Research letter

Defining the appropriate wait time between multiple breath nitrogen washout measurements

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Notation of prior abstract publication/presentation:

This work was presented at the 2010 European Respiratory Society annual scientific conference in Barcelona as an oral presentation.

Running title: Waiting times for lung volume measurement

Take home message (116 of 120 allowed characters): Repeated multiple breath washout tests should be twice the washout time apart to reduce avoidable measurement errors.

Word count (1200 allowed): 1199

Tables (1 allowed): 1

References (15 allowed): 11

Keywords: Functional residual capacity, multiple breath nitrogen washout, adult, paediatric, restrictive lung disease, obstructive lung disease, lung function testing

Introduction

Static lung volume measurements allow objective assessment of total lung capacity (TLC), functional residual capacity (FRC) and residual volume (RV), 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 allows 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 a wait between repeated MBNW tests of at least 15 minutes and that in obstructed patients a period of >1 hour 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 standardized collection protocols.

Materials and methods

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]

Paediatric protocol

Children attended on a single occasion and were classed as healthy or lung disease, the latter including asthma and cystic fibrosis. The initial MBNW (VMax Encore 229: Carefusion,

Australia) measurement of FRC was obtained for each child (t=0). Children repeated the FRC measurement after waiting 5 minutes, then after waiting a further 15 minutes, or after waiting 15 minutes then 5 minutes, with testing order randomized.

Adult protocol

The adults were classed as healthy, obstructive lung disease 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, United States) 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 randomized order.

Data Analysis

Data (mean and standard deviation (SD)) were normally distributed. Lung function is presented as predicted standardised residuals. [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 an σ of 0.35 (CV of 18.75%). Data were analysed using paired t-tests and a random effects longitudinal regression model to assess the change in FRC from baseline.

Results

Paediatric data

Acceptable and repeatable FRC were obtained in 19 healthy children and 18 with lung disease (n=8 with asthma and n=10 with cystic fibrosis) aged 7 to 18 (mean (SD) 12.76 (3.18)) years. Spirometry in the children with lung disease was -1.48 (1.75) for FEV_1, -0.89 (1.13) for FVC and -1.21 (1.51) for FEV_1/FVC. No clinically (≥10%) or statistically significant differences were detected between baseline FRC (FRC_0) and after five (FRC_5) or 15 (FRC_{15}) minutes in either group (Table). These was confirmed using random effects regression modelling with no associations between differences in FRC and wait time, test order or disease status.

Adult data

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)). Mean (SD) spirometry was -1.66 (1.22) for FEV_1, -1.90 (1.23) for FVC and 0.41 (1.28) for FEV_1/FVC in restricted lung disease while those with obstructive lung disease had spirometry of -3.17 (1.28), -1.29 (1.16) and -3.30 (1.36) for FEV_1, FVC and FEV_1/FVC, respectively. Waiting the initial washout time had no effect on FRC in the healthy or restrictive groups. The obstructive lung disease group exhibited a clinically significant fall in FRC of 360 mL (-10.2%; $p<0.001$) after waiting one times the washout time (Table). This effect was not evident with longer wait times (Table). 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.

Discussion

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 generalizability of our findings, both children and adults were included, with varying degrees of lung disease severity.

In children we found that waiting 5 minutes (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 minutes and significantly shorter than the 15 to 60 minutes recommendation in the 2005 ATS/ERS guidelines. Previous infant MBW testing guidelines [11] and the 2013 ATS/ERS MBW 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 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 that 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 wait 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 outcomes. We believe our recommendation should inform lung function testing practices in paediatric and adult settings and will help optimize the quality of lung volume measurements.

Acknowledgements The authors would like to acknowledge the participants of this study from Princess Margaret Hospital, and Royal Perth Hospital. They would also like to acknowledge Statistician Michael Phillips from the Medical Research Foundation at Royal Perth Hospital for providing statistical analysis. There are no conflicts of interest associated with this study. G Hall is funded by an Australian National Health and Medical Research Council Fellowship (APP1025550)

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TABLE 1: Impact of waiting times on repeat measurements of FRC in children and adults

Children

	FRC_0 SR	FRC_0	ΔFRC_5	ΔFRC_{15}
Healthy n=19	-0.65 (0.77)	1.90 (0.57)	0.09 (0.22)	0.01 (0.15)
With lung disease n=18	-0.47 (1.64)	1.54 (0.45)	0.01 (0.13)	0.03 (0.11)

Adults

	FRC_0 SR	FRC_0	ΔFRC_{1x}	ΔFRC_{2x}	ΔFRC_{3x}
Healthy n=24	-0.66 (1.44)	2.90 (0.76)	-0.08 (0.22)	-0.03 (0.44)	0.03 (0.31)
Restrictive disease n=16	-2.02 (0.62)	1.99 (0.42)	-0.07 (0.20)	-0.11 (0.27)	-0.03 (0.19)
Obstructive disease n=18	1.56 (2.23)	3.69 (1.03)	**-0.36 (0.44)**[#]	0.01 (0.29)	-0.15 (0.46)

Legend: Baseline FRC (FRC_0) is FRC measured at time 0 and is reported in absolute values (in litres) and predicted standardised residuals (FRC_0 SR) (T_0)); FRC_5 and FRC_{15} measured after 5 and 15 minutes. FRC_{1x}, FRC_{2x} and FRC_{3x} equates to FRC measured after waiting at 1, 2 and 3 times the initial washout time. Data presented as mean and standard deviation (mean (SD)). The difference (Δ) in FRC (in litres) from baseline is presented as the mean (SD) difference from FRC_0. Adults with obstructive lung disease had a significantly lower ($p<0.001$) FRC at FRC_{1x} compared to FRC_0, there were no other clinically or statistically differences in children or adults at any other time point.