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Research letter

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Effect of change of body position in spontaneous sleeping healthy infants on SF_6 based multiple breath washout

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To the editor,

Reference values previously published in the ERJ for sulfur hexafluoride (SF_6)-based Multiple Breath Washout (MBW)[1] highlight that lung clearance index (LCI) values were significantly higher in infancy (i.e. first two years of life) compared to the later preschool age range (2-6 years). A number of factors were postulated in recent ATS preschool MBW technical standards[2]: ongoing lung and chest wall development[3]; use of sedation and supine testing position in infancy; and relatively larger equipment-related dead space volume (V_D) in younger subjects. Use of alveolar-based LCI to correct for V_D did not change this pattern suggesting minimal V_D impact as a mechanism to explain these changes[4]. Specific to body position, infants are tested supine (as asleep) and preschoolers are tested sat upright (as awake). The impact of changing body position remains unclear on MBW outcomes. Our aim was to investigate effect of body position on ventilation distribution, resting lung volume (FRC) and breathing pattern in healthy infants during spontaneous sleep.

Parents/caregivers of infants in East Skaraborg County, Sweden (n=200) were identified via the Swedish population register and sent an information letter. Full-term infants without a history of congenital lung malformations or respiratory health problems other than common transient infections were eligible. We aimed to include a minimum of 40 subjects, over a 12 month period, based on the assumption that for a normally distributed variable we would be adequately powered to detect a difference of 0.5 SD of the within-person differences. The study was approved by the Ethics Committee of the University of Gothenburg (DNR 746–15), and parents gave written informed consent.

The commercial MBW device used (ExhalyzerD, Eco Medics AG, Spiroware 3.2.1) had been previously validated by our group for SF_6-based MBW in the infant age range[5]. This open-circuit MBW system measures SF_6 concentrations indirectly via recorded signals including main-stream CO_2, side-stream O_2, side-stream molar mass (MM_{ss}), and respiratory flow using a main-stream ultrasonic flow meter (UFM_{ms}). UFM_{ms} calibration using a 100 mL precision syringe (Hans Rudolph, Shawnee, KS) and static calibration of O_2 (air and 100% O_2, respectively) and SF_6 signals (air for zero, and 4.0% SF_6 in air, respectively) with certified test gases (Linde Healthcare, Lidingö, Sweden) were undertaken as per manufacturer's instructions. Dynamic synchronization of MM_{ss} and gas to respiratory flow was performed during room air breathing separately in all participants[5]. A #1 dead space reducer was used in all recordings. A putty-sealed stiff pediatric face mask Rüsch #1 or #2 (Teleflex Medical, Athlone, Ireland) was used depending on subject's face size. Pre and post gas-sampling point dead space volumes were set to 0 mL and 3.5 mL, respectively. Dead space volume of the mask was minimised using therapeutic putty, and was measured after the recordings. It was found to vary between individuals across the range of 3-8 mL and was not corrected for, in line with recent recommendations[2].

Prior to MBW, infants were fed and MBW recordings started after a sustained period of quiet sleep. Recordings were first made while sleeping horizontally in an infant pushcart and then whilst sitting seated upright with the backrest at 70 degrees. Priority was given to supine recordings, which were part of a larger study collecting SF_6 MBW reference values. At least two recordings (but ideally three) of acceptable quality were collected in each body position, i.e. recordings without evidence of mask leaks or artifacts such as sighs, irregular or fast breathing or breathing interrupted by swallows[6]. After three acceptable supine recordings, the infant was placed in the sitting position and recordings started after confirming ongoing quiet sleep. A prephase of at least 30 s of stable medical air breathing occurred before administration of 4.0% SF_6 gas mixture via the bias flow (SF_6 washin). When end-tidal SF_6 concentration had stabilised at 4.0% for approximately half a minute, the bias flow was switched medical air to start SF_6 washout, which continued until end-tidal SF_6 had fallen to below $1/40^{th}$ of its starting concentration for several breaths[6].

Data were analyzed in Spiroware 3.2.1. Raw data tables were exported from the software into Microsoft Excel 2010 for further statistical evaluation. FRC, LCI, moment ratios, and breathing pattern variables were calculated, using Excel templates made by the senior author, as described in previous publications[7-9], and consistent with recommendations of the ERS/ATS consensus statement[6]. Mean, standard deviation (SD) and coefficients of variation (100 x SD/mean) were calculated for all variables. Paired Student´s t-tests and correlation analyses were made using the Statistica 7 (StatSoft, Tulsa, OK). P-values < 0.05 were regarded as statistically significant.

Among 103 healthy infants tested over a 12 month period, 41 infants (40%) performed at least two acceptable tests in each position and were included in the final analysis. In the remaining 62/103 only supine recordings were obtained (data not reported here). Mean (SD; range) age of included infants was 1.00 (0.33: 0.40-1.63) years with 23 female infants. Mean (SD; range) weight and height were 10.2 (1.7: 7.3-13.6) kg and 75.3 (5.1: 65.0-92.8) cm. SF_6 MBW results are summarised in Table 1. All infants contributed three acceptable SF_6 MBWs supine and 35/41 (85%) performed three subsequent sitting MBWs. The remaining six had two acceptable tests in the sitting position. On average FRC did not change with posture. Small but statistically significant differences were seen in LCI and moment ratios (both 1st and 2nd moments), indicating a slightly better global ventilation efficiency sitting. Measured airway V_D using CO_2 was also lower. Tidal volumes were similar, but respiratory rate and minute ventilation were lower when sitting, resulting in a higher end-tidal CO_2 in that position. Between-subject variation in response to change of position was observed. Sitting FRC was lower in 19/41 (46%) infants by mean (SD: range) 11 (11: 0-43) mL and higher in the remaining 22/41 infants by 16 (10: 0-36) mL. Sitting LCI was lower in 27/41 (66%) infants by 0.33 (0.18: 0.03-0.82) lung turnovers and rose in the remaining 14 subjects by 0.12 (0.11: 0.00-0.40) lung turnovers. On univariate regression analyses, response to change in position from supine to sitting was age-dependent: FRC, both as actual (r=0.43, adjusted R^2 0.16, p=0.005) and mL/kg (r=0.37, adjusted R^2 0.12, p=0.016), and LCI (r=-0.33, adjusted R^2 0.08, p=0.036). Percent change in FRC and LCI correlated (r=-0.57, adjusted R^2 0.33, $p<0.001$). We speculate that response to change of position may reflect contributions of several factors influenced by age including active control of FRC, respiratory system mechanical properties (e.g. lung and chest wall compliance) and minor differences in sleep state.

This is the first study to describe how change of position affects measurements of lung volume (FRC) and indices of ventilation inhomogeneity within healthy infants, the specific age group of interest when discussing the impact of positional change on longitudinal MBW measurements. Of note our reported changes are markedly smaller than that previously reported in older healthy children, where change from supine to sitting led to a mean increase in FRC of 31-40%, and a mean decrease in LCI of 3.4-6.1%[10, 11]. In our cohort of infants, change of body position had no effect on FRC and only a minimal effect on MBW indices of ventilation inhomogeneity (e.g. 2.3% change in LCI). How the age-dependent effect we observed amongst our infants behaves beyond infancy is unclear, but our data highlights the error in extrapolating results from older age groups, and reinforces the importance of age-specific data. Our data supports the conclusion that healthy infants do not need to be tested in the seated position to attain a consistent body position with older children: change of body position contributes minimally to the difference observed between infant and preschool SF_6

MBW LCI values. This is an important finding for longitudinal studies both historically and in the future and for understanding the mechanisms of higher LCI values in infancy.

Table 1. SF_6 MBW and breathing pattern variables compared supine and sitting in 41 infants.

	Supine	**Sitting**	**p-value**
Washout time (s)	33 (6)	34 (7)	0.19
Washout breaths (n)	13.4 (2. 3)	12.9 (1.9)	0.009
FRC (mL)	185 (47)	189 (54)	0.21
FRC (mL/kg b.w.)	18.1 (2. 9)	18.4 (3.4)	0.39
LCI	6.60 (0.41)	6.45 (0. 45)	0.001
μ_1/μ_0	1.54 (0.10)	1.51 (0.10)	<0.001
μ_2/μ_0	4.46 (0.59)	4.26 (0.59)	<0.001
FRC (CV%)	2.0 (1. 2)	2.0 (1.5)	0.75
LCI (CV%)	2.4 (1.4)	2.8 (1.9)	0.37
VDaw, CO_2 (mL)	21 (4)	20 (4)	0.003
VDaw, CO_2 /VT (%)	22. (2.6)	20.8 (2.9)	<0.001
Tidal volume (mL)	96 (23)	98 (22)	0.09
VT/FRC (%)	53 (8)	53 (7)	0.63
Respiratory rate (/min)	24.3 (4. 3)	22.9 (2.9)	<0.001
Minute ventilation (mL/min)	2263 (323)	2180 (296)	<0.001
CO_2, end-tidal (%)	5.85 (0.32)	5.92 (0.34)	0.002

Footnote: Data shown as mean (SD).

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References

1. Lum S, Stocks J, Stanojevic S, Wade A, Robinson P, Gustafsson P, Brown M, Aurora P, Subbarao P, Hoo AF, Sonnappa S. Age and height dependence of lung clearance index and functional residual capacity. *Eur Respir J* 2013: 41(6): 1371-1377.
2. Robinson PD, Latzin P, Ramsey KA, Stanojevic S, Aurora P, Davis SD, Gappa M, Hall GL, Horsley A, Jensen R, Lum S, Milla C, Nielsen KG, Pittman JE, Rosenfeld M, Singer F, Subbarao P, Gustafsson PM, Ratjen F, Pediatrics ATSAo. Preschool Multiple-Breath Washout Testing. An Official American Thoracic Society Technical Statement. *Am J Respir Crit Care Med* 2018: 197(5): e1-e19.
3. Martin TR, Feldman HA, Fredberg JJ, Castile RG, Mead J, Wohl ME. Relationship between maximal expiratory flows and lung volumes in growing humans. *J Appl Physiol* 1988: 65(2): 822-828.
4. Haidopoulou K, Lum S, Turcu S, Guinard C, Aurora P, Stocks J, Sonnappa S. Alveolar LCI vs. standard LCI in detecting early CF lung disease. *Respir Physiol Neurobiol* 2012: 180(2-3): 247-251.
5. Gustafsson PM, Robinson PD, Lindblad A, Oberli D. Novel methodology to perform sulfur hexafluoride (SF6)-based multiple-breath wash-in and washout in infants using current commercially available equipment. *J Appl Physiol* 2016: 121(5): 1087-1097.
6. Robinson PD, Latzin P, Verbanck S, Hall GL, Horsley A, Gappa M, Thamrin C, Arets HG, Aurora P, Fuchs S, King G, Lum S, K.A. M, Paiva M, Pillow JJ, Ranganathan S, Ratjen F, Singer F, Sonnappa S, Stocks J, Subbarao P, Thompson B, Gustafsson PM. ERS/ATS Consensus statement for inert gas washout measurement using multiple and single breath tests. *Eur Respir J* 2013: 41(3): 507-522.
7. Aurora P, Bush A, Gustafsson P, Oliver C, Wallis C, Price J, Stroobant J, Carr S, Stocks J. Multiple-breath washout as a marker of lung disease in preschool children with cystic fibrosis. *Am J Respir Crit Care Med* 2005: 171(3): 249-256.
8. Aurora P, Gustafsson P, Bush A, Lindblad A, Oliver C, Wallis CE, Stocks J. Multiple breath inert gas washout as a measure of ventilation distribution in children with cystic fibrosis. *Thorax* 2004: 59(12): 1068-1073.
9. Gustafsson PM, Aurora P, Lindblad A. Evaluation of ventilation maldistribution as an early indicator of lung disease in children with cystic fibrosis. *Eur Respir J* 2003: 22(6): 972-979.
10. Ramsey KA, McGirr C, Stick SM, Hall GL, Simpson SJ, Arest CF. Effect of posture on lung ventilation distribution and associations with structure in children with cystic fibrosis. *J Cyst Fibros* 2017.
11. Smith LJ, Macleod KA, Collier GJ, Horn FC, Sheridan H, Aldag I, Taylor CJ, Cunningham S, Wild JM, Horsley A. Supine posture changes lung volumes and increases ventilation heterogeneity in cystic fibrosis. *PLoS One* 2017: 12(11): e0188275.