Analysis of alveolar ventilation in the newborn

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SUMMARY Twelve healthy term infants were examined at the median ages of 2½ and 26 hours. Their alveolar ventilation, efficiency of ventilation, functional residual capacity, and lung nitrogen elimination patterns were studied by means of a computerised nitrogen wash out method. The results showed that alveolar ventilation and functional residual capacity increased over the period studied. At the same time effective dead space decreased leaving minute ventilation unchanged. Distribution of ventilation did not change.

In one critical phase at birth the lungs of the newborn take over the gas exchange function from the placenta by establishing effective ventilation. In the healthy infant sufficient function is achieved within the first few breaths and steady state conditions are present after a few hours.¹

The efficiency of the ventilation obtained depends mainly on the volume of the ventilated airspace (functional residual capacity), the dead space, the distribution of ventilation, and the gas mixing efficiency within the lungs. These factors have not been studied in combination in newborn infants. In this investigation a computerised analysis of nitrogen wash out curves was used to calculate functional residual capacity and alveolar ventilation and to analyse gas mixing over the first day of life in healthy, term infants.

Methods

A detailed description of the method is given elsewhere.^{2,3} For the examination each infant was placed in the supine position in a 'face out' volume displacement body plethysmograph, with a pneumotachograph (Fleisch 1) in the wall. When the child had adapted to the plethysmograph, respiratory frequency, tidal volume, and minute ventilation were calculated. After this a face mask (dead space 2 ml) was gently placed over the infant's face and mouth. A nitrogen analyser (Hewlett Packard model 47302A) and a system of tubings were connected to the face mask. During an expiration the infant's breathing air was instantaneously changed to 100% oxygen and a nitrogen wash out was performed until the end expired nitrogen concentration was below 2%. If the infant was disturbed or if gas leaks were observed the test was

interrupted and repeated. A second test was not performed for at least 15 minutes to allow for gas equilibration. The nitrogen concentration in the face mask and the respiratory flow rate were sampled by a computer for subsequent calculations. The analysis of the nitrogen wash out curve was performed on a PDP 11/40 computer and the software was written in FORTRAN.

The total expired nitrogen volume during wash out was determined by integrating the product of the expired ventilatory flow rate and the nitrogen concentration in the expired air after compensation for equipment delay and plethysmograph characteristics. The functional residual capacity was obtained by dividing the total expired nitrogen volume after the beginning of oxygen breathing by the end expiratory nitrogen concentration before the nitrogen wash out. The method was designed to give the lung volume in BTPS.

The reproducibility of the functional residual capacity estimation was tested by means of a mechanical lung model inserted into the plethysmograph. This has been described in detail elsewhere.² The known volume of the mechanical lung fell within the 95% confidence interval of the estimated volume when 10 repeated estimations were performed. The coefficient of variation was 2.9%.

No correction was made for the elimination of tissue nitrogen in the estimation of functional residual capacity. According to Groom *et al*⁴ and Lundin⁵ one minute of oxygen breathing, which was the approximate time for a nitrogen wash out test in this study, would add approximately 0.7 ml N₂/kg body weight to the expired N₂ volume implying an overestimation of functional residual capacity by only about 1 ml/kg body weight.

A total lung nitrogen volume elimination curve

was constructed with breath number on the abscissa (Fig. 1). This volume elimination curve was used for the further analysis of the nitrogen elimination pattern. In the ideal case the nitrogen elimination was assumed to be described by a single exponential function:

$$V_{L_n} = V_{L_0} e^{-an} = V_{L_0} W^n \quad (\text{equation 1})$$

(n =breath number, V_{L_n} =nitrogen volume remaining in the lung after n breaths, V_{L_0} =nitrogen volume in the lung before the elimination, a =constant) where $e^{-a}=W$ is the dilution factor defined as W =functional residual capacity/(functional residual capacity+tidal volume-dead space).

Deviations from the ideal nitrogen elimination pattern were assumed to be described by a sum of exponential components with different dilution factors. In this case the nitrogen elimination can be described as

$$V_{L_n} = F_1 V_{L_0} W_1^n + F_2 V_{L_0} W_2^n + \dots + F_k V_{L_0} W_k^n \quad (\text{equation 2})$$

where $V_{L_0} = F_1 V_{L_0} + F_2 V_{L_0} + \dots + F_k V_{L_0}$ and $F_1, F_2, \dots$ and F_k , are fractions of the total nitrogen lung volume. $W_1, W_2, \dots$ and W_k are the dilution factors for the different exponential components in the elimination pattern.

In the analysis of the nitrogen elimination pattern the best estimate of the observed elimination curve was sought by fitting one, two, and three component models to the linear curve by using the z transform,⁶ multiple linear regression, least square fit, and F test of the residuals. The estimated curve was considered to fit the original nitrogen elimination curve well when the difference in curve areas—both curves having the first point in common—was less than 5%. If the difference was more than 5% the wash out curve was considered insufficiently described by our exponential models.

The value of tidal volume minus dead space was obtained from the dilution factor in the best single exponential fit to the wash out data according to equation 1. As functional residual capacity and tidal volume were known, dead space could be estimated. This estimated dead space is, by definition, the virtual part of the tidal volume not participating in the gas exchange between the inspired and alveolar gas, referred to as an effective dead space.⁷ In the single exponential elimination course dead space may easily be estimated from the dilution factor. In the multiple exponential course, however, the dead space changes continuously during nitrogen elimination and cannot easily be described by a single value.

Fig. 1 Example of the nitrogen volume elimination curve with percentage of the total expired nitrogen volume on the ordinate and breath number on the abscisse.

In these cases dead space was estimated from the dilution factor achieved by the best single exponential least square fit to the data (equation 1). In this way the estimated dead space is the one obtained in an ideal system having the same lung volume and tidal volume as the lung examined and represents a weighted value of the continuously changing dead space.

The alveolar ventilation was calculated as (tidal volume minus dead space) × respiratory frequency and the effective breath fraction as tidal volume minus dead space/tidal volume. The nitrogen clearance was calculated as the necessary ventilation for dilution of the lung nitrogen to the end tidal nitrogen concentration of 2% divided by the calculated functional residual capacity.

In the statistical analysis Student's paired *t* test, Fisher's exact test, and analysis of covariance were used. Ninety five per cent confidence intervals for the mean differences were calculated. Results are presented as mean (SEM).

Patients

Twelve vaginally delivered, healthy, term infants were studied during the neonatal period. The median gestational age and range were 40.5 (38 to 42) weeks and the median birthweight and range were 3.64 (2.95 to 4.15) kg. All infants were studied twice at a median age and range of 2½ (2 to 4) and 26 (21 to 33) hours. Six infants were boys and 6 were girls. No infant showed signs of respiratory disease (respiratory frequency greater than 60/minute, cyanosis, retractions, or grunting). Nor were there signs of perinatal asphyxia, cardiac disease, or infection. The neonatal period was uneventful in all infants. The investigation was approved by the local ethical committee and informed maternal consent was obtained before the examination in all cases.

Results

The ventilatory parameters before and during the nitrogen wash out are presented in Table 1. There was an increase in minute ventilation during the nitrogen wash out measurement compared with that found when the baby was sleeping in the plethysmograph without the face mask. There were, however, no significant increases in minute ventilation, tidal volume, and respiratory frequency between 2½ and 26 hours of age. During this time the functional residual capacity increased significantly from mean (SEM) 65 (5.4) ml to 81 (4.4) ml ($P<0.05$) and the alveolar ventilation also increased significantly from 383 (32) ml/min to 511 (39) ml/min ($P<0.05$).

Table 1 Ventilatory parameters

	Before nitrogen wash out				During nitrogen wash out			
	At 2½ h		At 26 h		At 2½ h		At 26 h	
	Mean (SEM)		Mean (SEM)		Mean (SEM)		Mean (SEM)	
	Difference		Difference		Included		Excluded	
	Mean		Mean		Mean (SEM)		Mean (SEM)	
	95% confidence interval		95% confidence interval		Mean (SEM)		Mean (SEM)	
	Mean		Mean		Mean (SEM)		Mean (SEM)	
	95% confidence interval		95% confidence interval		Mean (SEM)		Mean (SEM)	
FRC(ml)	47 (3.3)	44 (2.8)	2.2	-6.5 to 11	67 (5.4)	83 (4.4)	-15*	-30 to -0.6
f(l/min)	15 (1.0)	16 (1.1)	-1.1	-3.5 to 1.3	48 (4.0)	50 (2.6)	-1.8	-13 to 9.3
V _T (ml)	675 (53)	687 (41)	-12	-160 to 136	18 (0.9)	19 (0.9)	-1.3	-4.2 to 1.5
V _E (ml/min)					840 (55)	956 (66)	-116	-323 to 90
V _D (ml)					9.8 (0.7)	9.0 (0.6)	0.8	-2.2 to 2.8
V _A (ml/min)					383 (32)	511 (39)	-128*	-245 to -11

* $P<0.05$.

FRC=functional residual capacity; f=respiratory frequency; V_T=tidal volume; V_E=minute ventilation; V_D=dead space; V_A=alveolar ventilation.

During wash out the dead space decreased from 7.8 (0.7) ml at 2½ hours to 7.0 (0.6) ml at 26 hours of age. At both examinations, however, there was a significant correlation between dead space and tidal volume ($P<0.01$) (Fig. 2). When the variance in dead space related to differences in tidal volume was compensated for by means of covariance analysis, the difference in dead space at 2½ and 26 hours of age was significant, ($P<0.05$).

The ventilation efficiency and the nitrogen elimination pattern are presented in Table 2. There was significant improvement in nitrogen clearance from mean (SEM) 9.6 (0.3) to 8.5 (0.2) between 2½ and 26 hours of age ($P<0.01$). The effective breath fraction also increased significantly during this time from mean (SEM) 0.45 (0.02) to 0.53 (0.02) ($P<0.01$). When the equipment dead space was excluded in the calculation the values were mean

Fig. 2 The correlation between tidal volume (V_T) and corresponding dead space (V_D) at 2½ (●) and 26 (○) hours of age. Linear regression line at 2½ hours of age (I): $V_D = -4.06 + 0.66 V_T$ ($r=0.80$, $P<0.01$) and at 26 hours of age (II): $V_D = -3.18 + 0.53 V_T$ ($r=0.79$, $P<0.01$).

(SEM) 0.51 (0.02) and 0.60 (0.02) respectively ($P<0.02$).

The analysis of the nitrogen elimination curves (Table 2) showed single exponential courses as the best fit in 7 of 12 infants at 2½ hours and 5 of 12 infants at 26 hours of age. This difference was not statistically significant. The other infants showed a two exponential elimination curve as the best fit in 1 of 12 and 4 of 12 infants at the two examinations respectively. No infant had a three exponential wash out pattern. In four curves at 2½ hours of age and three curves at 26 hours of age the exponential estimates deviated more than 5% from the original data. Thus, these curves could not be described sufficiently by our nitrogen elimination models. The individual alveolar dilution factors, the lung fractions, and the deviations are presented in Table 3. In

Table 3 Nitrogen elimination curve analysis

Infant No	Age (h)	Alveolar dilution factors			Lung fractions		Deviation > 5%
		W	W ₁	W ₂	F ₁	F ₂	
1	2	0.934			1		
	26	0.884	0.238	0.898	0.08	0.92	
2	2½	0.924			1		
	24	0.900			1		
3	2	0.833	0.723	0.889	0.45	0.55	
	24	0.876	0.362	0.902	0.15	0.85	
4	2½	0.892			1		
	26	0.900			1		
5	2½	0.921			1		
	23	0.866			1		
6	3	0.890			1		
	28	0.915			1		
7	2	0.914			1		
	21	0.874	0.510	0.895	0.13	0.87	
8	4	0.857			1		
	33	0.902			1		
9	3	0.847	0.457	0.863	0.09	0.91	
	29	0.890			1		
10	3	0.899			1		
	25	0.897			1		
11	3	0.911			1		
	28	0.898			1		
12	2½	0.807			1		
	25	0.872	0.371	0.894	0.12	0.88	

Table 2 Efficiency of ventilation and nitrogen elimination pattern

	Age		Difference	
	2½ h Mean (SEM)	26 h Mean (SEM)	Mean	95% confidence interval
Nitrogen clearance	9.6 (0.3)	8.5 (0.2)	1.2 [*]	0.4 to 1.9
Effective breath fraction ($(V_T - V_D)/V_T$)	0.45 (0.02)	0.53 (0.02)	-0.08 [‡]	-0.13 to -0.03
Effective breath fraction [†]	0.51 (0.02)	0.60 (0.02)	-0.08 [‡]	-0.15 to -0.02
Nitrogen elimination pattern:				
One exponential	7	5	§	
Two exponential	1	4	§	
Three exponential	0	0		
Other	4	3		

* $P<0.01$; † $P<0.02$.

[‡]Equipment dead space (2 ml) excluded.

[§]Difference not significant (Fisher's exact test, $P>0.05$).

V_T =tidal volume; V_D =dead space.

the infants with a two exponential model as the best fit one of the components was small and fast in all cases but one.

Discussion

Although the nitrogen wash out method has not been used frequently on newborns,^{8,9} it has often been used on adults to study the distribution of ventilation and to measure the functional residual capacity.¹⁰ We have designed a nitrogen wash out method which minimises interference with the infants' breathing² and in addition, analyses objectively the nitrogen volume elimination curve without using semilogarithmic plots.³ A similar approach has been used by Cumming *et al*,^{11,12} they, however, analysed the efficiency of ventilation from a representative litre of the lung volume while our estimates of this and the nitrogen elimination pattern are based on the total expired nitrogen volume. This study method has been used to investigate ventilatory adaptation during the first day of life in healthy, vaginally delivered term infants.

There is one study only, that of Prod'hom *et al*,¹³ that investigates the development of alveolar ventilation during the first day of life starting at 1 hour of age, and in this no changes in total ventilation and alveolar ventilation between 1 and 24 hours of age were found. The infants studied were delivered by caesarean section and the mothers had diabetes mellitus. Some of these infants had signs of neonatal asphyxia, some had tachypnoea during the first hours of life, and they were also slightly premature with gestational ages ranging from 35 to 37 weeks. As asphyxia and caesarean section are factors affecting ventilation in neonates¹⁴ these infants can hardly be regarded as 'normal'.

All infants in our study were term, vaginally delivered, and without perinatal asphyxia. We found a significant increase in alveolar ventilation between 2½ and 26 hours of age while the total ventilation was unchanged. The increase in alveolar ventilation parallels the increase in oxygen consumption during the first day of life found in previous investigations.^{15,16} In a study of basal oxygen consumption in term infants at the ages of 3 and 24 hours, Hill *et al* found an increase in oxygen consumption of 38%.¹⁶ After the age of 24 hours only a slight further increase was found. This increase in oxygen consumption is in good agreement with our finding of an increase in alveolar ventilation of 33% between the ages of 2½ and 26 hours.

If alveolar ventilation increases under conditions of unchanged total ventilation, ventilation efficiency must have improved. We found that ventilation

efficiency, measured as nitrogen clearance and effective breath fraction, improved significantly between 2½ and 26 hours of age. This also means that the effective dead space decreased during this time. The dead space value measured in this way is not, however, a static volume but a function of other ventilatory variables. We found a significant correlation between dead space and tidal volume at both 2½ and 26 hours of age—a correlation that has been found previously in neonates and in adults.^{17,18} This means that comparison between dead space at different measurements can only be made in connection with the corresponding tidal volume. When, in this study, analysis of covariance was used to eliminate variance due to differences in tidal volume between the examinations, the difference in dead space between 2½ and 26 hours of age became obvious (Fig. 2).

Dead space as a function of other ventilatory variables can be understood from recent studies on gas mixing in the human lung.¹⁹ Ventilatory flow rate and lung expansion have implications for the diffusion between inspired and alveolar gas and consequently affect the effective dead space in the lung. From animal studies it is known that the newborn lung is hyperhydrated.²⁰⁻²² It is also known that lung oedema preferentially locates in the interstitial tissue round airways and vessels.²³ Accumulation of interstitial lung fluid during the first hours of life may affect the total cross sectional area of the small airways in the lung. As the contact area between inspired and alveolar gas is important for the efficiency of gas mixing by diffusion¹⁹ this may explain the reduced ventilatory efficiency found at 2½ hours of age compared with later. Since total ventilation was unchanged during this time continuous drainage of interstitial fluid with an increase in the total cross sectional area of the small airways may explain the resulting improvement in ventilatory efficiency found in this study. The significant increase in functional residual capacity is an indication of the same process.

During the period after birth when resorption of interstitial lung fluid occurs it could be assumed that the inspired gas is unevenly distributed into the lung and that some areas of the lung are poorly ventilated in comparison with others. This may lead to parallel inhomogeneity in the ventilation of the lung with different lung compartments ventilated at varying rates. In previous studies of nitrogen wash out curves great efforts have been made to analyse whether lung compartments are ventilated in parallel or whether stratified gas inhomogeneity exists.²⁴ Recent model analyses, however, have shown the complexity of gas mixing in the lung.²⁵ Evidently concentration gradients normally develop and

change during the whole breathing cycle throughout the lungs and interpretation of nitrogen elimination curves in terms of parallel or stratified inhomogeneity has been questioned.¹⁹ Astonishingly, in spite of this complexity in the distribution of alveolar gas concentrations, nitrogen elimination during oxygen breathing often follows a single exponential course and may be expressed by a single model. In this study we found single exponential elimination patterns in half of the infants at both examinations. Some of the other infants' curves could be described using the sum of two exponential curves but in some curves exponential fitting was not possible at all according to our model and criteria. When the curve could be described by the sum of two exponential components the additional component was often small and fast (Table 3). There were no significant differences in elimination patterns between the examinations (Table 2); consequently no detectable change in significant parallel ventilation due to elimination of interstitial lung fluid could be found. The presence of a single exponential elimination pattern in about half the infants is in agreement with findings in healthy adults.¹⁰

In summary, this study has shown that adaptive changes occur in healthy, term infants with increases in alveolar ventilation, efficiency of ventilation, and functional residual capacity between 2 and 4, and 21 and 33 hours of age.

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