Lung volume measurements in wheezy infants: comparison of plethysmography and gas dilution

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ABSTRACT: The accuracy both of plethysmographic measurements of thoracic gas volume (TGV) and determinations of functional residual capacity (FRC) by gas dilution techniques in infants with obstructive lung disease is subject to continued dispute.

We studied 25 wheezy infants and compared TGV derived from end-expiratory airway occlusions (TGVEE), corrected TGV after end-inspiratory airway occlusions (TGVEI), and FRC determined by nitrogen wash-out (FRCN2).

Group mean TGVEE and TGVEI differed significantly (25.8±7.7 versus 29.6±8.4 ml·kg\(^{-1}\)) as well as group mean TGVEI and FRCN2 (29.6±8.4 versus 24.6±7.1 ml·kg\(^{-1}\)). TGVEE and TGVEI, as well as TGVEE and FRCN2, and TGVEI and FRCN2 data, respectively, showed lack of agreement.

Based on 95% confidence intervals, calculated from TGVEE data, 14 of the 25 infants showed a significantly higher TGVEI than TGVEE; only one patient had a significantly lower TGVEI. Compared to FRCN2 data, TGVEE and TGVEI measurements yielded lower values in at least one third of our patients.

The present study illustrates, that there is no gold standard for the measurement of lung volume in infants with airway obstruction.

from analysis because the babies woke up before the end of the study. The remaining 25 infants and toddlers, 15 boys and 10 girls, had a mean age of 38 weeks (range 6–73 weeks). Their mean weight was 8.4 kg (range 3.2–12.3 kg), and the mean height was 70 cm (range 50–80 cm); weight and height were within the normal centiles and proportions were normal.

Informed written consent was obtained from the parents. One or both of the parents were present during the investigation. Before lung function testing, each infant fasted for 3 h, was then sedated with 60–100 mg·kg⁻¹ of orally administered chloral hydrate, and subsequently fed. The infants were studied in the supine position with their heads supported in the midline, so that their necks were slightly extended. Oxygen saturation was continuously monitored during the entire study by a pulse oximeter (Biox 3700e, Ohmeda, Louisville, CO, USA).

**Body plethysmography**

Thoracic gas volume was measured in a custom-built constant volume body plethysmograph (volume 66 l; time constant 14 s) according to the technique of DuBois et al. [1]. An appropriately sized face mask was connected to the airway opening of the sleeping infant by sealing it with a ring of silicone putty around nose and mouth. Connected to the face mask was an electro-mechanically-operated and electronically-controlled shutter system with a response time of 20 ms (Biegler, Mauerbach, Austria). Flow at the mouth was measured using a Fleisch No. 0 or No. 1 pneumotachograph (PNT), attached to a low pressure range HBM PD1 (0.01 bar=10.2 cmH₂O) differential pressure transducer and a HBM MVD 2406A amplifier (Hottinger Baldwin Meßtechnik, Darmstadt, Germany).

The PNT was attached distal to the shutter system and, thus, was not pressurized during occlusions. The flow signal obtained was electronically integrated to give volume. Airway opening pressure (Pao) was measured within the mask using a HBM PD1 (0.1 bar=102 cmH₂O) pressure transducer and a HBM MVD 2406A amplifier (Hottinger Baldwin Meßtechnik, Darmstadt, Germany), as was the pressure within the box (Pbox).

Box volume calibration was performed by placing saline bags, approximating the baby’s weight, within the plethysmograph and then alternately injecting and withdrawing 20 ml of air at the breathing frequency of the infant. Box pressure and airway pressure transducer calibrations were made with manometers. Flow calibration of the PNT was performed with 6 l·min⁻¹ and zero flow for No. 0 PNT; and with 9 l·min⁻¹ and zero flow for No. 1 PNT. Volume calibration of the PNT was performed by injecting and withdrawing 60 ml of air for No. 0 PNT; and 100 ml of air for No. 1 PNT, at the respiratory rate of the infant. Calibrations were considered satisfactory for all signals at an accuracy of ±1%. Flow, volume, and pressure signals were recorded in real time on an AT-personal computer with a WFS-8 sampling chart, having a sampling frequency of 300 Hz (Biosys, Vienna, Austria). After having reached thermal equilibrium, as indicated by minimal drift of the box pressure signal, measurements were performed. Thoracic gas volume was determined both at end-expiration (TGVEE) and end-inspiration (TGVII). At least five TGVEE and five TGVII measurements were performed without repositioning of the face mask. TGV at functional residual capacity (FRC) was calculated by subtracting the dead space of the apparatus (17.5 ml) plus the volume above FRC, at which the airway occlusion had been made. The resistance of the apparatus was 0.56 kPa·l⁻¹·s⁻¹ at a flow of 100 ml·s⁻¹ using the No. 0 PNT; and 0.21 kPa·l⁻¹·s⁻¹ using the No. 1 PNT. All tracings obtained were inspected visually and were only accepted when there was no evidence of a leak or of pharyngeal closure.

**Gas dilution technique**

In addition, functional residual capacity was measured by nitrogen wash-out (FRCN₂), using an open circuit method as described by Gerhardt et al. [16]. A computer-based data acquisition system ( Pediatric Pulmonary Cart 2600, SensorMedics, Anaheim, CA, USA), in line with a mass spectrometer, integrates the N₂ concentration signal electronically and provides a real time display of the N₂ concentration (N₂ wash-out curve) on the monitor. The operator has to activate a slider valve for switching the infant from breathing room air to breathing 100% oxygen and for terminating the measurement when an N₂ concentration of 0% is displayed on the screen. FRCN₂ is calculated automatically by the system.

A two-point calibration was performed prior to each measurement series by washing out known volumes (one less and one greater than the expected FRC) from a calibrated syringe (100 and 500 ml, Hans Rudolph, Kansas City, MO, USA) at a constant background oxygen flow set above the expected peak flow rate of the infant. In order to correct for end-expiratory level when switching the valve, a Fleisch No. 0 or No. 1 PNT was introduced into the circuit, while the infant was breathing room air. The PNT was attached to a low pressure range HBM PD1 (0.01 bar=10.2 cmH₂O) differential pressure transducer and a HBM MVD 2406A amplifier (Hottinger Baldwin Meßtechnik, Darmstadt, Germany). The dead space of the apparatus during the wash-out was 5.3 ml, the resistance less than 0.03 kPa·l⁻¹·s⁻¹ at a flow of 10 l·min⁻¹. At least five FRCN₂ measurements were performed in each patient. An interval of 5 min elapsed between two consecutive measurements.

The three series of TGVEE, TGVIİ, and FRCN₂ measurements were carried out in random order. The infants were not repositioned during the entire series of measurements.

**Statistical analysis**

The group mean and standard error of the mean of TGVEE, TGVIİ and FRCN₂ were calculated, and paired
t-tests were used to determine significant differences between TGVEE, TGVEI and FRCN\textsubscript{2} in grouped data, with p<0.05 taken as the limit of significance. The mean, standard deviation and coefficient of variation of TGVEE, TGVEI and FRCN\textsubscript{2} were calculated for each patient. The 95\% and 99\% confidence intervals, using TGVEE data, were calculated for each patient, and the individual mean TGVEI and mean FRCN\textsubscript{2} were considered significantly different when lying outside these intervals.

Agreement between TGVEE and TGVEI, between TGVEE and FRCN\textsubscript{2}, and between TGVEI and FRCN\textsubscript{2} was also determined using the methods of Bland and Altman [17]. "Lack of agreement" was expressed by two components, the relative bias, as estimated by the mean difference (d), and the random variation, as estimated by the standard deviation of differences (s). The "limits of agreement", or 95\% range, are usually given by d ± 2s; as the sample size, n, was less than 100, however, 2 was replaced by [18]: $t_{n-1, 0.05} \sqrt{\frac{n+1}{n}}$.

### Results

All children remained clinically stable throughout the entire study; no decrease of the oxygen saturation was observed in any of the patients. The mean $N_2$ wash-out time in the FRC measurements was 50 s (range 30–75 s).

For grouped data, there was a statistically significant difference between TGVEE and TGVEI (25.8±7.7 ml kg\textsuperscript{-1} versus 29.6±8.4 ml kg\textsuperscript{-1}; p<0.001) and between TGVEI and FRCN\textsubscript{2} (29.6±8.4 ml kg\textsuperscript{-1} versus 24.6±7.1 ml kg\textsuperscript{-1}; p<0.05), respectively. TGVEE and FRCN\textsubscript{2} did not differ significantly. Although differing considerably within the individual patient, mean coefficients of variation of TGVEE, TGVEI, and FRCN\textsubscript{2} were similar for the group. Each infant’s individual data are shown in table 1.

When using 95\% confidence intervals, calculated from TGVEE data, 14 of the 25 infants showed a significantly higher TGVEI than TGVEE, one patient had a TGVEI significantly lower than the corresponding TGVEE, and 10 patients did not show a significant difference between TGVEE and TGVEI measurements. The mean difference (95\% confidence interval) between TGVEE and TGVEI was -3.9 (-5.6 to -2.1) ml kg\textsuperscript{-1},

### Table 1. - TGVEE, TGVEI and FRCN\textsubscript{2} measurements with coefficient of variation (CV)

<table>
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<tr>
<th>Subject No.</th>
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Mean: 25.8, 29.6, 24.6
SEM: 1.6, 1.7, 1.4

TGVEE: thoracic gas volume derived from end-expiratory airway occlusions; TGVEI: thoracic gas volume derived from end-inspiratory airway occlusions; FRCN\textsubscript{2}: functional residual capacity determined by nitrogen wash-out.
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between TGVEE and FRCN₂, 0.6 (-3.4 to 4.6) ml·kg⁻¹, and between TGVEI and FRCN₂, 5.1 (0.4 to 9.7) ml·kg⁻¹. The differences between TGVEE and TGVEI, TGVEE and FRCN₂, and TGVEI and FRCN₂ were unrelated to the size of the measurements (figures 1–3).

The standard deviation of the differences between TGVEE and TGVEI was 4.2 ml·kg⁻¹, between TGVEE and FRCN₂, 9.7 ml·kg⁻¹, and between TGVEI and FRCN₂, 11.2 ml·kg⁻¹. Using the t-distribution for calculating the limits of agreement resulted in -12.7 to 5, -19.8 to 20.9, and -18.6 to 28.7 ml·kg⁻¹, respectively.

Discussion

This study shows a significantly higher group mean TGV for occlusions at end-inspiration than for occlusions at end-expiration in wheezy infants and toddlers recovering from acute viral bronchiolitis. Fourteen of the 25 patients had a significantly higher TGVEI than TGVEE, whilst only one subject showed a significantly lower TGVEI. Hence, agreement between TGVEI and TGVEE measurements was poor. We found a significantly lower group mean FRCN₂ when compared to the group mean TGVEI, but no significant difference between FRCN₂ and TGVEE. FRCN₂ and TGVEE data, as well as FRCN₂ and TGVEI data, showed lack of agreement.

For years, whole body plethysmography was considered the "gold standard" for measuring thoracic gas volume in health and disease. Conventionally, TGV is measured at end-expiration, but, in practice, occlusions are frequently performed at end-inspiration, with subsequent correction to the end-expiratory level. This procedure improves the signal-to-noise ratio and reduces the incidence of glottic closure, which can invalidate results [14]. In healthy infants, measurements made at end-expiration and at end-inspiration have been stated to agree within 5% [14]. The volume at which the occlusion should be performed, however, has remained subject to discussion.

Firstly, problems with plethysmographic lung volume measurements were realized in adult asthmatics [10]. Initially, abdominal gas compression was considered as a possible source of TGV overestimation [19]. The results of two studies [10, 20], however, proved that the...
effects of abdominal gas compression are too small to explain the large increases of TGV in asthmatics. Studies in sick infants confirmed, that the volume of gas in the gastrointestinal tract is either insignificant, or uncompressed, or both [7, 12].

It was then suggested, that locally applied pressures over closed noncommunicating areas of trapped gas might be greater than pressures at the mouth; thus, effecting an overestimation of TGV [3]. As infants tend to breathe at lower lung volumes than adults [21, 22], resulting in an increased risk of small airway closure, this mechanism could be particularly relevant in this age group. Such a concept of small airway closure might find support from the work of HELMS [12]. BEARDSMORE et al. [11] also found a discrepancy between TGV measured at high and at low lung volumes [11]; in some contrast to the results of HELMS [12], corrected TGV measured at high lung volumes was higher than that measured at FRC in six infants, and lower than that measured at FRC in only three infants. This finding was explained by airway closure at FRC, combined with an uneven distribution of pleural pressure.

In adult dogs, it was demonstrated that changes in mouth pressure might not reflect changes in mean alveolar pressure in the presence of airway closure [23], and that activities of various respiratory muscle groups produce different regional pressures and deformations of rib cage and abdomen [24]. In contrast, experimental occlusion of the right middle and lower lobes in healthy adults does not effect changes of TGV [25]. As the rib cage in adult human subjects might be less easy to distort than in dogs or infants, these different results [23–25] might not necessarily be incompatible. MARCHAL et al. [26] found a significantly higher TGV with end-expiratory than with end-inspiratory airway occlusions, and speculated, that an uneven distribution of alveolar pressure, as it may occur in infants with chest wall distortion, could result in relatively large errors, i.e. over- or underestimation of TGV.

Recently, LANTERI et al. [13] could not find consistent changes of TGV with lung volume in wheezy infants. Group mean TGV, derived from end-inspiratory occlusions, did not differ significantly from group mean TGV derived from end-inspiratory occlusions. In contrast to these results, SEIDENBERG et al. [27], who studied 10 infants with acute bronchiolitis, found a significantly higher (corrected) end-inspiratory TGV than end-expiratory TGV for the group. These findings are in agreement with our results and could be explained by the mechanisms proposed by BEARDSMORE et al. [11], i.e. a combination of airway closure and an uneven distribution of pleural pressure. Lung regions communicating with the airway opening might be subjected to greater pressure changes than regions of trapped gas. If this was the case, end-expiratory TGV would be measured falsely low; actually, 11 of the 25 infants we studied had an end-expiratory TGV below the predicted value for thoracic gas volume minus 2 sd [8]. GODFREY et al. [7] showed that whole body plethysmography yields such low TGV values in many infants with recurrent or persistent wheezing after bronchiolitis. As an explanation, they suggested uneven alveolar pressure changes within the chest leading to the exclusion of a part of the lung volume, or the presence of alveolar units with very low compliance, that change little in volume during respiratory efforts against an occlusion.

This theory of mechanical inhomogeneity has so far not been confirmed, but it may indeed be difficult to demonstrate the presence of such mechanical inhomogeneity in human subjects.

Alternatively, the so-called “upper airway artifact” could explain errors in the plethysmographic measurement of lung volumes. One of the basic assumptions for applying the plethysmographic technique is that there is no gas flow, and, hence, no flow-resistive pressure loss, during respiratory efforts against a closed airway. As a consequence, mouth pressure changes should equal alveolar pressure changes. This assumption has been challenged in adults. STANESCU et al. [3] found similar values for oesophageal and mouth pressure changes in healthy subjects; in the presence of airway obstruction, however, TGV derived from mouth pressure changes was significantly higher than TGV derived from simultaneously measured oesophageal pressure changes [4]. The central airways, compliant structures that are submitted to transmural pressure changes during respiratory efforts against a closed airway, allow gas to flow back and forth between alveoli and mouth. This gas flow may lead to pressure losses in the presence of airway obstruction, thereby resulting in an overestimation of TGV. TGV overestimation does not exist at a panting frequency of less than 1 Hz, but increases with increasing frequency [18]; thus, the central airway shunt impedance could be of increased relevance in sick infants with high respiratory rates. One can speculate, that a different compliance of the central airways plus different pressure losses across obstructed airways at different lung volumes could lead to TGV over- or underestimation. As the central airways of infants are more compliant than those of older subjects [29], such a mechanism might have special relevance for measurements in this age group.

All the factors discussed above, i.e. small airway closure, uneven distribution of pleural pressure and compliance of central airways, may combine in a given subject resulting in a rather unpredictable over- or underestimation of TGV.

The second physical principle, that is applied to the measurement of lung volumes in infants, is gas dilution. Both gas dilution techniques - helium dilution and nitrogen wash-out - yield comparable results in healthy infants, and also in infants with respiratory disease [30]. The accurate measurement of the washed-out nitrogen is difficult, however. The volume of nitrogen is either measured from a collection bag or obtained by continuous integration of the nitrogen concentration in the expired gas. Potential problems with this technique, encountered especially in infants with airway obstruction, include constant oxygen background flow, analyser response time, the unanswered questions of the final nitrogen concentration, and the minimal time interval between consecutive measurements [14].
Both gas dilution techniques require the full equilibration of all lung units with the airway opening. Apparently, these techniques will underestimate true resting lung volume in patients with airway obstruction and gas-trapping. The expected discrepancy between plethysmographically determined TGV and FRC measured by a gas dilution technique has been confirmed in a study of wheezy infants [7]. Some difference between TGV and \( FRC_N2 \) was also demonstrated for a group of healthy infants by GAPP et al. [31]. When comparing our TGV\(_{ME} \) and \( FRC_N2 \) data, however, we found 11 infants with a significantly lower, but 9 patients with a significantly higher, \( FRC_N2 \) value. A similar result was obtained when comparing TGV\(_{ME} \) and \( FRC_N2 \) data. The question arises whether such results could be due to the variability of the tests. LANTERI et al. [13] showed, that the time between two sets of TGV measurements does not affect the variability of TGV; thus, it seems unlikely that the time interval between our three series of measurements did contribute to the observed differences. MALLOL et al. [32] found that the variability of TGV measurements doubled, if the infant was taken out of, or repositioned within, the plethysmograph between sets of measurements. In the present study, care was taken to avoid any changes in the infant’s position during testing, and the face mask was not repositioned.

In conclusion, there is continued dispute about the accuracy and reliability of whole body plethysmography and gas dilution techniques, especially for measurements in infants and young children with respiratory disease [14]. The present study again illustrates, that there is no “gold standard” for assessing lung volume in infants with airway obstruction. Thus, our results support the opinion of several authors [6, 8, 9, 33], who have suggested that the continued use of lung volume measurements in infants with airway obstruction might be of questionable value. Lung volume measurements in wheezy infants with the techniques presently available might be erroneous and potentially misleading; thus, their role in the clinical management of such patients remains questionable.

References


