Multiple breath washout quality control in the clinical setting

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Abstract

Background: Multiple breath washout (MBW) is increasingly used in the clinical assessment of patients with cystic fibrosis (CF). Guidelines for MBW quality control (QC) were developed primarily for retrospective assessment and central overreading. We assessed whether real-time QC of MBW data during the measurement improves test acceptability in the clinical setting. Methods: We implemented standardized real-time QC and reporting of MBW data at the time of the measurement in the clinical pediatric lung function laboratory in Bern, Switzerland in children with CF aged 4-18 years. We assessed MBW test acceptability before (31 tests; 89 trials) and after (32 tests; 97 trials) implementation of real-time QC and compared agreement between reviewers. Further, we assessed the implementation of real-time QC at a secondary center in Zurich, Switzerland. Results: Before implementation of real-time QC in Bern, only 68% of clinical MBW tests were deemed acceptable following retrospective QC by an experienced reviewer. After implementation of real-time QC, MBW test acceptability improved to 84% in Bern. In Zurich, after implementation of real-time QC, test acceptability improved from 50% to 90%. Further, the agreement between MBW operators and an experienced reviewer for test acceptability was 97% in Bern and 100% in Zurich. Conclusion: Real-time QC of MBW data at the time of measurement is feasible in the clinical setting and results in improved test acceptability.

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Abstract

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Methods: We implemented standardized real-time QC and reporting of MBW data at the time of the measurement in the clinical pediatric lung function laboratory in Bern, Switzerland in children with CF aged 4-18 years. We assessed MBW test acceptability before (31 tests; 89 trials) and after (32 tests; 97 trials) implementation of real-time QC and compared agreement between reviewers. Further, we assessed the implementation of real-time QC at a secondary center in Zurich, Switzerland.

Results: Before implementation of real-time QC in Bern, only 68% of clinical MBW tests were deemed acceptable following retrospective QC by an experienced reviewer. After implementation of real-time QC, MBW test acceptability improved to 84% in Bern. In Zurich, after implementation of real-time QC, test acceptability improved from 50% to 90%. Further, the agreement between MBW operators and an experienced reviewer for test acceptability was 97% in Bern and 100% in Zurich.

Conclusion: Real-time QC of MBW data at the time of measurement is feasible in the clinical setting and results in improved test acceptability.

1. Introduction

The lung clearance index (LCI) derived from the multiple breath washout technique (MBW) is sensitive to detect early lung disease in patients with cystic fibrosis (CF) [1-4]. With the availability of commercial MBW devices, LCI is increasingly being used as an outcome in routine clinical surveillance [5-10]. While MBW testing requires minimal cooperation from the subject, an acceptable test requires relaxed tidal breathing and a leak-free system[11], which can be challenging in young children and individuals with respiratory disease[12]. Besides, prospective quality control (QC) of MBW measurements can be challenging in the busy clinical setting.

Quality control guidelines for MBW focus primarily on retrospective analysis and central overreading of MBW measurements by experienced users for research studies and clinical trials[11,13-15]. The 2013 European Respiratory Society (ERS) and American Thoracic Society (ATS) consensus statement for inert gas washout measurements proposed initial recommendations for testing procedure and technical acceptability criteria

[11]. Further to this, ATS published additional guidelines for the preschool age group [14]. Jensen *et al.* proposed comprehensive guidelines for retrospective quality control of MBW measurements, which involved both qualitative and quantitative criteria for trial grading and acceptability[13]. These guidelines were further implemented in a standardized MBW training and quality control platform for central overreading in clinical trials[15]. However, for LCI to be used as a clinical outcome, prospective reporting of acceptability and test results is required for clinical decision making.

Therefore, we aimed to implement prospective, real-time quality control of MBW measurements in the clinical pediatric lung function laboratory in Bern, Switzerland. The first aim was to evaluate the acceptability of clinical MBW measurements in children with CF before and after the implementation of real-time quality control. The second aim was to assess the implementation of real-time quality control of MBW measurements in a pediatric lung function laboratory with less experience in MBW testing, Zurich, Switzerland. The third aim was to evaluate agreement in MBW test acceptability between the operator and a retrospective reviewer.

2. Methods

2.1 Development of MBW quality control criteria

The quality control criteria used in this study was based on the ATS/ERS consensus statement guidelines, ATS pre-school MBW technical statement, and the publications by Jensen *et al* and Saunders *et al.*[11,13-15]. We used these guidelines to create a simplified matrix for qualitative assessment of clinical Nitrogen (N_2) MBW measurements that can be applied at the time of the measurement and did not require any further retrospective assessment.

Our quality control criteria are presented in Table 1 and details of how our criteria differ from the ERS/ATS consensus statement are provided in Supplemental Table E1. Detailed instructions on how to apply the guidelines are presented in the online supplemental. An A grade represents a perfect trial with relaxed, regular tidal breathing throughout the measurement, a B grade represents a good quality trial with only minimal deviations, and a C grade represents an acceptable trial with moderate deviations but no highly abnormal breaths during the pre-phase or start of washout. A, B and C grade trials are considered acceptable for outcome reporting. D grade represents trials with questionable quality due to variable breathing patterns, abnormal breaths, or evidence for hypo- or hyper-ventilation. D grade trials have no signs of leak and satisfy both the start and end of test criteria. Generally, D grade trials should be rejected and not used for reporting, however, sometimes the deviations in tidal breathing in a D trial do not significantly impact the primary outcomes. Therefore, we propose that D grade trials can be accepted if the primary outcomes (LCI and FRC) are within 10% of an acceptable trial (A, B or C grade). An F grade represents trials that need to be rejected due to not meeting the technical acceptability criteria for MBW: 1) Start of test criteria not met (last three breaths of pre-phase N_2-concentration with normalized N_2 concentration [?] 77%); 2) End of test criteria not met (three consecutive tidal breaths with normalized N_2 concentration $<$ 2.5%; 3) No evidence of leaks (for detailed instruction see online supplemental).

The overall test occasion is classified as acceptable when (i) at least two trials are graded as acceptable (A, B or C), or (ii) one trial was graded as acceptable (A, B, or C) and one trial was graded as questionable (D) given that both FRC and LCI are within 10% of the A-C grade trial when there are only two trials or 10% of the median when there are three or more trials for this test occasion. A test occasion with only D trials should be rejected. We used the overall test repeatability criteria described in the consensus document (i.e. FRC variability within 25%)[11]. MBW outcomes from acceptable and repeatable test occasions are reported as the mean from all acceptable trials.

2.2 MBW data collection and study population

The N_2MBW measurements were collected using the Exhalyzer D device (Ecomedics, Duernten, Switzerland) with Spiroware software (version 3.2.1) and were performed according to international guidelines [11] in both centers. We approached all pediatric patients with CF attending their regular three monthly outpatient

clinic visits aged 4 to 18 years. Approval was obtained from the local ethics committee in Bern. Patients and caregivers gave informed consent.

2.3 Test acceptability before implementation of real-time MBW quality control in Bern

Before implementation of real-time MBW quality control criteria into clinical routine in our centre, MBW operators were trained in data collection and general test acceptability. However, due to time restrictions, they were not required to perform a detailed assessment of test quality during the measurement. They also did not routinely mark trial classification on the lung function reports. To assess the quality of these MBW measurements, 31 clinic visits from children with CF aged five to 18 years were evaluated. The visits were randomly selected by an independent person not involved in this study and only one visit per patient was included in the analysis. Retrospective quality control was performed by an experienced reviewer who was involved in the development of the criteria and was blinded to any test comments by the MBW operator. The reviewer graded each trial individually and then assessed overall test acceptability.

2.4 Test acceptability after implementation of real-time MBW quality control in Bern

To implement real-time quality control of MBW measurements, operators in our center received instruction on how to perform quality control. A printed copy of the quality control criteria matrix was provided and operators were given a presentation on how to use the matrix, grade individual trials, determine test acceptability and repeatability, and report outcomes (detailed information provided in online supplement). All MBW operators were required to perform real-time quality control of each MBW measurement. The operators reported a grade for each trial and provided a standardized comment regarding the acceptability of the test occasion in the clinical report (example provided in the online supplement).

To assess the quality of MBW measurements after implementation of real-time quality control in routine clinical testing, 32 clinic visits from the same population of children with CF were evaluated. The visits were randomly selected by an independent person not involved in this study and only one visit per child was assessed. The experienced reviewer performed retrospective quality control of these measurements while being blinded to the real-time quality control assessment of the operator.

2.5 Assessment of real-time MBW quality control in secondary centre in Zurich

To validate our findings, we implemented real-time MBW quality control in a centre (Zurich, Switzerland) with less experience in MBW methodology. We first assessed MBW measurements from a random subset of 34 clinical visits from pediatric patients with CF attending their routine care in Zurich, Switzerland. The MBW operators were then instructed on how to use the quality control matrix and given access to the supplementary teaching material (see online supplemental). Mandatory real-time MBW quality control and reporting of test acceptability was implemented for all measurements. We then retrospectively assessed test acceptability and agreement between the operator and reviewer in a random subset of 30 MBW measurements.

2.6 Outcomes before and after real-time quality control

To determine whether performing real-time quality control influenced outcomes, we compared mean outcomes (LCI; FRC) and variability (coefficient of variation; (CV)) before and after implementing real-time quality control. Further, we assessed the impact on MBW outcomes of including D grade trials within 10% variability of good quality trials as proposed in this manuscript.

2.7 Data analysis

For this study, we examined MBW test acceptability before and after implementation of real-time quality control in the clinical setting. Before the implementation of real-time quality control, as primary outcome, we compared test acceptability reported in the clinical reports generated by MBW operators to those reported following retrospective quality control by the experienced reviewer (BF). After the implementation of real-time quality control, as primary outcome, we compared test acceptability and trial acceptability reported at the time of the measurement by MBW operators to those reported following retrospective quality control by the experienced reviewer (BF). As a secondary outcome, we assessed the agreement in test acceptability and trial grading between the MBW operator and an experienced reviewer. Agreement was assessed using kappa statistics. We also compared MBW outcomes (mean and within-test coefficient of variation for FRC and LCI) reported by the operator and reviewer using unpaired t-tests. All statistical analysis was performed using Stata 16.0 (StataCorp 2019)[16].

3. Results

3.1 Study population

The demographic characteristics of study participants from both centers are summarized in Table 2. The population in Zurich was on average younger, however, the age range of patients was similar between both centers. Anthropometric characteristics (height, weight, BMI, and age) and MBW outcomes (LCI and FRC) were well matched between the two study populations.

3.2 MBW test and trial acceptability before implementing real-time quality control

MBW test acceptability results are summarized in Table 3. In Bern, before implementing real-time quality control, 89 MBW trials from 31 test occasions were evaluated. After retrospective analysis of quality control by the reviewer, 68% of test occasions were deemed acceptable. In terms of MBW trials, 51 (57%) were accepted and 38 (43%) were rejected following retrospective quality control by the reviewer. The reasons for trial rejection (details provided in Table 4) included F grade trials whereby the technical acceptability criteria were not met, D grade trials with irregular breathing patterns, and good quality trials (A-C grade) from test occasions without at least two acceptable trials.

In Zurich, before implementing real-time quality control, 97 MBW trials from 34 test occasions were evaluated. After retrospective quality control by the reviewer, only 50% of the test occasions were deemed acceptable. In terms of MBW trials, 47 (49%) were accepted and 50 (51%) were rejected following retrospective quality control by the reviewer. The reasons for trial exclusion (details provided in Table 4) were similar to Bern.

3.3 MBW test and trial acceptability after implementing real-time quality control

Test acceptability after implementing real-time MBW quality control is summarized in Table 3. In Bern, 97 trials from 32 MBW test occasions were evaluated. Test acceptability improved from 68% to 84% and trial acceptability improved from 57% (51/89) to 70% (68/97) (Table 5). In Zurich, 91 trials from 30 MBW test occasions were evaluated after implementing real-time quality control. Test acceptability improved from 50% (17/34) to 90% (27/30), trial acceptability improved from 49% (47/97) to 74% (67/91) (Table 5).

3.4 Agreement between MBW operator and reviewer after implementing real-time quality control

After implementing real-time quality control, the agreement between operator and reviewer was high in both centers. For test acceptability agreement was 97% (= 0.9, $p < 0.001$) in Bern and 100% (= 1.0, $p < 0.001$) in Zurich. In Bern, only one test occasion was rejected by the reviewer but not by the operator. The remaining four test occasions rejected by the reviewer were also rejected by the operator. In Zurich, all test occasions rejected by the reviewer were also rejected by the operator.

For trial grading, agreement was 68% (= 0.6, p < 0.001) in Bern and 73% (= 0.6, p < 0.001) in Zurich. In Bern, the operators were able to recognize all technically invalid trials (F grade). All F grade trials consisting of leaks were identified by the operator. The only trials in which the end of test criteria was not met were trials that were prematurely terminated by the operator. All the trials evaluated satisfied the start of test criteria, which meant that operators were consistently waiting enough time between trials. Three trials were given a C grade by the operator and a D grade by the reviewer due to irregular breathing pattern. However, these trials were then excluded by both as not being accompanied by a second good quality trial. Only one trial with a D grade was rejected by the reviewer but not by the operator. In Zurich, only one F grade trial that did not meet the end of test criteria was not recognized by the operator. Leaks were all correctly identified by the operator. As in Bern all trials satisfied the start of test criteria. One trial was given a D grade by the reviewer and a C grade by the operator, however, both were rejected for final reporting as not being accompanied by a second good quality trial.

3.5 MBW outcomes before and after quality control

We determined whether performing quality control significantly influenced MBW results in our subset of measurements. We found no differences in LCI or FRC mean values or variability reported by the MBW operator compared with the reviewer before and after real-time quality control (Supplemental Table E2 and E3). Further, we assessed the impact of accepting D grade trials with LCI and FRC values within 10% of an acceptable trial on MBW outcomes and variability. We found no significant differences in LCI, FRC, or outcome variability (LCI/FRC coefficient of variation) between tests with and without accepting these D trials (Supplemental Table E4).

4. Discussion

We assessed the quality of MBW measurements collected in clinical routine before and after implementing mandatory real-time quality control in two centers. We provided the MBW operators with a simplified quality control matrix according to current guidelines and assessed whether real-time quality control of MBW data during the measurement improves test acceptability in routine clinical testing. Following implementation of real-time quality control, acceptability of MBW measurements improved from 68 to 84% in Bern and from 50% to 90% in the validation center Zurich, and resulted in excellent agreement between the operator and reviewer.

Implementing mandatory real-time quality control improved overall test acceptability and the ability of MBW operators to recognize and perform good quality MBW measurements in routine clinical testing. Before implementation of real-time quality control criteria, operators reported outcomes to the clinicians with trials that should have been rejected according to current quality control guidelines[11,13-15]. After implementing mandatory real-time quality control and providing the simplified guidelines in Bern, operators were able to correctly identify all technically not acceptable trials. These findings were validated in a center with less experience in MBW measurements (Zurich). These results indicate that performing standardized real-time quality control is feasible in the clinical setting, improves overall test acceptability, and results in good agreement between reviewer and operator.

Our quality control guidelines are a simplified version of the current MBW consensus guidelines, preschool technical standards, and quality control guidelines by Jensen *et al.* and *Saunders et al* [11 14 13,15]. Due to the complexity and time consuming nature of the MBW test, there has been a focus on the need for detailed retrospective quality control and central over-reading by highly experienced MBW researchers. While central over-reading is a suitable approach for large, multi-centre research studies[15,17], clinical MBW testing requires immediate reporting of outcomes. Therefore, real-time quality control by the operator is the only way to ensure that good quality MBW outcomes are used for clinical interpretation. Our quality control criteria (Table 1) provide simplified guidelines for MBW trial grading, trial acceptability, and test acceptability. They can be applied at the time of the measurement to allow immediate reporting of MBW data in clinics.

To maintain high quality MBW data in the clinical setting we suggest that centres implement regular training sessions with operators, provide updates of recent literature in the field, and perform regular over-reading of random subsets of MBW measurements in order to provide feedback to the operators.

We found that systematic quality control of MBW measurements by an experienced reviewer did not lead to differences in mean LCI or FRC values compared with values reported without quality control. These findings are similar to those reported by Jensen et al, who found no differences in mean LCI values following qualitative and quantitative review[13]. However, while both studies reported no significant differences in outcomes on a population level, reporting outcomes from technically not acceptable MBW trials can impact the outcomes of a test occasion on an individual level[18]. In the clinical setting, longitudinal changes in MBW outcomes from one visit to the next are likely to influence treatment decisions. Therefore, it is essential to ensure that only data from good quality MBW trials are reported.

In the clinical setting, trials with highly irregular breathing pattern (D grade) but meeting technical acceptability criteria are a frequent challenge. Especially in younger children, where individual attention may be limited and time restricted in busy outpatient clinics, collecting three immaculate trials can be challenging. We, therefore, decided to follow a pragmatic approach and include them for outcome reporting if at least one good quality trial (A, B or C trial) within the same test occasion was available and LCI and FRC are within 10% of this acceptable trial. The consensus statement suggests repeatability of FRC to be within 25% of the median FRC of technically acceptable trials[11] and states that trials exceeding those limits should prompt further investigation. We did not find an influence on MBW outcomes and test variability when including these D grade trials and variability was substantially lower than the limits proposed by the consensus statement[11]. However, these criteria need to be validated in a larger dataset.

There are some limitations to our quality control criteria. Trial grading is based on qualitative criteria for breathing pattern that are inherently subjective. Users need to have familiarity with the MBW test to differentiate between minimally and moderately variable breathing pattern. However, many of these subjective criteria will only influence whether a trial is graded as either A, B or C, all of which are technically acceptable trials. Our criteria could have been simplified further to only include acceptable, questionable, or rejected trial grading, however, MBW operators stated that it was beneficial to be able to recognize what constitutes a technically perfect trial and understand which deviations can still be accepted. Further, our quality control criteria are only applicable to N_2MBW measurements. This study was performed using Ecomedics equipment and Spiroware 3.2.1 software whereby flow-volume loops, nitrogen, oxygen, and carbon dioxide signals are visible during and after the measurement. It is unclear how easily these criteria can be applied to data collected in other devices, software, and alternative tracer gases.

Conclusion

Real-time quality control of MBW data at the time of the measurement is feasible in the clinical setting and results in improved test acceptability with excellent agreement between MBW operators and experienced reviewers. Our quality control criteria provide simplified guidelines for MBW trial grading, trial acceptability, test acceptability, and outcome reporting that can be applied even in centers with less experience in MBW methodology. Applying these criteria by MBW operators at the time of the measurement ensures that only good quality MBW outcomes are reported to the clinician.

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Conflicts of Interest

Dr. Latzin: personal fees from Vertex, Novartis, Roche, Polyphor, Vifor, Gilead, Schwabe, Zambon, Santhera, grants from Vertex, all outside this work. All other authors have no conflicts of interest.

References

1. Gustafsson PM, Aurora P, Lindblad A. 2003. Evaluation of ventilation maldistribution as an early indicator of lung disease in children with cystic fibrosis. Eur Respir J. 2003; 22(6):972.

2. Gustafsson PM, De Jong PA, Tiddens HA, Lindblad A. 2008. Multiple-breath inert gas washout and spirometry versus structural lung disease in cystic fibrosis. Thorax. 2008; 63(2):129-134.

3. Jensen R, Stanojevic S, Gibney K, Salazar JG, Gustafsson P, Subbarao P, Ratjen F. 2013. Multiple breath nitrogen washout: A feasible alternative to mass spectrometry. PLoS One. 2013; 8(2):e56868.

4. Owens CM, Aurora P, Stanojevic S, Bush A, Wade A, Oliver C, Calder A, Price J, Carr SB, Shankar A et al. 2011. Lung clearance index and hrct are complementary markers of lung abnormalities in young children with cf. Thorax. 2011; 66(6):481-488.

5. Aurora P, Stanojevic S, Wade A, Oliver C, Kozlowska W, Lum S, Bush A, Price J, Carr SB, Shankar A et al. 2011. Lung clearance index at 4 years predicts subsequent lung function in children with cystic fibrosis. Am J Respir Crit Care Med. 2011; 183(6):752-758.

6. Davies J, Sheridan H, Bell N, Cunningham S, Davis SD, Elborn JS, Milla CE, Starner TD, Weiner DJ, Lee PS et al. 2013. Assessment of clinical response to ivacaftor with lung clearance index in cystic fibrosis patients with a g551d-cftr mutation and preserved spirometry: A randomised controlled trial. Lancet Respir Med. 2013; 1(8):630-638.

7. Fuchs SI, Gappa M. 2011. Lung clearance index: Clinical and research applications in children. Paediatr Respir Rev. 2011; 12(4):264-270.

8. Kent L, Reix P, Innes JA, Zielen S, Le Bourgeois M, Braggion C, Lever S, Arets HG, Brownlee K, Bradley JM et al. 2014. Lung clearance index: Evidence for use in clinical trials in cystic fibrosis. J Cyst Fibros. 2014; 13(2):123-138.

9. Stanojevic S, Davis SD, Retsch-Bogart G, Webster H, Davis M, Johnson RC, Jensen R, Pizarro ME, Kane M, Clem CC et al. 2017. Progression of lung disease in preschool patients with cystic fibrosis. Am J Respir Crit Care Med. 2017; 195(9):1216-1225.

10. Fuchs SI, Eder J, Ellemunter H, Gappa M. 2009. Lung clearance index: Normal values, repeatability, and reproducibility in healthy children and adolescents. Pediatr Pulmonol. 2009; 44(12):1180-1185.

11. Robinson PD, Latzin P, Verbanck S, Hall GL, Horsley A, Gappa M, Thamrin C, Arets HGM, Aurora P, Fuchs SI et al. 2013. Consensus statement for inert gas washout measurement using multiple- and single-breath tests. Eur Respir J. 2013; 41(3):507.

12. Yammine S, Summermatter S, Singer F, Lauener R, Latzin P. 2016. Feasibility of nitrogen multiple-breath washout in inexperienced children younger than 7 years. Pediatr Pulmonol. 2016; 51(11):1183-1190.

13. Jensen R, Stanojevic S, Klingel M, Pizarro ME, Hall GL, Ramsey K, Foong R, Saunders C, Robinson PD, Webster H et al. 2016. A systematic approach to multiple breath nitrogen washout test quality. PLoS One. 2016; 11(6):e0157523.

14. Robinson PD, Latzin P, Ramsey KA, Stanojevic S, Aurora P, Davis SD, Gappa M, Hall GL, Horsley A, Jensen R et al. 2018. Preschool multiple-breath washout testing. An official american thoracic society technical statement. Am J Respir Crit Care Med. 2018; 197(5):e1-e19.

15. Saunders C, Jensen R, Robinson PD, Stanojevic S, Klingel M, Short C, Davies JC, Ratjen F. 2019. Integrating the multiple breath washout test into international multicentre trials. Journal of Cystic Fibrosis. 2019.

16. StataCorp. 2019. Stata statistical software: Release 16. In: LLC S, editor.: College Station, TX.

17. O'Neill K, Lakshmipathy GR, Ferguson K, Cosgrove D, Hill AT, Loebinger MR, Carroll M, Chalmers JD, Gatheral T, Johnson C et al. 2018. Quality control for multiple breath washout tests in multicentre bronchiectasis studies: Experiences from the bronch-uk clinimetrics study. Respir Med. 2018; 145:206-211.

18. Lenherr N, Ramsey KA, Jost K, Hornwall L, Singer F, Yammine S, Latzin P. 2018. Leaks during multiple-breath washout: Characterisation and influence on outcomes. ERJ Open Res. 2018; 4(1).

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