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LETTER

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Comparison of functional residual capacity between updated infant SF_6 multiple-breath washout setups

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To the editor,

Multiple-breath inert gas washout (MBW) is a sensitive technique to assess lung volumes and ventilation inhomogeneity from infancy, but technical and methodological issues limit its widespread application.[1] There are two setups currently being used for the collection of infant MBW measurements, the WBreath (ndd Medizintechnik AG) and the more recent Spiroware (Eco Medics AG) setup. In WBreath, outcomes are based on changes in the main-stream molar mass of expired air caused by the wash-in and wash-out of the tracer gas sulfur hexafluoride (SF_6). However, previous studies have shown that the outcomes are heavily dependent on the software version, system settings, and analysis protocol.[1] The Spiroware setup utilizes additional information from simultaneously measured and synchronized main-stream CO_2 and side-stream molar mass and O_2 signals to calculate SF_6 concentrations.[2] Despite using the same hardware (Exhalyzer D, Eco Medics AG), functional residual capacity (FRC) can differ by up to 7% in vitro and 40% in vivo between the two setups.[3]

We recently identified, characterized, and corrected a significant sensor-crosstalk error in the Exhalyzer D device that led to an overestimation of tracer gas concentration.[4] Likewise, we identified and corrected discrepancies from current ATS/ERS consensus guidelines in WBreath analysis software that led to an overestimation of FRC.[1] As a result, the respective manufacturers released new software versions which incorporated updated analysis algorithms. The updated analysis in the Spiroware software resulted in improved agreement between N_2 and SF_6 MBW outcomes in this setup in infants and young children.[5] However it is yet unclear whether the updates described above also result in better agreement in N_2 MBW outcomes between Spiroware and WBreath.

We aimed to perform in vitro validation and characterization of any remaining differences between the updated WBreath (3.52.3) and Spiroware (3.3.1) infant SF_6-MBW setups. We first assessed the accuracy of FRC measurement by generating five infant FRC volumes (80, 120, 150, 180, and 210 mL), three FRC volumes (80, 150, and 210 mL) with 5% CO_2, and artificially increasing ventilation inhomogeneity under body temperature, pressure, saturated with water vapor conditions. We hypothesized that improved analysis algorithms would reduce differences in FRC between the two setups.

We performed in vitro SF_6-MBW measurements using a customized infant lung model (ARTORG Center for Biomedical Engineering Research, University of Bern, Switzerland) consisting of two communicating compartments representing the pulmonary and ventilatory compartment (Supporting Information S1: Figure S3) with real-time monitoring of ambient temperature and temperature within the lung model. Flow and molar mass signals were measured by an

ultrasonic flowmeter (Exhalyzer D, Eco Medics AG) using either the WBreath 3.52.3 (ndd Medizintechnik AG) or Spiroware 3.3 software (Eco Medics AG). A 100-mL automated calibration syringe (Hans Rudolph Inc.) allowed precise adjustment of FRC volumes by regulating end-expiratory water levels. Syringe stroke volumes were set to physiologic tidal volumes (28, 48, or 78 mL) and respiratory rates (30, 40, or 50/min). We assessed the possible influence of varying F_{CO2} by including CO_2 in the wash-in (3.7% SF_6, 5% CO_2, 16% O_2, rest N_2) and wash-out (5% CO_2, 16% O_2, rest N_2) gas mixtures (Carbagas AG). A detailed summary of the in vitro measurements is provided in the online supplement.

FRC from Spiroware was closer to the lung model (median (SD) absolute difference 2.6 (2.4) mL; relative difference 2.2 (1.1)%) than FRC from WBreath (median (SD) absolute difference 4.5 (8.6) mL; relative difference 2.5 (5.9)%; Figure 1). Overall, there was no statistically significant difference between 15 paired FRC measurements from the two setups (mean [95% confidence interval] difference 1.2 (−4.7; 7.1) mL; $p = 0.664$). Intratest variability was low for both setups (mean (SD) CV was 0.97 (0.24)% and 1.34 (0.46)% for the Spiroware and WBreath setups, respectively; Figure 1). In the Spiroware setup, all FRCs were within the 5% error limit (mean error [range] 1.9 [0.0; 4.0]%), whereas in the WBreath setup only 6/15 (40%) FRCs were within the 5% error limit (mean error [range] 5.5 [0.8; 10.9]%; Figure 2). The largest errors for WBreath were seen at the lowest volume (80 mL; mean error [range] 10.2 [9.1; 10.9]%, Figure 2).

The addition of 5% CO_2 to the wash-in and wash-out gas mixtures had no substantial impact on FRC from Spiroware (median [SD] absolute difference −3.9 [7.5] mL; relative difference −4.9 [3.5]%) but significantly increased FRC from WBreath (median [SD] absolute difference 24.1 [6.7] mL; relative difference 17.7 [6.2]%; $p \le 0.001$). With CO_2 present, paired FRC measurements (80, 150 and 210 mL) differed significantly between the setups (mean [95% CI] difference −36.9 [−50.4; −23.3] mL; $p \le 0.001$). Artificially increased ventilation inhomogeneity caused increased FRCs from Spiroware (median [SD] absolute difference 3.5 (3.9) mL; relative difference 4.1 (2.1)%; $p = 0.0068$) but changed FRCs from WBreath such that they were closer to the lung model (median [SD] absolute difference −3.0 [6.8] mL; relative difference −1.9 [6.6]%).

We report an improved agreement of FRC between the updated WBreath 3.52.3 and Spiroware 3.3.1 infant SF_6-multiple-breath washout setups. The mean (range) difference between the two setups was 5.1 (0.4–9.9)%, thus indicating an improvement to previous in vitro reports.[3] Both setups measured the generated lung volumes reproducibly with low intra-test variability. Spiroware demonstrated greater measurement accuracy for FRC, especially for small volumes. Of note, Spiroware's FRC was below the 5% error limit over the whole range of generated volumes, whereas the majority (60%) of measurements in WBreath had errors greater than 5%.[6] Despite improved agreement between setups in vitro, our data indicate they should not be used interchangeably for infant MBW measurements. Future research is needed to assess the reproducibility and agreement of *clinical* measurements in infants using these setups.

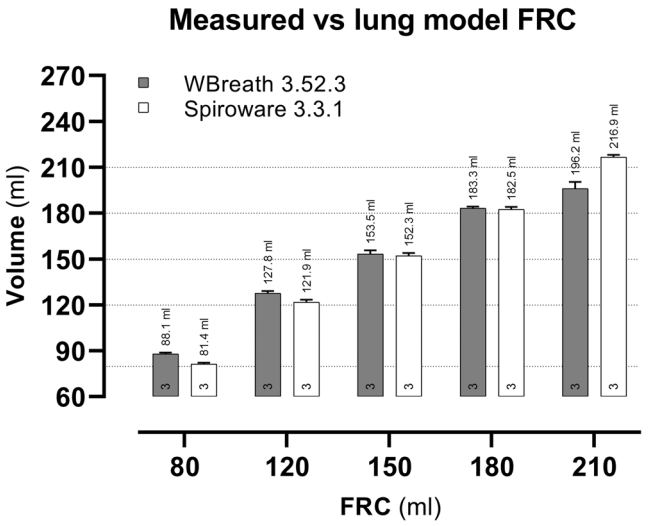

FIGURE 1 Absolute difference between measured functional residual capacity (FRC) and lung model volume. Shown are mean (SD) values of triplicates of FRC measurements for the WBreath 3.52.3 (gray) and Spiroware 3.3 (white) infant SF_6-MBW setups. Horizontal dashed lines indicate the generated lung volumina (80, 120, 150, 180, and 210 mL).

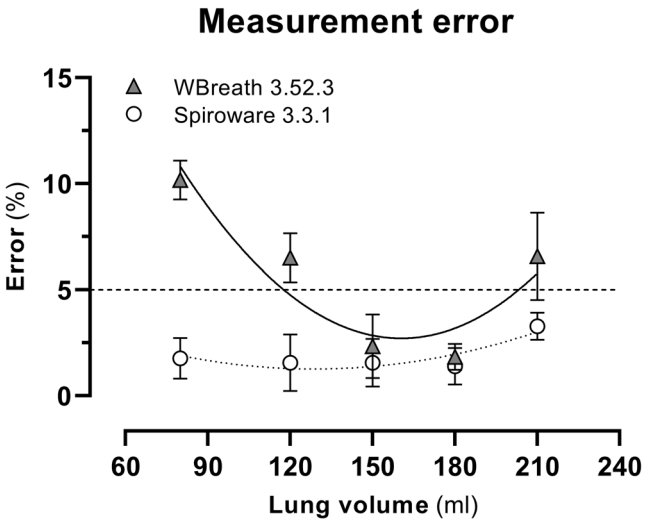

FIGURE 2 Association of measurement error with measured lung volume. Relative functional residual capacity (FRC) measurement error (given as the ratio of absolute error of measured and lung model volume in percent) is plotted over lung volume for the WBreath 3.52.3 and Spiroware 3.3 infant SF_6-MBW setups. The dashed line indicates the 5% limit of acceptable measurement error. Statistics: mean (SD) of triplicates with nonlinear fit (solid line for WBreath; dotted line for Spiroware).

AUTHOR CONTRIBUTIONS

Marc-Alexander Oestreich, Florian Wyler, Anne-Christianne Kentgens, Dominik Obrist, Philipp Latzin, and Kathryn A. Ramsey conception and design of research. Marc-Alexander Oestreich and Robin Hänni data collection. Marc-Alexander Oestreich data analysis.

Marc-Alexander Oestreich, Florian Wyler, Sophie Yammine, Philipp Latzin, and Kathryn A. Ramsey interpreted results. Marc-Alexander Oestreich drafted the manuscript. Marc-Alexander Oestreich and Kathryn A. Ramsey edited and revised the manuscript. Marc-Alexander Oestreich, Robin Hänni, Florian Wyler, Anne-Christianne Kentgens, Sophie Yammine, Dominik Obrist, Philipp Latzin, and Kathryn A. Ramsey approved the final version of the manuscript.

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CONFLICTS OF INTEREST STATEMENT

Marc-Alexander Oestreich, Florian Wyler, Philipp Latzin, and Kathryn A. Ramsey are in regular contact with manufacturers of MBW devices (Eco Medics AG, Duernten, Switzerland and ndd Medizintechnik AG, Zurich, Switzerland). Prof. Philipp Latzin: personal fees from Vertex, Novartis, Roche, Polyphor, Vifor, Gilead, Schwabe, Zambon, Santhera, grants from Vertex, all outside this work. The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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