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Changes in Multiple Breath Washout Measures After Raised Volume Rapid Thoracoabdominal Compression Maneuvers in Infants

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SUMMARY. Multiple breath inert gas washout (MBW) measurements in infants are performed supine and often obtained under sedation and thus are combined with other lung function tests such as raised volume rapid thoracoabdominal compression (RVRTC). In this study, we sought to determine the effects of RVRTC maneuvers on MBW measures. Compared with tests performed prior to RVRTC, MBW measured after RVRTC was associated with a small reduction in functional residual capacity and a more pronounced decrease in cumulative expired volume in both healthy children and children with obstructive lung disease (cystic fibrosis or recurrent wheeze) indicating a more efficient washout after the raised volume maneuvers. Lung Clearance Index (LCI) decreased significantly in infants with respiratory disease (change in LCI of −0.24 units post RVRTC; standard error (SE) ± 0.07 units; $P = 0.0004$), but not in healthy infants (change in LCI of −0.08 units; SE ± 0.11 units; $P = 0.44$). As the RVRTC maneuver affects MBW measurements in infants, the timing of testing procedures needs to be standardized in longitudinal studies. **Pediatr Pulmonol. 2016;51:183–188.**

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INTRODUCTION

Forced expiratory flow-volume curves are the most commonly used technique to assess airway function in patients with obstructive lung disease. In infants, forced expiratory flow-volume curves were initially generated at tidal breathing volumes using rapid thoracoabdominal compression. Given the narrow range of volumes studied, it was not surprising that the results from these tests had limited discriminative value.[1] The introduction of the raised volume rapid thoracoabdominal compression (RVRTC) technique allowed the study of flow limitation in infants at a range of lung volumes in a manner similar to older children and adults.[3] The maneuver requires passive inflation during inspiration to achieve a mouth pressure (P_m) of 30 cm H_2O, followed by a rapid compression of the thorax and abdomen via an inflatable jacket.[3] This maneuver had greater reproducibility and sensitivity to detect abnormalities in flow than the tidal flow measures[1,4] and is used extensively in infant pulmonary function studies.[5]

The Multiple Breath Washout (MBW) test is rapidly gaining attention due to its sensitivity to early changes in the peripheral airways and its feasibility in young children.[6,7] In infants, sulfur hexafluoride (SF_6) or helium are the most commonly used inert tracer gases. The most commonly used MBW parameter is the Lung Clearance Index (LCI), a marker of average overall lung ventilation inhomogeneity. It is calculated as the number of functional residual capacity (FRC) lung volume turnovers required to reduce the end-tidal concentration of the inert gas of interest to 1/40th of the starting gas concentration.

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As lung ventilation distribution worsens, increasing numbers of tidal breaths and expired volumes are required to wash out the inert gas resulting in an increasing LCI value.

In infants, MBW testing is often performed under sedation and combined with other lung function measures such as the RVRTC technique. There have been some data suggesting that the RVRTC maneuver influences the subsequent measurement of tidal flow, yet not on tidal breathing parameters such as tidal breathing ratios.[8] Theoretically, both inflation and forced expiration could affect ventilation homogeneity and thus LCI through increased airway closure due to compression of a compliant chest wall in a supine infant. The effect of these maneuvers may be amplified in children also compromised with lung disease characterized by mucus plugging and inflammation which may also increase airway closure. In this study, we aimed to explore the effects of RVRTC on LCI and lung volumes to give further insights into the physiological effects of these maneuvers. We therefore performed MBW on infants prior to performing RVRTC measures and repeated MBW after the RVRTC maneuver.

MATERIALS AND METHODS

Subjects

The study was performed in infants that either underwent clinically indicated lung function testing (patients with CF and recurrent wheezing) or who were participating in the Canadian Healthy Infant Longitudinal Development (CHILD) study, an ongoing birth cohort study of general population children. The study was approved by the Research Ethics Board of the Hospital for Sick Children; informed consent was obtained in all cases.

Infants included in this analysis had to be between 4 and 30 months of age to be eligible for this study. Subjects born $<$35 weeks gestational age, having congenital heart disease, severe gastroesophageal reflux, an active seizure disorder, or known upper airway obstruction were excluded. Healthy controls were defined as having been clear of a history of wheezing, respiratory distress, hospitalization, and were not exposed to maternal smoking during pregnancy. Written consent was obtained from parents of all subjects. Only those children with repeated acceptable measures of LCI at baseline and post RVRTC maneuver were included in this analysis.

Each child was studied in clinically stable condition, at least 3 weeks after resolution of a lower respiratory infection or acute exacerbation of respiratory symptoms. A detailed medical history and physical examination was performed to assess their medical status. Length and weight were measured using a calibrated stadiometer and digital scale just prior to lung function testing.

Lung Function Measurements

All lung function measurements were performed on children under sedation with chloral hydrate (60–80 mg/kg) with infants in the supine position. All children underwent MBW testing, followed by RVRTC, and followed by a repeat multiple breath washout measurement.

Multiple Breath Washout

MBW tests were performed using an infant facemask (Silkomed, Rendell Baker Masks sizes 2 and 3, Rusch Canada, Inc., Benson Medical Industries, Markham, Ontario) sealed with therapeutic putty. A mass spectrometer (AMIS 2000; Innovision A/S, Odense, Denmark) based set-up and technique was used to perform MBW testing with a sulfur hexafluoride (SF_6)/Helium (He) gas mixture as previously described.[9] Briefly, during wash in, participants inhaled the dry tracer gas of interest 4% SF_6 mixed with 4% He, 21% O_2, and balance N_2 via an open circuit bias flow system through a mask and an attached pneumotachograph (Hans Rudolph, Shawnee, KS) until the inhaled and exhaled concentrations are the same for the tracer gas of interest, Once the concentration of SF_6 has stabilized at 4%, wash out can commence. During the wash out phase, the gas source was removed and the subject breathed room air until [SF_6] reached 1/40th of its starting concentration. End of test was considered to be the first of three consecutive breaths where the end-tidal concentration of SF_6 was below target concentration.[7] Tests were performed in triplicate. A minimum of three acceptable MBW measurements, including LCI, FRC_{MBW}, cumulative expired volume (CEV), tidal volume (V_T), and respiratory rate (RR) were achieved for each subject at baseline and post-RVRTC.

RVRTC AND FRC by Body Plethysmography

Forced expiratory volumes and flows (FVC, $FEV_{0.5}$, $FEF_{25\text{-}75}$, and FEF_{75}) were measured using the RVRTC technique according to ATS/ERS guidelines for raised volume forced expirations in infants[3] via the nSpire® Infant Pulmonary Lab (Longmont, CO). All curves used for analysis had FVC measurements within 10% of the highest FVC. Lung function outcomes are reported as the single best maneuvers with the highest sum of FVC and $FEF_{25–75}$.

The same equipment was used to measure functional residual capacity (FRC_{pleth}) by body plethysmography according to ATS/ERS guidelines prior to RVRTC maneuvers.[10] FRC was calculated from the average of three acceptable occlusions. Lung function parameters were analyzed both as raw values and as z-scores calculated from published normative data.[11–13]

Statistical Analysis

Height, weight, and BMI measurements were converted to centiles using the Centers for Disease Control and Prevention (CDC) growth charts for infants and preschool children.[14] Baseline characteristics were reported as arithmetic mean and standard deviation (SD) for continuous variables and frequency for categorical variables. LCI and FRC_{MBW} were standardized to z-scores (zLCI and zFRC) using a reference population to account for the height related changes during early childhood.[12] For comparing baseline characteristics, two-sample *t* tests (or Mann–Whitney *U* tests, where appropriate) were used for continuous variables and Fisher's exact tests were used for categorical variables. The LCI and $FRC_{(MBW\ and\ Pleth)}$ in raw scales were reported as least square mean (LSM) and standard error (SE) based on linear regression models, adjusted for age, gender, and ethnicity. For comparisons of LSM between groups, *t* tests based on linear regression models were used.

To assess the effects of RVRTC maneuvers on MBW measures, linear mixed effect models with random intercept (between-subject variances) were used to account for the correlation between repeated measures within each test occasion (baseline and post-RVRTC). Analyses were performed separately for the healthy children and those with respiratory disease. All models were controlled for age and height. Statistical analyses were performed using SAS version 9.3 (SAS statistical software, Cary, NC). All tests were 2-sided and statistical significance was set at $P < 0.05$.

RESULTS

Baseline characteristics of study participants are presented in Table 1. Repeatable acceptable LCI measures were obtained before, and after a successful RVRTC maneuver in 23 healthy children and 34 children with respiratory disease (23 with cystic fibrosis and 11 with recurrent wheezing). FRC_{pleth} measurements (pre-RVRTC) were available in 21 healthy infants and 33 children with respiratory disease (23 with cystic fibrosis and 10 with recurrent wheezing).

Healthy control participants were younger ($P < 0.001$) and more likely to be non-Caucasian ($P = 0.02$) than the subjects with respiratory disease (Table 1). Given the known height and age dependency of LCI in the infant range, the raw LCI values were converted to z-scores.[12] The within-test coefficient of variation for LCI measurements was 4.6% in health and 3.5% in disease. After age adjustment, there were no longer significant differences in weight and height between the two groups; similarly there was no difference between weight for height percentiles

TABLE 1— Baseline Data on Infants Pre-RVRTC Maneuver

Variable[1]	Healthy (N = 23)	Respiratory disease[5] (N = 34)	*P*-value
Age (year)	0.71 (0.37)	1.27 (0.61)	<0.001
Caucasian, N(%)	15 (65.22%)	32 (94.12%)	0.010
Male, N(%)	13 (56.52%)	17 (50.00%)	0.788
Weight (kg)	8.61 (1.99)	10.20 (1.73)	0.001
Height (cm)	69.83 (5.91)	77.09 (8.29)	0.001
Weight for age z-score	0.04 (0.98)	−0.12 (1.07)	0.637
Height for age z-score	0.09 (0.97)	−0.01 (1.25)	0.298
Weight for height percentile	58.88 (26.76)	56.99 (31.27)	0.909
LCI z-score	−0.38 (1.15)	0.35 (1.44)	0.157
FRC_{MBW} z-score	0.02 (0.04)	0.01 (0.04)	0.222
V_T/weight (ml/kg)	8.30 (1.07)	9.07 (1.34)	0.032
FRC_{pleth} z-score	−0.55 (1.30)[†]	−0.17 (1.43)[‡]	0.308
$(FRC_{pleth}–FRC_{MBW})$/FRCpleth	0.10 (0.14)[†]	0.12 (0.23)[‡]	0.361
LCI[2]	7.05 (0.17)	7.14 (0.14)	0.697[4]
FRC_{MBW}[2]	0.20 (0.01)	0.21 (0.01)	0.414[4]
V_T/Weight[2]	8.62 (0.26)	8.85 (0.21)	0.516[4]
FRC_{pleth}[3]	0.24 (0.01)[6]	0.25 (0.01)[7]	0.415[4]
$(FRC_{pleth}–FRC_{MBW})/FRC_{pleth}$[3]	0.15 (0.05)[6]	0.11 (0.05)[7]	0.598[4]

[1]Unless otherwise specified, data are expressed as arithmetic mean (standard deviation), *P* values for comparing Healthy and Respiratory Disease are based on two-sample *t* tests (or Mann–Whitney *U* tests, where appropriate) for continuous variables, and Fisher's exact test for categorical variables.
[2]Data are expressed as least square mean (standard error), adjusted for age.
[3]Data are expressed as least square mean (standard error), adjusted for age, gender, and ethnicity.
[4]*P* values are calculated based on *t* tests from linear regression models.
[5]Includes subjects with cystic fibrosis and severe recurrent wheeze.
[6]N = 21.
[7]N = 33.

between the two groups (Table 1). There were no significant differences in most of the baseline pulmonary function data between healthy infants and this subset of infants with respiratory disease, but children with respiratory disease had significantly higher pre-RVRTC tidal volume corrected for weight compared to healthy children ($P = 0.01$).

For the 23 healthy subjects and 34 children with respiratory disease, an average of 5.4 RVRTC maneuvers (5.5 in Health and 5.4 in disease) were performed per subject. Figure 1 showed the individual raw LCI values plotted by diagnosis. After controlling for age, the RVRTC maneuvers were associated with a significant reduction in LCI in children with respiratory disease (change in LCI −0.24 units; SE ± 0.07 units; $P = 0.0004$) (Table 2), but not in healthy children (change in LCI −0.08 units; SE ± 0.11 units; $P = 0.44$). From the mixed model analysis, we also calculated the intra-subject variability in health and disease (0.39 and 0.21, respectively). The results remained consistent when converted to LCI z-scores (respiratory disease, −0.37 z-scores; SE ± 0.11 z-scores; $P = 0.0007$ vs. health, −0.18 z-scores; SE, ± 0.16 z-scores; $P = 0.26$).

LCI is the cumulative expiratory volume (CEV) divided by the functional residual capacity (FRC) measured with the inert gas used for MBW. Both in healthy children and children with respiratory disease, FRC_{MBW} decreased after RVRTC maneuvers (Table 2). This per se would increase LCI; however, there was a concomitant significant decrease in CEVs in both healthy and diseased children ($P < 0.001$) (Table 2).

Finally, breathing pattern was examined (Table 2). Tidal volume (V_T) did not change after RVRTC in healthy children ($P = 0.09$), but decreased by an average of 4.38 ml in children with disease ($P < 0.0001$). A similar pattern was seen when tidal volume was corrected for weight [no change in healthy children (−0.14 ml/kg; SE ± 0.1ml/kg; $P = 0.18$), but a significant decrease in those with respiratory disease (−0.41 ml/kg; SE ± 0.10 ml/kg; $P < 0.001$).

We repeated the analysis by controlling for height values and similar results were seen for all MBW parameters (results not shown).

DISCUSSION

In this study, we assessed the effect of rapid thoracoabdominal compression maneuvers obtained with the raised volume technique on measurements of MBW. RVRTC maneuvers led to small, but significant

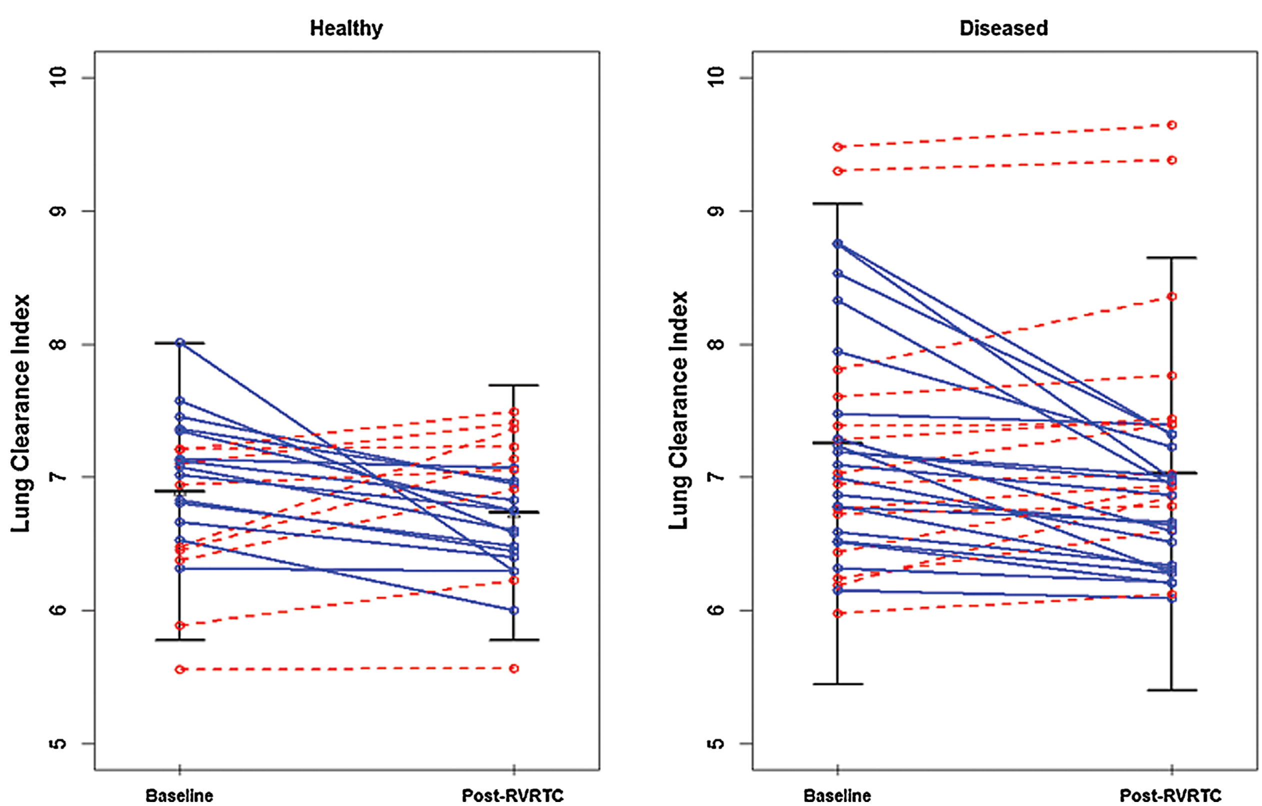

Fig. 1. Individual raw LCI values plotted by diagnosis. Solid line and dashed line represent positive and negative change between LCI at baseline and LCI post-RVRTC. The solid bar represents mean and the 95% confidence interval in each group at each test occasion.

TABLE 2— RVRTC Effects on MBW Measures Controlled for Age Based on Linear Mixed Models

	Healthy			Respiratory disease[3]		
Change in measure	Estimate[1]	SE[2]	*P*-value	Estimate[1]	SE[2]	*P*-value
LCI	−0.08	0.11	0.44	−0.24	0.07	0.0004
FRC(L)	−0.01	0.003	0.01	−0.02	0.003	<0.0001
Number of breaths	−0.88	0.46	0.06	−1.04	0.41	0.01
CEV (L)	−0.07	0.02	<0.0001	−0.17	0.02	<0.0001
RR	−1.21	0.44	0.01	−0.17	0.41	0.69
V_T (ml)	−1.45	0.84	0.09	−4.38	1.03	<0.0001
V_T/weight	−0.14	0.10	0.18	−0.41	0.10	<0.0001
V_T/FRC (ml)	0.01	0.01	0.12	0.01	0.01	0.13

[1]Pre-RVRTC maneuver was the reference category.
[2]Standard error.
[3]Includes both wheezy and CF subjects.

reductions in FRC in both healthy children and children with obstructive airway disease. The cumulative expiratory volume was more markedly reduced by RVRTC maneuvers than FRC; an effect that was more pronounced in children with obstructive airway disease. LCI, the most common parameter reported from MBW studies representing an overall "average" of lung ventilation inhomogeneity, was affected in disease, but not in health. Therefore, the timing of LCI measurement in the infant sedated study protocol is critically important to prevent effects of lung function maneuvers impacting LCI variability and its interpretation.

The noted reduction in measured lung volumes (FRC_{MBW}) is counter-intuitive to the findings of improved LCI (decreased LCI value) in disease and is in contrast with our previously reported findings of unchanged plethysmographic FRC measurements pre and post-RVRTC maneuver in both health and disease.[15] If all other factors were unchanged, this decrease in FRC would normally result in a worsening LCI (increased LCI value). This reduction in communicating FRC, however, has been alluded to by other groups studying the effects of the raised volume maneuver. Lum et al.[8] noted a 20% reduction in tidal flow measures post RVRTC maneuvers associated with reductions in forced vital capacity. The proposed mechanism may be introduction of gastric air and distention, which can occur during the inspiratory portion of the maneuver when positive pressure is used to induce an augmented inspiration. The resultant gastric distention in an infant can lead to change in the end-expiratory level and upward displacement of the diaphragm with resultant decrease in functional residual capacity as measured by MBW, but may not change the overall plethysmograhic FRC, which measures all compressible intrathoracic gas including lung volume and potentially compressible gastric volumes as well. We did not measure plethysmograhic FRC and MBW FRC before and after RVRTC in the same population which would help to clarify this question.

Cumulative expired volume (CEV) decreased significantly in infants after RVRTC maneuver suggesting a more physiologically efficient washout. A number of mechanisms could account for this observed phenomenon. Firstly, a lung recruitment maneuver can open previously partially closed peripheral lung units which may improve the washout efficiency. In adults, shallow tidal breathing as well as forced expirations with normal tidal breathing can impair ventilation uniformity (worsen LCI); however these effects could be reversed with deep inspiration[17]. This effect could be more pronounced in sedated infants compared to spontaneously breathing infants as ventilation inhomogeneity could potentially be induced by sedation. Currently, there are no data available to address this question. Alternatively, the lung inflation maneuver could have a bronchodilator effect similar to what has been reported for sighs.[16,17] In general, this effect is less pronounced in patients with airway obstruction, whereas the CEV changes were larger in this group of infants. Finally, the changes in CEV could be related to the forced expiratory maneuver rather than the lung inflation; our study did not try to separate these two aspects of the technique which would best be done by assessing the effects of lung inflations alone.[18]

Previous studies examining the effects of thoracoabdominal compression maneuvers on tidal flow measures support our findings that tidal volume decreases after thoracoabdominal compressions. In a study by Platzker et al.,[19] tidal breathing compression technique decreased compliance and respiratory system time constants post tidal compression maneuvers. Furthermore, there was a differential effect of the disease status on the time constant with more severe lung disease being associated with a greater decrease in time constants. A possible proposed mechanism may be that forces applied to the chest and abdomen may move air from stable expanded portions of the lung into smaller, unexpanded units which would require higher opening pressures, resulting in improved time constants due to enhanced retractive forces acting on airways of the expanded lung units. This mechanism would explain the improved efficiency in the gas washout despite a decreased tidal volume seen differentially in children with respiratory disease.

Studies in infants of lung function are difficult given the need for sedation and stable sleep state. Tidal breathing tests such as MBW suggest there is an effect of lung function tests that require a respiratory maneuver such as RVRTC. Ideally, imaging studies combined with lung function are needed to understand the physiologic effects the respiratory maneuvers such as RVRTC.

In conclusion, we document for the first time that in infants, raised volume maneuvers sufficiently change respiratory mechanics, leading to a more efficient gas washout maneuver selectively in children with respiratory disease, but not in healthy children. Given the physiologic effects of the raised volume maneuver alone on LCI, it is critical to standardize the timing of LCI measurement in the infant pulmonary function protocol to account for these effects.

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