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Defining the appropriate waiting time between multiple-breath nitrogen washout measurements

To the Editor:

Static lung volume measurements allow objective assessment of total lung capacity (TLC), functional residual capacity (FRC) and residual volume, and assist in the diagnosis and management of lung disease [1, 2]. The use of gas dilution techniques, such as multiple-breath nitrogen washout (MBNW), require minimal patient cooperation and allow FRC to be determined in those individuals unable to complete plethysmographic measurements. The MBNW technique is used clinically and for research, and provides accurate and repeatable measures in both children and adults [3, 4].

The 2005 American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines recommend waiting between repeated MBNW tests for ⩾15 min and that in obstructed patients a period of >1 h may be required [2].

This study aimed to develop an evidence-based recommendation for the wait required between repeated MBNW tests using contemporary equipment and standardised collection protocols.

Children were tested in the Respiratory Laboratory of Princess Margaret Hospital for Children and the adults at the Respiratory Laboratory of Royal Perth Hospital, both located in Perth, Western Australia. The study was approved by the relevant ethics committees (EC LR.2008/127 and EC06-91), and written informed consent obtained from all participants and/or their parents, as relevant.

The study commenced in children between November 2006 and January 2008, and then expanded to the adult population from December 2007 to November 2009. Spirometry was only obtained in participants with lung disease according to current guidelines [5]. All MBNW tests were conducted according to the 2005 ATS/ERS criteria for the MBNW technique [2].

Children attended on a single occasion and were classed as healthy or as having lung disease, including asthma and cystic fibrosis. The initial MBNW (VMax Encore 229; Carefusion, Sydney, Australia) measurement of FRC was obtained for each child (t=0). Children repeated the FRC measurement after waiting for 5 min then after waiting a further 15 min, or after waiting for 15 min then 5 min, with the testing order randomised.

The adults were classed as healthy, or as having obstructive or restrictive lung disease. On review of the paediatric data and considering that the time to clear gas from the lungs is dependent on disease severity, the protocol for adults was modified such that the time between MBNW tests was determined as a multiple of the initial washout time. An initial MBNW (Medgraphics Corporation, St Paul, MN, USA) was performed (t=0) to provide the baseline washout time. The measurement was then repeated after waiting once, twice and three times their initial washout time, in randomised order.

Data (mean±SD) were normally distributed. Lung function is presented as standardised residuals derived from relevant prediction equations [6–9]. We defined acceptable between-test repeatability as a change in FRC <10%, in line with current MBW testing guidelines [10]. Power analysis showed that group sample sizes of 14 would detect a change of 10% assuming a SD of 0.35 (coefficient of variation, 18.75%). Data were analysed using paired t-tests and a random-effects longitudinal regression model to assess the change in FRC from baseline.

Acceptable and repeatable FRCs were obtained in 19 healthy children and 18 with lung disease (eight with asthma and 10 with cystic fibrosis) aged 7–18 years (mean±SD 12.76±3.18 years). Spirometry (in standardised residuals) in the children with lung disease was: forced expiratory volume in 1 s (FEV_1) −1.48±1.75; forced vital capacity (FVC) −0.89±1.13; and FEV_1/FVC −1.21±1.51. No clinically (⩾10%) or statistically significant differences were detected between baseline FRC (FRC_0) and after 5 min (FRC_5) or 15 min (FRC_{15}) in either group (table 1). This was confirmed using random-effects regression modelling, with no associations between differences in FRC and waiting time, test order or disease status.

TABLE 1 Impact of waiting times on repeat measurements of functional residual capacity (FRC) in children and adults

	Children n	FRC_0 SR	FRC_0 L	ΔFRC_5 L	ΔFRC_{15} L	
Healthy	19	−0.65±0.77	1.90±0.57	0.09±0.22	0.01±0.15	
Lung disease	18	−0.47±1.64	1.54±0.45	0.01±0.13	0.03±0.11	
	Adults n	**FRC_0 SR**	**FRC_0 L**	**$\Delta FRC_{1\times}$ L**	**$\Delta FRC_{2\times}$ L**	**$\Delta FRC_{3\times}$ L**
Healthy	24	−0.66±1.44	2.90±0.76	−0.08±0.22	−0.03±0.44	0.03±0.31
Lung disease						
Restrictive	16	−2.02±0.62	1.99±0.42	−0.07±0.20	−0.11±0.27	−0.03±0.19
Obstructive	18	1.56±2.23	3.69±1.03	−0.36±0.44***	0.01±0.29	−0.15±0.46

Data are presented as mean±SD unless otherwise stated. FRC_0: baseline FRC; SR: standardised residual; Δ: difference from FRC_0 in; FRC_5: FRC measured after waiting 5 min; FRC_{15}: FRC measured after waiting 15 min; $FRC_{1\times}$: FRC measured after waiting for the initial washout time; $FRC_{2\times}$: FRC measured after waiting for twice the washout time; $FRC_{3\times}$: FRC measured after waiting for three times the initial washout time. ***: $p<0.001$.

Measurements of FRC were obtained in 24 healthy adults (aged 35±16.3 years), 16 adults with interstitial lung disease (aged 64.8±8.6 years) and 18 adults with chronic obstructive pulmonary disease (aged 61.6±17.1 years)). Among those with restrictive lung disease, spirometry was: FEV_1, −1.66±1.22; FVC, −1.90±1.23; and FEV_1/FVC 0.41±1.28. Among those with obstructive lung disease, spirometry was: FEV_1 −3.17±1.28; FVC −1.29±1.16; and FEV_1/FVC −3.30±1.36. Waiting for the initial washout time had no effect on FRC in the healthy or restrictive lung disease groups. The obstructive lung disease group exhibited a clinically significant fall in FRC of 360 mL (−10.2%; $p<0.001$) after waiting for the washout time (table 1). This effect was not evident with longer waiting times (table 1). Random-effects regression analysis indicated that obstructive disease severity (assessed by FEV_1/FVC) had no effect ($p=0.98$) on the change in FRC between measurements. Similarly, restrictive disease severity (assessed by predicted TLC) also had no effect ($p=0.69$) on FRC.

This study investigated the time required for nitrogen levels in the lungs to return to baseline following repeated MBNW testing, thereby avoiding the introduction of measurement errors. To increase the generalisability of our findings, both children and adults were included, with varying degrees of lung disease severity.

In children we found that waiting 5 min (an average of 2.6 times the initial washout time) between measurements allowed nitrogen to return to baseline. In healthy adults and in adults with restrictive lung disease, a wait time of a single washout was sufficient for nitrogen to return to baseline. In adults with obstructive lung disease, a period of twice their initial washout time was required to measure FRC with acceptable repeatability. Nonetheless, waiting twice the initial washout time was, on average, 5.5 min, and significantly shorter than the 15–60 min recommendation in the 2005 ATS/ERS guidelines. Previous infant MBNW testing guidelines [11] and the 2013 ATS/ERS MBNW consensus statement [10] recommend that a wait time of at least twice the washout period be used, and these data support that recommendation.

The study does have limitations. The protocol differed between the adult and paediatric groups, with the adult protocol informed by the paediatric data. We do not believe this alters our recommendations, as the children had a mean wait time of 2.6 times the initial washout time, which is in line with our recommendation of waiting at least twice the initial washout time in adults. This is further supported by the fact that the adults had more severe obstruction and, therefore, the likelihood of twice the washout time not being adequate in children is low. It should be acknowledged that patients with more severe lung disease that those in this study may require longer wait times and the observation of alveolar nitrogen levels prior to testing commencing, as recently recommended [10], would increase certainty around test commencement. We were not able to measure lung clearance index (LCI). However, errors that affect FRC will also impact LCI and we suggest that studies using ventilation distribution outcomes incorporate these findings into the measurement protocols.

In conclusion, we recommend a uniform approach to waiting time between MBNW tests, and to wait at least twice the initial washout time and to monitor post-test nitrogen levels before repeating the MBNW measurement. Further studies should examine further optimising these recommendations for all MBW

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outcomes. We believe our recommendation should inform lung function testing practices in paediatric and adult settings and will help optimise the quality of lung volume measurements.

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Repeated multiple-breath washout tests should be twice the washout time apart to reduce avoidable measurement errors http://ow.ly/HPgW4

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