1/40th of its initial concentration.^{1–3} It offers complementary information to standard lung function tests, such as spirometry¹

The procedure is strongly dependent on skilled operators and a relaxed testing environment is key to obtaining good quality measurements.⁴ Operator training and certification in performance of the MBW measurement is imperative to achieving high-quality data, and standardization of LCI is part of an ongoing collaborative, multicentre process.²

Aim: to assess the feasibility of N_2 MBW in a paediatric lung function laboratory in children with different clinical conditions [Cystic Fibrosis (CF), primary ciliary dyskinesia (PCD) and healthy controls].

School-aged children with a confirmed diagnosis of CF or PCD were recruited from a Paediatric Pulmonology clinic in a tertiary-care hospital, and healthy controls from the community, throughout December/2018–November/2019. Patients were clinically stable at inclusion and the study procedures were performed during the patients' routine clinic visits. Height and weight were measured prior to the lung function assessments, and BMI z-scores standardized using WHO reference values.

Exhalizer[®] D and the associated software Spiroware[®] version 3.1 (EcoMedics AG, Duernten, Switzerland) were

utilized for the N_2 MBW measurements and calculation of the N_2 MBW indices. The means of the N_2 MBW indices from intentionally three and at least two technically acceptable measurements performed at each test occasion were reported in absolute values.¹ Prior to implementing this technique in our setting, three operators completed a European standardization and certification process for measuring LCI through N_2 MBW with a commercial device (specific training and sharing of data for central over-reading).

Static and dynamic lung volumes were measured by body plethysmography and spirometry (Jaeger MasterScreen Body, CareFusion, Hoechberg, Germany) after the N_2 MBW procedure. Absolute values for static lung volumes and z-scores for dynamic lung volumes and flows were recorded and performed according to the ERS/ATS standards.

Patient characteristics were presented by medians (ranges) or numbers and percentages of total. Patients with CF and PCD were grouped for comparison with healthy controls. Group differences were analysed using the independent *t*-test, Mann–Whitney *U*-test, and Chi-squared test as appropriate; $p < 0.05$ was accepted as statistically significant. Data analyses were performed using Microsoft Excel for Office 365 MSO and SPSS 24.0.

The study was approved by a local ethics community (*Comissão de Ética para a Investigação Clínica*). Informed consent for participation was obtained.

During the study period 34 children were assessed, five were excluded due to invalid MBW readings and two successfully repeated the procedure in a different testing session. The success rate for performing N_2 MBW for the first time was 75% (22 out of 29). Additionally, all healthy controls were naïve to lung function testing, and one was unable to perform spirometry properly.

We analysed data from 29 children: ten CF, six PCD and thirteen healthy controls (Table 1). There were no differences between patients and healthy children regarding gender, age, or BMI. The diseased group had higher LCI [10.8 (7.6; 15.3) vs 6.9 (6.5; 7.5)], and lower FEV1 [-0.8(-2.8; 0.4) vs. 0.7(-0.9; 1.8)] and MMEF [-1.0 (-2.6; 0.3) vs. 0.03 (-0.5; 2.4)] when compared to healthy controls ($p < 0.001$).

Executing MBW took 28 (16; 76) minutes [patient group 29 (16; 76) minutes; healthy controls 22 (16; 53 min)], and it was attempted for 5 (3; 15) trials in each testing session (Table 2). For nine individuals (four healthy controls, two CF and three PCD), only two technically acceptable trials were achieved.

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		Healthy controls (n = 13)*	CF (n = 10)	PCD (n = 6)	Controls vs. Patients (p-value)
	Gender ♂ [n (%)]	10 (77%)	4 (40%)	2 (33%)	0.034
	Age [years (min; max)]	12.2 (8; 17.3)	13.9 (7.7; 16.8)	13.8 (11; 19.2)	0.195
	BMI z-score (min; max)	-0.4 (-1.5; 2.7)	-0.4 (-2.2; 1.0)	-0.3 (-1.5; 0.5)	0,376
N₂MBW	LCI (min; max)	6.9 (6.5; 7.5)	10.9 (7.6; 15.3)	10.7 (8.6; 13.2)	<0.001
	FRC [L (min; max)]	1.9 (1.3; 4.9)	2.1 (1.0; 3.6)	2.6 (1.6; 2.8)	0.656
Plethis.	ITGV [L (min; max)]	2.1 (1.2; 3.7)	2.3 (1.2; 3.4)	2.6 (1.7; 3.2)	0.405
	RV/TLC (min; max)	0.25 (0.22; 0.32)	0.31 (0.23; 0.36)	0.33 (0.26; 0.52)	0.005
Spirometry	FEV ₁ z-score (min; max)	0.7 (-0.9; 1.8)	-0.5 (-1.8; 0.4)	-1.0 (-2.8; -0.3)	<0.001
	FVC z-score (min; max)	0.4 (-0.9; 1.4)	0.1 (-1.5; 0.8)	-1.3 (-2.7; 0.2)	0.014
	FEV ₁ /FVC (min; max)	0.88 (0.83; 0.98)	0.82 (0.75; 0.90)	0.84 (0.74; 0.95)	0.021
	MMEF z-score (min; max)	0.03 (-0.5; 2.4)	-0.9 (-2.2; 0.3)	-1.5 (-2.6; 0.2)	<0.001

* Performed spirometry n = 12
CF: Cystic Fibrosis, PCD: Primary Ciliary Dyskinesia, BMI: Body Mass Index, N₂MBW: nitrogen multiple breath washout, Plethis: plethysmography.

	Healthy controls (n = 13)	CF (n = 10)	PCD (n = 6)
Median duration [minutes (min; max)]	22:20 (15:48; 52:50)	25:18 (15:54; 70:46)	41:22 (16:24; 76:24)
Total of trials (min; max)	5.0 (3; 12)	4.0 (3; 10)	7.5 (5; 12)
Trials aborted (min; max)	1 (0; 8)	1 (0; 3)	4 (1; 10)

CF: Cystic Fibrosis, PCD: Primary Ciliary Dyskinesia

We have shown that LCI is feasible with a high success rate on first attempt (75%) in school-age children, and throughout the first year of implementing N₂MBW. Nevertheless, the procedure is time-consuming and largely dependent on specialized technicians.² Also, N₂MBW takes more time than routine spirometry and the time needed increases relative to the increase of LCI. In our setting, the duration of the test was influenced by the pathology and cooperation, and these challenges were concordant with guidelines and recommendations regarding this technique.^{1,5}

Even though N₂MBW tests were done as part of a research project, they were included in the patients' clinic visits, allowing us to estimate its burden on routine lung function assessments, if we were to add this tool to the evaluation of children with chronic, progressive, obstructive lung disease.

In agreement with published data,^{6,7} we found that LCI was raised in children with CF and PCD compared to healthy controls, even in those with FEV₁ within normal range. This is important as it shows that LCI in a clinical setting provided reliable data that reflects previous findings from studies in which the test had been undertaken in a research setting. Additionally, children with well-preserved spirometry, are those for whom monitoring with LCI will be most useful, and

it is increasingly being adopted in CF centres for clinical decision making.²

Accordingly, anticipating the success rates within a clinical setting and assigning appropriate time slots for its inclusion is crucial when planning to implement this technique.

This brief, pragmatic report, provides information about the feasibility of N₂MBW in children during routine visits, using the Exhalyzer®D.

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