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

E. Eber, B. Steinbrugger, M. Modl, E. Weinhandl, M.S. Zach

Lung volume measurements in wheezy infants: comparison of plethysmography and gas dilution. E. Eber, B. Steinbrugger, M. Modl, E. Weinhandl, M.S. Zach. ©ERS Journals Ltd 1994.

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 (FRCN$_2$)

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 FRCN$_2$ (29.6±8.4 *versus* 24.6±7.1 ml·kg^{-1}). TGVEE and FRCN$_2$ did not differ significantly. TGVEE and TGVEI, as well as TGVEE and FRCN$_2$, and TGVEI and FRCN$_2$ 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 FRCN$_2$ 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.
Eur Respir J., 1994, 7, 1988–1994.

Pediatric Department, University of Graz, Austria

Correspondence: E. Eber
Respiratory and Allergic Disease Division
Pediatric Dept,
University of Graz
Univ.-Kinderklinik
Auenbruggerplatz 30 A-8036 Graz
Austria

In 1956, DuBois *et al.* [1] described a plethysmographic technique for measuring thoracic gas volume (TGV) in adults. Subsequently, Klaus *et al.* [2] first applied whole body plethysmography in newborn infants. Since the development of this technique, several papers have questioned the accuracy of these measurements in patients with obstructive lung disease [3–9]. Brown *et al.* [10] first reported problems with the measurement of TGV in adult asthma patients. They found TGV values to be higher, when determined after occlusion at end-expiration, than those measured from occlusions at higher lung volumes. The hypothesis was, that, caused by small airway closure at lower lung volumes, locally applied pressures over closed noncommunicating areas of trapped gas might be greater than pressures measured at the mouth; thus, TGV would be overestimated. This phenomenon could be particularly relevant for infants, who tend to breathe at lower lung volumes than adults, and for patients with airway obstruction. Subsequently, this hypothesis was studied in infants by several authors; Beardsmore *et al.* [11], Helms [12], and Lanteri *et al.* [13] found discrepancies between corrected TGV measurements made at different lung volumes.

In addition to whole body plethysmography, a second physical principle, *i.e.* gas dilution, can be used for measuring functional residual capacity (FRC) in infants. Gas dilution techniques, however, require full communication of all lung units with the airway opening. Thus, these techniques may tend to underestimate lung volume in patients with gas-trapping.

Lung function studies in infancy are essential for understanding the normal growth and development of the lung and for determining the effects of respiratory diseases and treatments on the developing lung [14, 15]. The accuracy of lung volume measurements is, however, increasingly questioned.

Therefore, the aims of the present study in wheezy infants were: 1) to determine whether TGV measured from end-expiratory occlusion differs significantly from TGV measured from end-inspiratory occlusion; and 2) to compare TGV from occlusions at both end-expiration and end-inspiration with FRC, as determined by nitrogen wash-out.

Methods

Patients

Twenty nine wheezy infants and toddlers recovering from acute viral bronchiolitis were recruited for the study. Measurements in four infants were excluded

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 cmH$_2$O) differential pressure transducer and a HBM MVD 2406A amplifier (Hottinger Baldwin Meβtechnik, 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 cmH$_2$O) pressure transducer with a HBM MVD 2406A amplifier (Hottinger Baldwin Meβtechnik, 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 (TGVEI). At least five TGVEE and five TGVEI 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 at a flow of l00 ml·s^{-1} using the No. 0 PNT; and 0.21 kPa·l^{-1}·s 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 (FRC$_{N_2}$), 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 N$_2$ concentration signal electronically and provides a real time display of the N$_2$ concentration (N$_2$ 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 N$_2$ concentration of 0% is displayed on the screen. FRC$_{N_2}$ 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 (l00 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 cmH$_2$O) differential pressure transducer and a HBM MVD 2406A amplifier (Hottinger Baldwin Meβtechnik, 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 at a flow of 10 l·min^{-1}.

At least five FRC$_{N_2}$ measurements were performed in each patient. An interval of 5 min elapsed between two consecutive measurements.

The three series of TGVEE, TGVEI, and FRC$_{N_2}$ 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, TGVEI and FRC$_{N_2}$ were calculated, and paired

Table 1. – TGVEE, TGVEI and FRCN$_2$ measurements with coefficient of variation (CV)

Subject No.	TGVEE		TGVEI		FRCN$_2$	
	ml·kg^{-1}	CV %	ml·kg^{-1}	CV %	ml·kg^{-1}	CV %
1	36.2	2.2	43.0	6.5	22.0	10.9
2	17.2	16.9	17.8	14.0	26.1	4.6
3	21.3	9.9	29.8	7.0	17.6	7.4
4	24.7	9.3	24.5	9.0	33.1	15.1
5	22.9	10.9	28.7	5.9	16.4	12.8
6	17.9	24.6	20.6	6.8	36.5	15.9
7	26.0	9.2	31.0	4.8	25.3	4.7
8	24.2	9.1	27.3	7.0	21.9	9.6
9	15.0	20.0	20.1	4.5	31.7	2.8
10	17.2	11.0	22.3	8.1	25.8	10.9
11	22.2	3.6	31.1	3.2	16.6	7.2
12	37.2	18.0	42.6	4.7	29.2	6.5
13	40.2	16.2	37.6	5.3	36.8	25.3
14	29.4	6.8	31.7	8.8	37.2	12.9
15	17.4	10.9	18.2	7.1	21.4	11.7
16	31.2	6.7	33.0	9.4	18.1	5.5
17	30.8	8.1	30.1	7.6	27.8	11.9
18	16.8	6.5	19.2	9.9	12.2	18.0
19	31.7	13.6	46.0	16.1	16.1	5.6
20	25.0	14.0	35.5	20.3	19.5	5.6
21	24.4	6.1	33.1	15.1	30.6	19.3
22	42.8	16.8	44.4	19.1	24.3	16.5
23	19.3	7.8	22.8	2.6	25.9	10.4
24	21.9	7.3	24.2	19.4	17.7	21.5
25	30.1	7.6	25.8	5.8	25.0	25.2
Mean	25.8	10.9	29.6	9.1	24.6	11.9
SEM	1.6	1.1	1.7	1.0	1.4	1.3

TGVEE: thoracic gas volume derived from end-expiratory airway occlusions; TGVEI: thoracic gas volume derived from end-inspiratory airway occlusions; FRCN$_2$: functional residual capacity determined by nitrogen wash-out.

t-tests were used to determine significant differences between TGVEE, TGVEI and FRCN$_2$ 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$_2$ 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$_2$ were considered significantly different when lying outside these intervals.

Agreement between TGVEE and TGVEI, between TGVEE and FRCN$_2$, and between TGVEI and FRCN$_2$ 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±2 s; as the sample size, n, was less than 100, however, 2 was replaced by [18]: $t_{n-1,\ 0.05}\ \sqrt{(n+1)/n}$ ·

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 SD versus 29.6±8.4 ml·kg^{-1}; p<0.001) and between TGVEI and FRCN$_2$ (29.6±8.4 versus 24.6±7.1 ml·kg^{-1}; p<0.05), respectively. TGVEE and FRCN$_2$ did not differ significantly. Although differing considerably within the individual patient, mean coefficients of variation of TGVEE, TGVEI, and FRCN$_2$ measurements 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 comparison between TGVEE and FRCN$_2$ data showed, that 11 infants had a significantly lower, and 9 infants had a significantly higher, FRCN$_2$ value. When using 99% confidence intervals, calculated from TGVEE data, 11 of the 25 infants showed a significantly higher TGVEI than TGVEE, and 14 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^{-1},
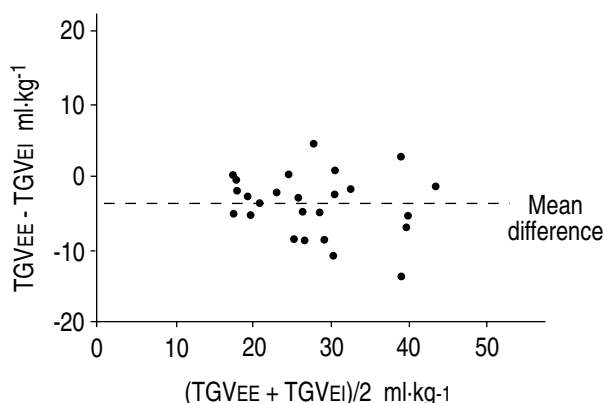
Fig. 1. – Difference between thoracic gas volume derived from end-expiratory airway occlusions (TGVEE) and corrected thoracic gas volume after end-inspiratory airway occlusions (TGVEI) against the average value of TGVEE and TGVEI. The differences are unrelated to the size of the measurements. The figure displays considerable lack of agreement between TGVEE and TGVEI data with discrepancies of up to 14 ml·kg^{-1}.
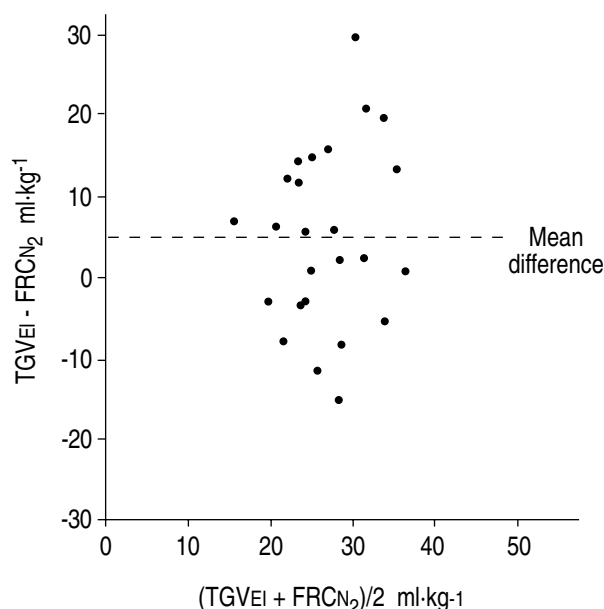

Fig. 2. – Difference between thoracic gas volume derived from end-expiratory airway occlusions (TGVEE) and functional residual capacity, as determined by nitrogen washout (FRCN$_2$) against the average value of TGVEE and FRCN$_2$. The differences are unrelated to the size of the measurements. The figure displays considerable lack of agreement between TGVEE and FRCN$_2$ data with discrepancies of up to 18 ml·kg^{-1}.
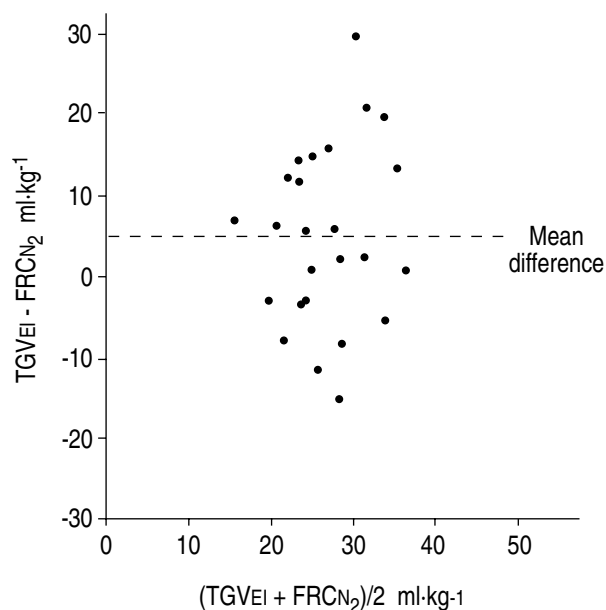

Fig. 3. – Difference between corrected thoracic gas volume after end-inspiratory airway occlusions (TGVEI) and functional residual capacity, as determined by nitrogen washout (FRCN$_2$) against the average value of TGVEI and FRCN$_2$. The differences are unrelated to the size of the measurements. The figure displays considerable lack of agreement between TGVEI and FRCN$_2$ data with discrepancies of up to 30 ml·kg^{-1}.

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 FRCN$_2$ when compared to the group mean TGVEI, but no significant difference between FRCN$_2$ and TGVEE. FRCN$_2$ and TGVEE data, as well as FRCN$_2$ 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

between TGVEE and FRCN$_2$ 0.6 (-3.4 to 4.6) ml·kg^{-1}, and between TGVEI and FRCN$_2$ 5.1 (0.4 to 9.7) ml·kg^{-1}. The differences between TGVEE and TGVEI, TGVEE and FRCN$_2$, and TGVEI and FRCN$_2$ 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 FRCN$_2$ 9.7 ml·kg^{-1}, and between TGVEI and FRCN$_2$ 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.

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-expiratory 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_{N_2} was also demonstrated for a group of healthy infants by GAPPA *et al*. [31]. When comparing our TGV_{EE} and FRC_{N_2} data, however, we found 11 infants with a significantly lower, but 9 patients with a significantly higher, FRC_{N_2} value. A similar result was obtained when comparing TGV_{EI} and FRC_{N_2} 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 effect 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

1. DuBois AB, Botelho SY, Bedell GN, Marshall R, Comroe JH. A rapid plethysmographic method for measuring thoracic gas volume: a comparison with a nitrogen wash-out method for measuring functional residual capacity in normal subjects. *J Clin Invest* 1956; 35: 322–326.
2. Klaus M, Tooley WH, Weaver KH, Clements JA. Lung volume in the newborn infant. *Pediatrics* 1962; 30: 111–116.
3. Stanescu DC, Rodenstein DO, Cauberghs M, Van de Woestijne KP. Failure of body plethysmography in bronchial asthma. *J Appl Physiol: Respirat Environ Exercise Physiol* 1982; 52: 939–948.
4. Rodenstein DO, Stanescu DC, Francis C. Demonstration of failure of body plethysmography in airway obstruction. *J Appl Physiol: Respirat Environ Exercise Physiol* 1982; 52: 949–954.
5. Shore SA, Milic-Emili J, Martin JG. Reassessment of body plethysmographic technique for the measurement of thoracic gas volume in asthmatics. *Am Rev Respir Dis* 1982; 126: 515–520.
6. Castile RG, Brown R. More problems with Boyle's Law or, "Vtg or not Vtg, that is the question". *Am Rev Respir Dis* 1986; 133: 184–185.
7. Godfrey S, Beardsmore CS, Maayan C, Bar-Yishay E. Can thoracic gas volume be measured in infants with airways obstruction? *Am Rev Respir Dis* 1986; 133: 245–251.
8. Godfrey S. TGV or not TGV in WB? That is the question. *Pediatr Pulmonol* 1991; 10: 73–77.
9. Stanescu DC. Was it just our problem, or yours too? Errors in body plethysmography, in infants, children and adults. *Pediatr Pulmonol* 1991; 11: 285–288.
10. Brown R, Ingram RH, McFadden ER. Problems in the plethysmographic assessment of changes in total lung capacity in asthma. *Am Rev Respir Dis* 1978; 118: 685–692.
11. Beardsmore CS, Stocks J, Silverman M. Problems in measurement of thoracic gas volume in infancy. *J Appl Physiol: Respirat Environ Exercise Physiol* 1982; 52: 995–999.
12. Helms P. Problems with plethysmographic estimation of lung volume in infants and young children. *J Appl Physiol: Respirat Environ Exercise Physiol* 1982; 53: 698–702.
13. Lanteri CJ, Raven JM, Sly PD. Should TGV be measured from end-inspiratory occlusions rather than end-expiratory occlusions in wheezy infants? *Pediatr Pulmonol* 1990; 9: 214–219.
14. American Thoracic Society/European Respiratory Society. Respiratory mechanics in infants: physiologic evaluation in health and disease. *Eur Respir J* 1993; 6: 279–310.
15. Zach MS. To understand how babies breathe. *Eur Respir J* 1993; 6: 158–159.
16. Gerhardt T, Hehre D, Bancalari E, Watson H. A simple method for measuring functional residual capacity by N_2 wash-out in small animals and newborn infants. *Pediatr Res* 1985; 19: 1165–1169.
17. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; 1: 307–310.
18. Chinn S. Repeatability and method comparison. *Thorax* 1991; 46: 454–456.
19. Habib MP, Engel LA. Influence of the panting technique on the plethysmographic measurement of thoracic gas volume. *Am Rev Respir Dis* 1978; 117: 265–271.
20. Brown R, Hoppin FG Jr, Ingram RH Jr, Saunders NA, McFadden ER Jr. Influence of abdominal gas on the Boyle's law determination of thoracic gas volume. *J Appl Physiol: Respirat Environ Exercise Physiol* 1978; 44: 469–473.
21. Agostoni E. Volume-pressure relationships of the thorax and lung in the newborn. *J Appl Physiol* 1959; 14: 909–913.
22. Helms P, Beardsmore CS, Stocks J. Absolute intraesophageal pressure at functional residual capacity in infancy. *J Appl Physiol: Respirat Environ Exercise Physiol* 1981; 51: 270–275.
23. Brown R, Scharf S, Ingram RH Jr. Nonhomogeneous alveolar pressure swings in the presence of airway closure. *J Appl Physiol: Respirat Environ Exercise Physiol* 1980; 49: 398–402.
24. Brown R, Scharf S, Ingram RH Jr. Nonhomogeneous alveolar pressure swings: effect of different respiratory muscles. *J Appl Physiol: Respirat Environ Exercise Physiol* 1982; 52: 638–641.

25. Rodenstein DO, Francis C, Stanescu DC. Airway closure in humans does not result in overestimation of plethysmographic lung volume. *J Appl Physiol: Respirat Environ Exercise Physiol* 1983; 55: 1784–1789.

26. Marchal F, Duvivier C, Peslin R, Haouzi P, Crance JP. Thoracic gas volume at functional residual capacity measured with an integrated-flow plethysmograph in infants and young children. *Eur Respir J* 1991; 4: 180–187.

27. Seidenberg J, Masters IB, Hudson I, Olinsky A, Phelan PD. Disturbance in respiratory mechanics in infants with bronchiolitis. *Thorax* 1989; 44: 660–667.

28. Rodenstein DO, Stanescu DC. Frequency dependence of plethysmographic volume in healthy and asthmatic subjects. *J Appl Physiol: Respirat Environ Exercise Physiol* 1983; 54: 159–165.

29. Croteau JR, Cook CD. Volume-pressure and length-tension measurements in human tracheal and bronchial segments. *J Appl Physiol* 1961; 16: 170–172.

30. Tepper RS, Asdell S. Comparison of helium dilution and nitrogen wash-out measurements of functional residual capacity in infants and very young children. *Pediatr Pulmonol* 1992; 13: 250–254.

31. Gappa M, Fletcher ME, Dezateux CA, Stocks J. Comparison of nitrogen wash-out and plethysmographic measurements of lung volume in healthy infants. *Am Rev Respir Dis* 1993; 148: 1496–1501.

32. Mallol J, Hibbert ME, Robertson CF, Olinsky A, Phelan PD, Sly PD. Inherent variability of pulmonary function tests in infants with bronchiolitis. *Pediatr Pulmonol* 1988; 5: 152–157.

33. Phelan PD, Sly PD. Commentary. *Pediatr Pulmonol* 1991; 10: 77.