Moment ratio analysis of multiple breath nitrogen washout in infants with lung disease

A. Schibler, M. Schneider, U. Frey, R. Kraemer

Moment ratio analysis of multiple breath nitrogen washout in infants with lung disease. A. Schibler, M. Schneider, U. Frey, R. Kraemer. ©ERS Journals Ltd 2000.
ABSTRACT: Measurement of lung volumes at end expiratory level and assessment of ventilation inhomogeneity is important for respiratory management in infants with lung disease.

This study compared multiple breath nitrogen washout was compared with body plethysmography to measure functional residual capacity in infants and assessed ventilation inhomogeneity using mean dilution numbers and alveolar based gas dilution numbers. Measurements were performed in 23 infants with lung disorders, eleven had wheezing bronchitis, four bronchopulmonary disease, and eight cystic fibrosis. Mean age was 11.2±5.8 months.

Functional residual capacity of nitrogen washout (29.8±11.4 mL·kg^{-1}) was significantly (p<0.05) lower than the plethysmographically measured functional residual capacity (40.3±11.4 mL·kg^{-1}). Tidal volumes before nitrogen washout (90.4±35.1 mL) were significantly larger than at the end of the washout (72.2±26.9 mL). Alveolar based gas dilution numbers (6.7±2.3) were significantly lower (p<0.001) than mean dilution numbers (10±5.7).

Functional residual capacity determination by nitrogen washout and plethysmography in infants with lung disease showed evidence of air trapping and ventilation inhomogeneity. Ventilation inhomogeneities are best described by alveolar based dilution numbers, since rebreathing of 100% oxygen changes ventilation pattern.
Eur Respir J 2000; 15: 1094–1101.

Division of Paediatric Respiratory Medicine, Dept of Paediatrics, University of Bern, Bern, Switzerland.

Correspondence: A. Schibler, Division of Paediatric Respiratory Medicine, Dept of Paediatrics, University of Bern, Inselspital, CH-3010 Bern, Switzerland. Fax: 41 316329468.

Infant lung function testing for diagnosis and monitoring of therapy has become more and more important in infants suffering from early lung disease. In this age group, lung function measurements are difficult because of the subject's inability to cooperate. Attempts have been made to assess airway function by various techniques [1], but airway function should be evaluated in close relationship to the corresponding lung volume, the end-expiratory resting level. Apart from radiological assessment [2], two techniques have been proposed to measure lung volume at end-expiration (FRC): these techniques are infant whole-body plethysmography and gas dilution. Both approaches have advantages and disadvantages, which have to be considered in the interpretation of data. Plethysmographic measurement of FRC$_{pleth}$, assumes that the pressures within all alveoli that communicate with the airway opening are homogeneous, and measures the volume of all gas within the thorax whether it communicates with the airway opening or not. Therefore, it measures trapped gas in the lung as well as gas within the gastrointestinal tract. Gas dilution techniques measure only the volume of gas that communicates with the airway opening. Both FRC measurements are not correct in the diseased lung which results in discrepancies in lung volume measurements [3–6]. This is particularly the case in the presence of ventilation inhomogeneity [7].

The multiple-breath nitrogen washout (MBNW) technique and its moment ratio analysis (MRA) using mean dilution numbers (MDN) have been successfully used in older children and adults to measure ventilation inhomogeneity as well as lung volume [7–13]. However, HABIB and LUTCHEN [14] demonstrated that the MDN is not independent of the breathing pattern. They introduced an alternative moment analysis approach, the alveolar-based gas dilution number (AMDN). The AMDN removes all sensitivity to volume ratios (anatomical dead space (V_D) to FRC) for homogeneous systems and, hence, should reflect gas-mixing inhomogeneity at the alveolar level more directly. In infants there is a decrease in the measured tidal volumes (V_T) during MBNW resulting in an lower V_T/FRC-ratio at the end of the washout than before it. The findings of HABIB and LUTCHEN [14] suggest that the standard MDN must be inaccurate in the presence of such changes of the breathing pattern. In order to investigate the effect of changes in the breathing pattern during MBNW, the MBNW technique normally used in adults was adapted to the requirements of infants with lung disease (low equipment dead space). Accuracy and reproducibility of the MBNW technique was tested in mechanical lung model. The aim of the study therefore was to compare MDN with AMDN in infants.

Materials and methods

Study design

In part A the technical aspects of the MBNW were validated using on a mechanical model with volumes similar to end tidal lung volumes in infants of this age range. In

part B the variability of MBNW measurements and the MDN as well as the AMDN were assessed in a group of infants with lung disease (the clinical target group), in which parallel inhomogeneities are most likely to be found. Lung volumes (FRC$_{N_2}$) measured by the MBNW technique were compared to those obtained by infant whole-body plethysmography (FRC$_{pleth}$).

Subjects

MBNW measurements and infant whole-body plethysmography were performed in a total of 23 (18 males and 5 females) infants with lung disorders. Eleven had wheezy bronchitis, four chronic lung disease due to bronchopulmonary disease (BPD) and eight infants had cystic fibrosis. Mean age was 11.2±5.8 month (range: 3–21 months). All measurements were performed 15–20 min after a feed, and under sedation with chloral hydrate (80–100 mg·kg^{-1}). The study was approved by the ethic committee of the medical faculty and parental informed consent was obtained before the measurements. Ethical consent was not accorded by the ethical committee to perform measurements on healthy sedated infants because the technical aspects of this new measuring device have not yet been established.

Multiple-breath nitrogen washout measurement device

The MBNW measurement device was designed by the Dept of Paediatrics, University of Bern, and Gambro AG, Hünenberg, Switzerland). The setup of the system (fig. 1) consists of a face mask, a pneumotachograph (H. Rudolph, 8311 Series, 0-10 LPM; Gambro AG), a nitrogen analyser (SensorMedics 2600; Gambro AG) and a valveless oxygen/air supply. The gas sampling rate of the N_2 analyser was set to 3 mL·min^{-1}. The gas sampling rate was maintained using a stable vacuum in the emission chamber in the analyser head. The linearity of the N_2 analyser was tested using six different gas mixtures with oxygen/nitrogen ratios between 21:79 and 100:0. Total instrumental V_D was found to be 4–8 mL using a water displacem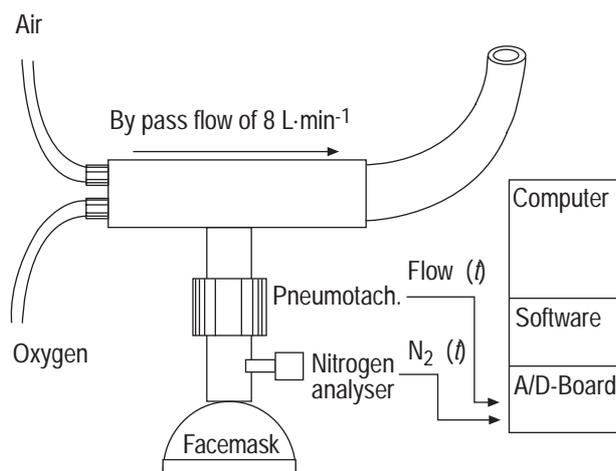ent technique. This minimal V_D enabled complete washout of the head device at each breath even in small babies. The delay time between flow and nitrogen signals was adjusted for each measurement as explained below. Prior to the washout the measurement device was flushed with room air at a bypass flow of 8–10 L·min. Washout was triggered at the beginning of expiration by switching the bypass flow from room air to 100% oxygen. The washout was stopped when end expiratory nitrogen concentration fell <2%. The analogue signals from the flow transducer and N_2 analyser were analogue/digital (A/D) converted (AT-MID-16, National Instruments®, Austin, USA) with 16-bit resolution and 200 Hz sampling frequency per channel before computation (IBM compatible 486 PC). Relays to the electromagnetic valves of the air and oxygen supply were controlled *via* the in/out port of the A/D-board with the help of a software code written in LabView 4.0® (National Instruments®). The N_2 washout curve and the airflow were graphically displayed on the screen during washout. Data were then analysed offline. The lag time between the airflow and N_2 signal was measured separately for each patient, allowing individual adjustment as proposed by BRUNNER *et al.* [15]. Flow was corrected for viscosity changes due to variation in the O_2/N_2 ratio and water vapour in the expired gas [10, 11] as well as for the varying temperature during inspiration (22°C) and expiration (34°C). To calculate the cumulative expired volume of nitrogen, the corrected flow and nitrogen concentration signals were multiplied point by point with each other, and consecutively integrated breath by breath separately for inspiration and expiration.

Whole-body plethysmography

In all infants FRC$_{pleth}$ was determined using a variable pressure type infant whole-body plethysmograph (Jaeger, Würzburg, Germany), applying a method that has previously been described [16–18]. The infant was placed in supine position inside the whole-body plethysmograph. A mask, sealed around the nose and mouth to ensure an airtight fit, was carefully manipulated into place for the measurements. After the body-box had been closed the infant breathed air from the box through a triple-valve system until thermal equilibrium had been reached between the infant and the box. A differential pressure transducer was used to detect changes in box pressure (ΔP_b) relative to a compensating chamber of similar volume. The infant was then switched to the body temperature, pressure saturated (BTPS)-bag from which air at 36.5°C and 100% relative humidity was rebreathed. The phase relationship between flow, measured by a baby-size pneumotachograph (Jaeger), and ΔP_b was checked by displaying both signals on an oscilloscope until a stable almost closed pressure-flow loop was obtained. Changes in mouth pressure (ΔP_m) were obtained after the shutter was closed to occlude the airway while the infant made 2–3 respiratory efforts.

Mechanical model. Validation of volume measurement with nitrogen washout technique was investigated with a mechanical lung model to determine the accuracy and reproducibility of the technique. The lung model had a single compartment made of copper with breathing cycles (30 cycles·min^{-1}) performed by a sinusoidal pump. Defined volumes (15, 35, 45, 60, 90, 120, 140, 170, 290, 340, 490

Fig. 1. – Configuration of the multiple-breath nitrogen washout equipment. A/D: analogue/digital; *t*: time.

Air

By pass flow of 8 L·min^{-1}

Computer

Flow (*t*)

Pneumotach.

Software

N_2 (*t*)

Oxygen

Nitrogen analyser

A/D-Board

Facemask

and 670 mL) were washed out with the same equipment as for the human subjects. The software had to be adapted, since there was neither humidification of the air, nor change in temperature in the lung model. The measurements were repeated five times for each volume.

Measurements in infants. After the plethysmographic measurements having at least five end-inspiratory occlusions of 2–3 respiratory efforts for the determination of FRCpleth the MBNW was performed through a face mask during quiet sedated sleep in the supine position. An airtight seal was achieved by placing a rim of therapeutic silicone putty between the infant's face and the mask. The patients were monitored during the investigation with transcutaneous oxygen saturation. Great care was taken to not change the patient's position and to obtain at least five sets of MBNW measurements. The time of a complete measurement did not exceed 45 min. During FRCpleth and FRCN$_2$ measurements the subjects were in quiet sleep.

Data analysis

The equations for computation of the MDN and AMDN obtained from the MBNW curve are given in the appendix. Briefly, the lung clearance index (LCI), MDN1 and MDN2 as previously described [9, 10, 19]. As standard abbreviation, MDN1 refers to the ratio between the first and the zeroth moment (m1/m0) and MDN2 refers to the ratio between the second and the zeroth moment (m2/m0). Quantitatively, the moments can be understood as follows: m0 is simply the area under washout curve using the dilution number (cumulative expired volume (CEV) divided by FRC) as x-axis while m1, m2 and higher moments are weighted values of area segments under the washout curve. The tail regions of the curve are given more weight for successively higher moments as indicated by the exponent r in the formula (Equation AS). The higher the value of MDN1 and MDN2 the more ventilation inhomogeneities are present. AMDN1 and AMDN2 are obtained by continuously correcting the measured moment ratios for the patient's dead space. HABIB and LUTCHEN [14] in their study used the dead spacecorrected moment ratio between m1/m0 for assessing alveolar-based gas dilution number (AMDN1). Additionally the AMDN2 (*V*D corrected ratio m2/m0) was calculated. The FRC is obtained by dividing this calculated volume by the patient's baseline end-tidal nitrogen concentration (mean±SD, 79±2.0%) of the last tidal breath before the washout. Because minimizing of dead space is limited by the size of the face mask and by the size of the pneumotachograph, rebreathing of expired nitrogen can never be prevented. Therefore the volume of inspired nitrogen is subtracted from the expired nitrogen volume during the washout. The FRC is obtained by dividing this calculated volume by the patient's baseline end-tidal nitrogen concentration (79±2.0) of the last tidal breath before the washout. FRCpleth was measured from the angle of the *P*b/*P*m-plot and corrected for instrument *V*D (30 mL). Data were considered to be satisfactory when there was no evidence of a leak and the changes in plethysmograph pressure and pressure at the airway opening were in phase with no artefacts, ensuring BPTS conditions.

Statistics

For each parameter and set of measurements the means, standard deviations (SD) and coefficients of variation (CV) were calculated. In addition, intrasubject variability using the mean of relative differences (MRD):

$$MRD = \frac{Z_0 - Z_1}{0.5\ (Z_0 + Z_1)} \qquad (1)$$

where Z_0 and Z_1 are the values of any index Z of the washout, was computed [9]. Differences between volume measurements in the lung model and the parameters of standard MDN and AMDN were assessed by using a paired t-test. A p-value <0.05 was considered as significant. Comparison between FRCpleth and FRCN$_2$ was assessed using the method described by ALTMAN and BLAND [20].

Results

Mechanical model

Accuracy and variability of the MBNW was assessed *in vitro* using a mechanical model. The average CV for all volumes was 2.5%. The mean difference between known and measured volumes using the nitrogen washout technique was 2.3 mL (NS) and represented a mean percentage error of 1.95% (range -9.8–10.7%). No differences were found between standard MDN1 (1.8±0.2) and AMDN1 (1.9±0.4) nor between the standard MDN2 (5.1±1.3) and the AMDN2 (5.0±2.5).

Measurement in infants

The mean washout time for the 23 infants was 34 s (16–56 s). Washout times for repeated measurements were always within 6 s of each other, in each infant. Table 1 shows the results for FRCN$_2$·kg^{-1} and FRCpleth·kg^{-1} of all 23 infants. Measurements of FRCN$_2$·kg^{-1} showed significantly less intrasubject variability (lower MRD and CV) than FRCpleth·kg^{-1} (p<0.05). The correlation between FRCN$_2$·kg^{-1} and FRCpleth·kg^{-1} can be seen in figure 2. The

Table 1. – Biometric data, functional residual capacities (FRC) and tidal volume (*V*T) of 23 investigated infants

	Weight kg	FRCN$_2$·kg^{-1} mL	MRD	CV %	FRCpleth·kg^{-1} mL	MRD	CV %	*V*T(0) mL	*V*T(n) mL
Mean	5.9	29.7	0.09	8.2	40.2	0.36*	12.7	90.4	72.1***
±SD	1.7	11.4	0.04	3.8	11.3	0.38	9.5	35.1	26.9

MRD: mean of relative differences; FRCN$_2$: FRC determined using nitrogen washout; FRCpleth: FRC determined using plethysmography; CV: coefficient of variance; *V*T(0): *V*T prior to washout; *V*T(n): *V*T at the end of measurement; *: p<0.05 *versus* FRCN$_2$·kg^{-1}; ***: p<0.001 *versus* *V*T(0).
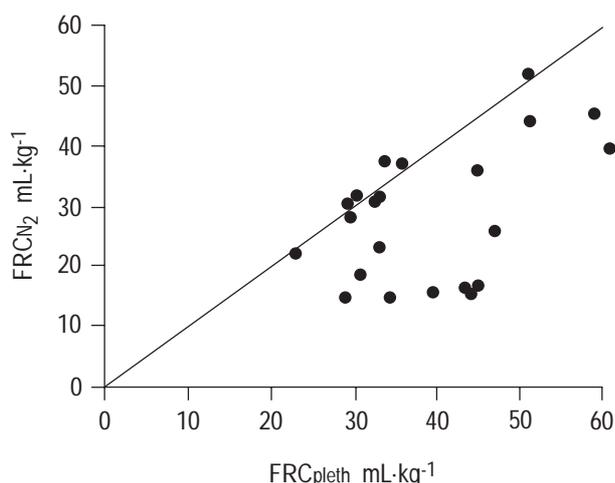
Fig. 2. – Correlation between whole-body plethysmography functional residual capacity ($FRC_{pleth}\cdot kg^{-1}$) and nitrogen washout ($FRC_{N_2}\cdot kg^{-1}$) in all 23 measured infants (r=0.48), p<0.001.

ALTMANN and BLAND [20] plot in figure 3 shows poor agreement between the two techniques. V_T decreased in all investigated infants significantly from 90.4±35.1 mL prior to the washout to 72.2±27.0 mL at the end of the washout (table 1). Table 2 shows the standard MDN_1 and MDN_2 as well as $AMDN_1$ and $AMDN_2$. No statistical difference could be found between the MDN_1 and $AMDN_1$ whereas MDN_2 showed significantly higher values than $AMDN_2$ (p<0.001). The relationship between MDN and AMDN is displayed in figure 4. The intrasubject CV of the $AMDN_1$ and $AMDN_2$ was significantly lower than that of MDN_1 and MDN_2 (p=0.008 for MDN_1 and $AMDN_1$, and p=0.002 for MDN_2 and $AMDN_2$). Mean LCI was 5.6±1.9 and intrasubject CV was 11.1±6.7 (table 2).

Discussion

MBNW is a highly attractive clinical procedure because it is minimally invasive and requires minimal subject co-operation. To assess ventilation inhomogeneity during
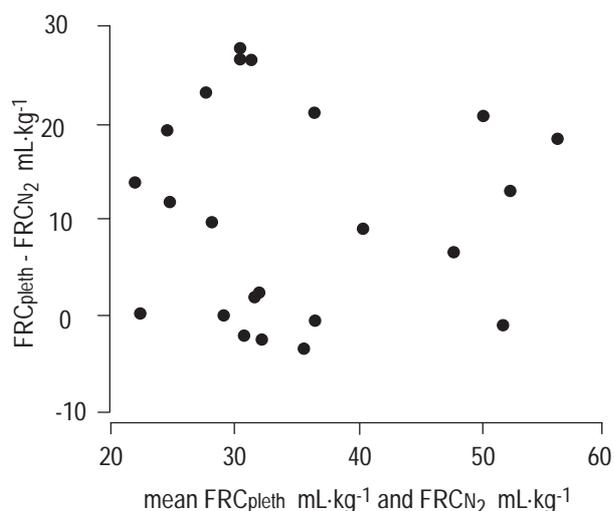

Fig. 3. – Plot of the difference between functional residual capacity (FRC) measurements by the two techniques (plethysmography: pleth; N_2 washout: N_2) against the mean of the two in all 23 measured infants.

normal tidal breathing the moment analysis of the MBNW curve was introduced by SAIDEL et al. [9]. Subsequent studies showed that the MDN is not independent of V_D or V_T/FRC ratio [14, 21, 22]. In the present study it was demonstrated that 100% oxygen rebreathing changes the breathing pattern and ventilation distribution significantly during MBNW and makes correct interpretation of FRC values difficult.

Technical aspects of data acquisition

The equipment presented in this study is based on an open washout technique. The volume measurement in a mechanical lung model were highly reproducible (CV= 2.5%) provided the following technical procedures are followed: the flow and nitrogen signals should be measured point by point during the whole washout and displayed on the computer screen in real time in order to detect air leakage (fig. 5). The nitrogen concentration must fall to zero at the end of each inspiration to prove that pure oxygen is being inhaled during each breath. The accuracy and reproducibility of the MBNW measurements in this study show comparable results to other studies using the open nitrogen washout technique proposed by GERHARDT et al. [24, 25].

Lung volume measurement in infants

Measurement of lung volume at end-expiration with the MBNW technique (FRC_{N_2}) in 23 infants suffering from severe lung disease showed poor, but still significant, correlation to whole-body plethysmography (FRC_{pleth}). Reproducibility of lung volume measurement is higher using MBNW technique (table 1). The discrepancy between MBNW and plethysmography in FRC measurement in infants with lung disease is similar to that found in previous studies [1, 25, 26]. A common explanation for higher lung volumes at end-expiration measured with plethysmography is that locally applied pressures over closed noncommunicating areas of trapped gas might be greater than the pressure at the mouth, causing overestimation of FRC_{pleth} [27, 28]. As infants tend to breathe at relatively lower lung volumes than adults [4], resulting in an increased likelihood of small airway closure, this phenomenon could be particularly relevant in this age group, possibly explaining the findings of GAPPA et al. [26] that in healthy infants there is a discrepancy between FRC_{pleth} and FRC_{N_2}. BEARDSMORE et al. [29] proposed a possible explanation for the higher measured FRC_{pleth} in that airway closure and uneven distribution of pleural pressure are combined. GODFREY and coworkers [30, 31] suggested that uneven alveolar pressure changes within the chest may lead to exclusion of a part of the lung volume, or that poorly compliant alveolar units may change little in volume during respiratory efforts against an occlusion. Direct comparison of FRC_{pleth} and FRC_{N_2} remains difficult and the presence of changes in breathing pattern and of ventilation inhomogeneities makes the interpretation of the above-described discrepancy even more controversial. It is hypothesized that only a gas washout technique, which does not affect the breathing pattern of the investigated child, and its moment analysis will allow an interpretation of the difference between FRC_{pleth} and FRC_{N_2}.

Table 2. – Standard moment ratios (MDN1 and MDN2), moment ratios derived from alveolar based dilution numbers (AMDN1 and AMDN2) and lung clearance (LCI) index of 23 infants

	AMDN1	MRD	CV	AMDN2	MRD	CV	MDN1	MRD	CV	MDN2	MRD	CV	LCI	MRD	CV
Mean	2.2	0.1	9.6	6.6	0.2[#]	19.4	2.3[+]	0.2	13.4	10.0*	0.4[§]	27.2	5.6	0.1	11.1
±SD	0.4	0.1	7.1	2.4	0.1	15.0	0.6	0.2	6.3	5.7	0.2	11.7	1.9	0.1	6.7

[+]: p=0.12 *versus* AMDN1; *: p<0.05 *versus* AMDN2; [#]: p=0.008 *versus* AMDN1 MRD; [§]: p=0.002 *versus* MDN1 MRD.

Changes in breathing pattern during MBNW

It was demonstrated that all of the 23 infants decreased their V_T significantly during MBNW (from 90.4±35.1 mL to 72.2±26.9 mL). To eliminate an error caused by the measurement technique the breathing pattern prior to the washout was observed. The infants showed no change of V_T while breathing through the face mask inspiring room air. Why should breathing 100% oxygen affect V_T? It has been postulated that lung volume may be lower by breathing high concentrations of oxygen [32]. High FiO_2 causes absorption atelectasis and therefore reduces V_T. Also peripheral chemoreceptors will respond to increased arterial oxygenation to some extent, reducing the breath rate and minute volume. Measurements in this study showed that there is a significant change in the V_T/FRC ratio. This is reflected by significantly higher values for MDN2 than AMDN2. Because we have observed a decrease in the measured V_T during the washout procedure in infants, resulting in an lower V_T/FRC-ratio at the end of the washout than prior to the measurement, it seems to us mandatory to apply the alveolar-based correction of MDN to AMDN as proposed by HABIB and LUTCHEN [14].

Multiple-breath nitrogen washout analysis

The 23 investigated infants showed significantly lower values of MDN2 than of AMDN2. The results of the MDN calculation are therefore biased by the change in breathing pattern, which followed pure O_2 breathing. While standard MDN1 and AMDN1 reflect more the first part of the washout curve, MDN2 and AMDN2 describe the tail of the washout curve. The difference between MDN2 and AMDN2 is more pronounced because the decrease in V_T occurs during the second half of the washout. A possible explanation for this phenomenon has been given by EDELMANN *et al.* [21] who showed that LCI and moment ratio increased by high V_D/V_t or by a low V_T/FRC ratio. LARSSON *et al.* [33] related the sensitivity of several MBNW indices including MDN to the breathing pattern of healthy ventilated subjects. It must be assumed that these effects are guise important in children, especially in infants, since the breathing pattern of children is largely dependent on age and disease severity. According to the finding of HABIB and LUTCHEN [14], that standard MDN analysis is biased by low V_T/FRC ratios, the higher MDN2 numbers can be
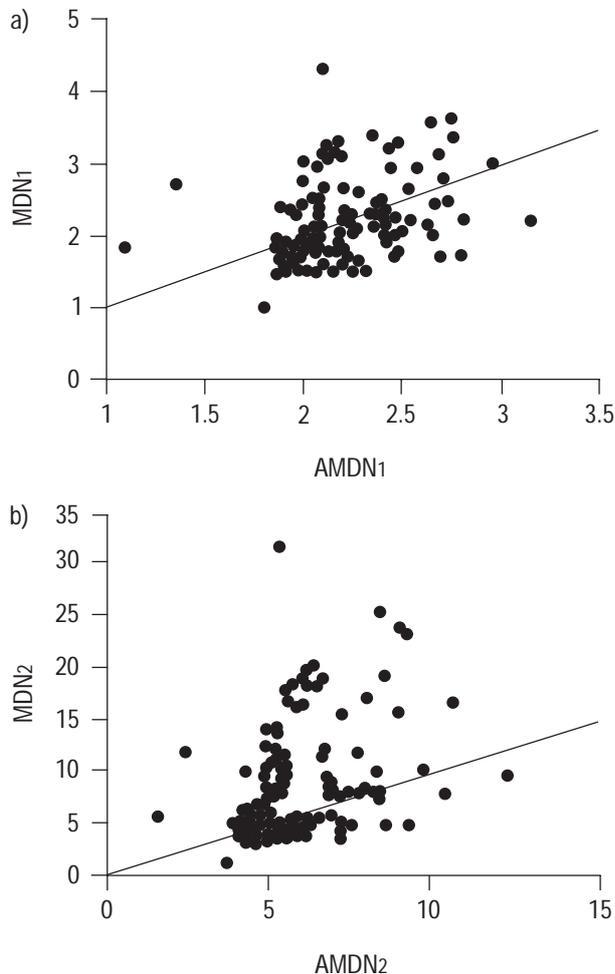
Fig. 4. – Plot of the first mean dilution number (MDN1) *versus* first alveolar based dilution number (AMDN1) on the left hand side and second mean dilution number (MDN2) *versus* second (AMDN2) on the right hand side. There is poor correlation between both techniques since the measured data should be close to the line of identity (——).
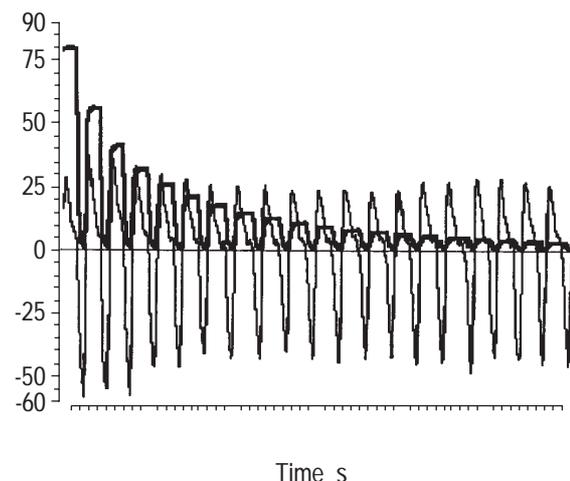
Time s

Fig. 5. – The complete washout trace of an infant is displayed *versus* time in s. The bold line indicates the nitrogen concentration (%) and the thin line the flow signal $mL·s^{-1}$.

explained mathematically by the reduction of the V_T/FRC ratio during the washout, whereas AMDN2 is not affected by the altered breathing pattern. High measured values of MDN1 and MDN2 resulting from severe ventilation inhomogeneity cannot he distinguished from high values obtained because of the presence of V_T/FRC changes during nitrogen washout. Therefore, MDN1 and MDN2 are inappropriate to describe ventilation inhomogeneity in infants with lung disease. Comparison of AMDN obtained in healthy adults to AMDN found in our infants with severe lung disease shows, that there is evidence of ventilation inhomogeneity (table 3).

Comparison of the moment analysis in literature

Previous reported moment analysis of MBNW in healthy children and infants show large variations as seen in table 3 [13, 14, 23, 34]. MDN1 and MDN2 of healthy preterm infants were first reported by SHAO *et al.* [23] and as expected are lower than the values measured in the 23 infants with lung disease. The intrasubject variability in all reported studies is higher for MDN2 than MDN1. In accordance with the data presented by HABIB and LUTCHEN [14] AMDN1 and AMDN2 are lower in the present study than MDN1 and MDN2. AMDN2 values in our patients were much lower than MDN2 values of the healthy preterm infants, indicating again that changes in breathing pattern bias the moment ratio of the MBNW unless AMDN is used (fig. 6).

Conclusion

A discrepancy was found between volumes measured by plethysmography and nitrogen washout similar to that observed by previous authors. This may be explained by the presence of ventilation inhomogeneity in infants with severe lung disease. Furthermore, in the present study, it was observed, that pure oxygen rebreathing during the nitrogen washout changes the breathing pattern of the sedated infants. Since moment ratio analysis using mean-dilution numbers is dependent on the tidal volume/functional residual capacity ratio, accurate interpretation of these results in the present study is difficult and therefore the use of alveolar based gas dilution numbers instead may be advisable. Since the decrease of tidal volume during washout with 100% oxygen was significant, 100% oxygen rebreathing is not suitable for measuring lung volumes in infants and we suggest that in future studies oxygen as a washout gas should be abandoned and be replaced by a gas mixture which has less effect on the breathing pattern of the investigated infant.
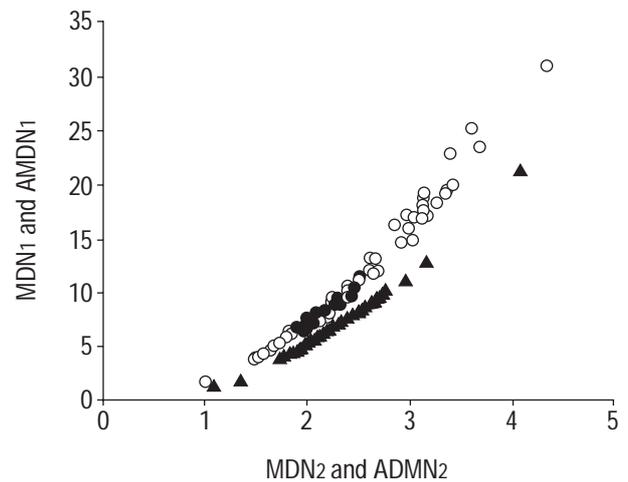

Fig. 6. – Plot of the first man dilution number (MDN1) *versus* the second mean dilution number (MDN2) of the 23 children with lung disease (○) in comparison to the MDN1 and MDN2 (●) obtained in the study of SHAO *et al.* [23]. The plot of first and second alveolar based dilution number (AMDN1 and AMDN2) in the children with lung disease (▲) show less scattering of data, indicating less bias by breathing pattern of the investigated subjects.

Appendix

Standard mean dilution number (MDN)

The envelope of the washout curve, *i.e.* the dimensionless N_2 concentration as a function of the dilution number η, is the distribution to be analyzed. The dilution number (η) is defined as:

$$\eta = CEV/FRC \qquad (A1)$$

where CEV is the cumulative expired volume and FRC is the forced residual capacity. This independent variable was taken suitably scaled to minimize the effects of different breathing patterns, respiratory frequency, variations in lung volume and hence in lung size. Then the *r*th moment, m_r, becomes:

$$m_r = \int_{i=0}^{k} \eta^r X(\eta) d\eta \qquad (A2)$$

where $X(\eta) = F_{N_2}(k)/F_{N_2}(0)$ and is the normalized end-tidal N_2 concentration for each interval number running from $i=0$ to k. $F_{N_2}(0)$ = initial N_2 concentration; $F_{N_2}(k)$ N_2 concentration at interval number k. Quantitatively, the moments can be understood as follows: m_0 is simply the area under the washout curve. The tail regions of the curve are

Table 3. – Comparison of moment ratios reported in the literature for healthy subjects and patients with lung disease

Subjects	No	MDN1	CV	MDN2	CV	AMDN1	CV	AMDN2	CV	Author	[Ref]
Healthy children	17	2.2±0.3	10	8.0±2.4	17					KRAEMER	[13]
Healthy children	36	2.3±0.19	8	9.3±1.2	13					WALL *et al*	[34]
Healthy preterm infants	20	2.2	8	8.7±1.2	14					SHAO *et al*	[23]
Healthy adults	7	1.9±0.09				1.4±0.04				HABIB &LUTCHEN	[14]
Asthmatic children	28	2.8±0.9	9	15.7±12.3	17					KRAEMER	[13]
Asthmatic adults	10	2.2±0.1				1.8±0.21				HABIB &LUTCHEN	[14]
Infants with lung disease	23	2.3±0.6	13	10.0±5.7	27	2.2±0.36	10	6.5±2.36	19	present study	

given more weight for successively higher moments, as indicated by the exponent r in the formula (Equation A5). The ratio between the first and the zeroth moment (MDN1) or the second and the zeroth moment (MDN2) of the MBNW curve has been demonstrated to be a good index for ventilation inhomogeneity [9–13].

Alveolar gas dilution number

HABIB and LUTCHEN [14] suggested an alternative moment analysis that removes sensitivity to V_T/FRC and V_D/FRC. First the washout is expressed in terms of a dilution number relative to cumulative expired alveolar volume (CEAV):

$$CEAV(k) = \int_{k=0}^{n} [V_T(k) - V_D(k)] \qquad (A3)$$

where $V_T(k)$ and $V_D(k)$ are the tidal and dead space volumes on breath k. The alveolar dilution number is:

$$\eta a(k) = CEAV(k)/FRC \qquad (A4)$$

so that

$$m_r = \int_{k=0} \eta a^r(k) X_{ET}(k)[\eta a(k+1) - \eta a(k)] \qquad (A5)$$

To implement equation A3 through A5, it is proposed that $V_D(k)$ be the Bohr dead space evaluated at each breath (k) according to the following relationship:

$$V_D(k) = V_T[(X_{ET}(k) - X_{ME}(k))/ (X_{ET} - X_{IN})] \qquad (A6)$$

where $X_{ME}(k)$ represents the mean expired N_2 fraction during breath k, X_{IN} denotes the inspired N_2 fraction found in the O_2 mixture (usually zero) and X_{ET} is the N_2 concentration at end-expiration. This ensures that the analysis is based on the functional ventilated alveolar volume. AMDN1 is the ratio m_1/m_0 using formula A5, and AMDN2 is the ratio m_2/m_0.

References

1. Eber E, Steinbrugger B, Modl M, Weinhandl E, Zach MS. Lung volume measurements in wheezy infants: comparison of plethysmography and gas dilution. *Eur Respir J* 1994; 7: 1988–1994.
2. Fumey MH, Nickerson BG, Birch M, McCrea R, Kao LC. A radiographic method for estimating lung volumes in sick infants. *Pediatr Pulmonol* 1992; 13: 42–44.
3. Gustafsson PM, Johansson HJ, Dahlback GO. Pneumotachographic nitrogen washout method for measurement of the volume of trapped gas in the lungs. *Pediatr Pulmonol* 1994; 17: 258–268.
4. Helms P. Problems with plethysmographic estimation of lung volume in infants and young children. *J Appl Physiol Respir Environ Exercise Physiol* 1982; 53: 698–702.
5. Schmalisch G, Wauer RR. Percentile curves of functional residual capacity of newborn infants. *Monatsschr Kinderheilkd* 1993; 141: 714–720.
6. Godfrey S, Beardsmore CS, Maayan C, Bar-Yishay E. Can thoracic gas volume measured in infants with airway obstruction? *Am Rev Respir Dis* 1986; 133: 245–251.
7. Gozal D, Bailey SL, Keens TG. Evolution of pulmonary function during an acute exacerbation in hospitalized patients with cystic fibrosis. *Pediatr Pulmonol* 1993; 16: 347–353.
8. Kraemer R. Assessment of functional abnormalities in infants and children with lung disease. *Agents Actions Suppl* 1993; 40: 41–55.
9. Saidel GM, Salmon RB, Chester EH. Moment analysis of multibreath nitrogen washout. *J Appl Physiol* 1975; 38: 328–334.
10. Saidel GM, Saniie J, Chester EH. Modeling and moments of multibreath lung washout. *Ann Biomed Eng* 1978; 6: 126–137.
11. Saidel GM, Saniie J, Chester EH. Lung washout during spontaneous breathing: parameter estimation with a time-varying model. *Comput Biomed Res* 1980; 13: 446–457.
12. Saniie J, Saidel GM, Chester EH. Real-time moment analysis of pulmonary nitrogen washout. *J Appl Physiol* 1979; 46: 1184–1190.
13. Kraemer R, Meister B. Fast real-time moment-ratio analysis of multibreath nitrogen washout in children. *J Appl Physiol* 1985; 59: 1137–1144.
14. Habib RH, Lutchen KR. Moment analysis of multiple nitrogen washout based on an alveolar gas dilution number. *Am Rev Respir Dis* 1991; 144: 513–519.
15. Brunner JX, Wolff G, Cumming G, Langenstein H. Accurate measurement of N_2 volumes during N_2 washout requires dynamic adjustment of delay time. *J Appl Physiol* 1985; 59: 1008–1012.
16. Kraemer R. Whole-body plethysmography in clinical assessment of infants with bronchopulmonary disease. *Respiration* 1993; 60: 1–8.
17. Kraemer R, Frey U, Wirz C, Russi E. Short-term effect of albuterol, delivered *via* a new auxiliary devicee, in wheezy infants. *Am Rev Respir Dis* 1991; 144: 347–351.
18. Bates JHT, Turner MT, Lanteri CJ, Jonson B, Sly PD. Measurement of flow and volume. *In*: Infant respiratory function testing. Wiley-Liss, 1996; 81–107.
19. Fleming GM, Chester EH, Saniie J, Saidel GM. Ventilation inhomogeneity using multibreath nitrogen washout: comparison of moment ratios and other indexes. *Am Rev Respir Dis* 1980; 121: 789–794.
20. Altman DG, Bland JM. Measurements in medicine: the analysis of method comparison studies. *Statistician* 1983; 32: 307–317.
21. Edelmann NH, Mittman C, Norris AH, Shock NW. Effects of respiratory pattern on age differences in ventilation uniformity. *J Appl Physiol* 1968; 24: 49–53.
22. Bouhuys A. Distribution of inspired gas in the lungs. *In*: Handbook of physiology. Section 3, Vol 1: Respiration. Washington, DC, American Physiological Society, 1964; 715–733.
23. Shao H, Sandberg K, Sjöqvist BA, Hjalmarson O. Moment analysis of multibreath nitrogen washout in healthy preterm infants. *Pediatr Pulmonol* 1998; 25: 52–58.
24. Gerhardt T, Hehre D, Banclalari E, Watson H. A simple method for measuring functional residual capacity by N_2 washout in small animals and newborn infants. *Pediatric Research* 1985; 19: 1165–1169.
25. Gerhardt T, Reifenberg L, Hehre D, Feller R, Bancalari E. Functional residual capacity in normal meonates and children up to 5 years of age determined by a N_2 washout method. *Pediatric Research* 1987; 20: 668–671.
26. Gappa M, Fletcher ME, Dezateux CA, Stocks J. Comparison of nitrogen washout and plethysmographic measurements of lung volume in healthy infants. *Am Rev Respir Dis* 1993; 148: 1496–1501.

27. Stanescu DC, Rodenstein DO, Cauberghs M, Van de Woesteijne KP. Failure of body plethsymography in bronchial asthma. *J Appl Physiol* 1982; 52: 939–954.
28. Tepper RS, Asdell S. Comparison of helium dilution and nitrogen washout measurements of functional residual capacity in infants and very young children. *Pediatr Pulmonol* 1992; 13: 250–254.
29. Beardsmore CS, Stocks J, Silvermann M. Problems in measurement of thoracic gas volume in infancy. *J Appl Physiol* 1982; 52: 995–999.
30. Godfrey S. TGV or not TGV in WB? That is the question. *Pediatr Pulmonol* 1991; 10: 73–77.
31. Godfrey S, Beardsmore CS, Maayan C, Bar-Yishay E. Can thoracic gas volume measured in infants with airway obstruction? *Am Rev Respir Dis* 1986; 133: 245–251.
32. Geubelle F, Francotte M, Beyer M, Louis I, Loginoff MM. Functional residual capacity and thoracic gas volume in normoxic and hyperoxic newborn infants. *Acta Paediat Belg* 1977; 33: 221–225.
33. Larsson A, Jonmarker C, Werner O. Ventilation inhomogeneity during controlled ventilation: which index should be used. *J Appl Physiol* 1985; 65: 2030–2039.
34. Wall MA, Misley MC, Brown AC, Vollmer WM, Buist SA. Relationship between maldistribution of ventilation and airway obstruction in children with asthma. *Respir Physiol* 1987; 69; 287–297.