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Pulmonary function during the first year of life in healthy infants born prematurely

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Pulmonary function during the first year of life in healthy infants born prematurely. I.T. Merth, J.P. de Winter, G.J.J.M. Borsboom, Ph.H. Quanjer. ©ERS Journals Ltd 1995.

ABSTRACT: Premature birth is associated with increased respiratory morbidity. We investigated cross-sectionally, in 69 healthy infants who had never had cardiorespiratory problems, whether premature birth is associated with diminished pulmonary function.

The study comprised 26 healthy infants born prematurely (PT), median gestational age 32 (26–36) weeks, and 43 healthy controls born full-term (FT), median gestational age 40 (37–42) weeks. Static respiratory system compliance (C_{rs}) was assessed by weighted spirometry, combined with the measurement of the functional residual capacity by closed circuit helium dilution (FRC$_{He}$) and with assessment of ventilation distribution from the mixing index (MI). Repeatability of these indices was also assessed.

Premature and full-term infants had the same length-corrected FRC$_{He}$; their C_{rs} was different, but the difference disappeared when gestational age was taken into account. Mixing index was unrelated to body size and was not different between full-term and premature infants. Crown-heel length and lung volume were not different for any postconceptional age. However, infants born prematurely were smaller and had smaller lung volume at any postnatal age compared to those born at term. Repeatability of the indices was fair.

These findings suggest that gestational age <37 weeks is associated with normal respiratory system mechanics for body size, and normal distribution of ventilation in healthy infants who never had cardiorespiratory problems.

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Recent data on ventilatory function [1–3] as well as epidemiological evidence [4, 5] suggests that gestational age at birth rather than perinatal respiratory problems may be associated with long-term respiratory morbidity. At less than 37 weeks of gestation, only the saccular phase of intrauterine lung development has been reached [6]. Hence, premature delivery may be associated with stunting of parenchymal growth, resulting in altered mechanical properties of lungs and airways. The influence of gestational age on pulmonary function should be detectable in healthy infants born prematurely when compared with those born at term. Diminished initial lung function may explain the high morbidity due to respiratory disease in preterm infants during the first year of life [7, 8], and may be associated with chronic obstructive lung disease in adults [4].

CHU *et al.* [9] found the compliance per unit of lung volume to be lower in prematurely born neonates without respiratory problems at birth, compared with healthy full-terms, whilst others failed to show this [10, 11]. It should be borne in mind, however, that a normal finding might arise from a combination of abnormally stiff and compliant lung areas, which would still allow overall lung volume and compliance to be in the normal range. In that case, the uneven distribution of lung distensibility and airways resistance would give rise to uneven ventilation [12]. Indeed, ventilation distribution has been found to be affected in acute and chronic lung disease during infancy [13, 14].

Several noninvasive tests are available to study the above aspects of pulmonary function in infants [15]. Respiratory system compliance (C_{rs}) can be assessed by weighted spirometry [16], where, because of the very compliant chest wall during infancy [17], the measured compliance practically reflects that of the lungs. This can be combined with the measurement of the functional residual capacity by closed circuit helium dilution (FRC$_{He}$). Moreover, during the latter measurement the mixing index (MI), a measure of distribution of ventilation during wash-in of helium [18], can be assessed. The MI, C_{rs} and FRC$_{He}$ provide a picture of ventilatory function in relation to lung mechanics.

We studied whether infants born prematurely (PT) differed from those born at term (full-term (FT)) with respect to their pulmonary function. To that end, we measured C_{rs} and FRC$_{He}$ in a cross-section of healthy newborns and infants during the first year of life. We also estimated MI from the recordings of the FRC$_{He}$

Table 1. – Characteristics of the infants studied

	Subjects n	GA weeks	Birth weight kg	Study age* weeks	Study weight kg	Study length cm
Boys						
FT	19	40	3.4	4.3	3.6	52.0
		37–42	1.9–4.5	0.2–60	2.4–9.8	46.0–77.5
PT	14	30	1.4	14.2	5.8	59.7
		26–36	0.94–2.5	-1.70–51	1.5–10	44.0–79.0
Girls						
FT	24	40	3.3	3.9	3.4	50.0
		37–42	2.0–4.0	0.74–39	2.0–7.9	45.0–69.5
PT	12	34	1.9	18.5	5.1	59.0
		28–36	0.79–2.6	-1.68–5.1	1.8–9.4	43.0–75.0

Data are presented as median and range. FT: born full-term; PT: born preterm; GA: gestational age. *: corrected for 37 weeks gestational age (postconceptional age in weeks minus 37 weeks gestation).

measurements. Regression equations of pulmonary function indices as a function of body size were derived. The repeatability of the tests was also assessed.

Material and methods

Subjects

Sixty nine healthy newborns and infants without cardiorespiratory illness at birth were recruited from the departments of Obstetrics and Paediatrics of our hospital; 43 were full-term at birth and 26 were born prematurely, *i.e.* before 37 weeks gestational age. All but three were of Caucasian origin. Characteristics are given in table 1. Infants older than 30 days of age received 50–100 $mg \cdot kg^{-1}$ chloral hydrate orally prior to testing. All infants were tested 30–60 min postprandially. Parental consent was obtained and the study was approved by the Medical Ethics Committee of the University Hospital Leiden.

Equipment

The spirometer has been described in detail previously [19]. To accommodate the rapidly increasing lung volume during the first year of life, two instruments were used with a system volume of 520 and 670 mL, respectively. The spirometers had an inlet for continuous oxygen supply, a CO_2 absorber unit, and a blower providing sufficient continuous flow (6.2 and 10.2 $L \cdot min^{-1}$, respectively) to avoid rebreathing from the instrumental deadspace. Pressure changes were measured *via* a port in the facemask using a differential pressure transducer and amplifier (Validyne MP45 and model MC1-3, respectively, Validyne Corp., Northridge, CA, USA). The volume and pressure signals were recorded on a multichannel recorder (Linseis, LG510, Germany).

Methods

Infants were lying supine with the head-end elevated approximately 30° relative to horizontal, and the neck held in a neutral position by placing a foam ring under the occiput. A Rendell-Baker type facemask (Laerdal No. 0 or 1, Norway) was placed gently on the infant's face and sealed with silicon putty (George C. Bishop Co., USA) to accomplish an airtight seal at the edges. The functional residual capacity (FRC) was always measured first, followed by assessment of C_{rs}.

Functional residual capacity by helium dilution. The method has been described previously [20]. After defining a stable end-expiratory level by adjusting the oxygen flow into the spirometer, the infant was switched into the circuit at or near end-expiration. If the infant was not switched in at end-expiratory volume, this was taken into account in the computation of FRC. At least 3 min were allowed for helium equilibration to occur. To compensate for inadequate oxygen supply and for the slight uptake of helium in blood during the test, the final concentration of helium was defined by extrapolating the linear portion of the trace to the onset of decline in helium concentration [20]. Absence of leak during the dilution was established by placing a weight on the bell, which generated a pressure of 0.3 kPa (2.95 cmH_2O). If feasible, measurements were repeated at least once. Reported values are that of a single measurement or the mean of a set of technically acceptable measurements (*i.e.* equilibration time of helium at least 3 min, no leak detected, behaviourally quiet sleep suggested by stable end-expiratory level with regular breathing pattern: frequency and tidal volume). Volumes were corrected to body temperature, atmospheric pressure, and saturation with water vapour (BTPS) conditions.

Respiratory system compliance. Weights generating pressures of 0.14 kPa (1.37 cmH_2O) and 0.30 kPa (2.94 cmH_2O), respectively, were placed on the spirometer bell at least three times in random order [3–10] with and without the subject connected to the spirometer. In the former case, the weight was left in place at least 30 s. The slope of the volume-pressure relationship of the lung-spirometer system was derived from linear regression of volume deflections on applied pressures. C_{rs} was obtained by subtracting the compliance of the spirometer from that of the subject-spirometer system [21]. Volume and pressure changes were calibrated before and after each testing session.

Mixing index. The ratio of the ideal to the actual number of breaths to achieve 90% of the final helium concentration whilst measuring the FRC was calculated according to Bates and Christie [18]. In establishing the time required to achieve 90% gas mixing, account was taken of the response time of the helium analyser. Reported values are those of one or the mean of up to four assessments in the same infant.

Miscellaneous. The reproducibility of measurements was assessed from as many repeated measurements (up to four) as could be performed within an hour, *i.e.* before the infant woke up.

Following the testing session, the crown-heel length of the infant was measured by two adults (the investigator and a parent) using an infant stadiometer; the mean of two measurements is reported.

From the literature, we retrieved data on static respiratory system compliance and analysed whether these and the data collected in this study differed systematically, taking crown-heel length into account.

Statistical analysis

*C*rs, FRCHe and MI, stratified by gender, were analysed as a function of crown-heel length, gestational age and gender-gestational age interaction (analysis of covariance). Gestational age was used both as a continuous and as a categorical (<37 weeks being PT and ≥37 weeks being FT) variable. The scatter of *C*rs increased with length, but logarithmic transformation stabilized the variance. No transformation was required for MI and FRCHe. Function indices were linearly regressed on crown-heel length, as well as on postnatal and postconceptional age.

Repeatability was assessed from the first two measurements, and expressed as the single determination standard deviation [22] ($SDSD=SD/\sqrt{2}$), provided the difference between the two measurements was not dependent on their mean value. For FRCHe up to four measurements per infant were available. As the within subject SD of FRC was proportional to the mean, FRCHe was log transformed. If more than two measurements were available, the reproducibility was also assessed by one-way analysis of variance (ANOVA).

The comparison of the present data on respiratory system compliance and those from the literature was performed by analysis of variance with crown-heel length as covariate.

Table 2. – Results of linear regressions of pulmonary function variables on crown-heel length (cm)

Variable	Slope (±SE)	Intercept (±SE)	RSD	r^2
log *C*rs	0.035 (±0.004)	1.93 (±0.25)	0.37	0.48
FRCHe	5.16 (±0.26)	-175.72 (±14.9)	21.52	0.85

RSD: residual standard deviation; *C*rs: respiratory system compliance; FRCHe: functional residual capacity by helium dilution method.

Analyses were performed with the SAS statistical package (SAS Institute, Carey, North Carolina, USA). Values of p less than 0.05 and less than 0.10 (for interaction terms) were regarded as statistically significant.

Results

Respiratory system compliance and FRC by closed circuit helium dilution

As *C*rs and FRC vary with body size, some size correction is in place. For clinical application, weight is a less ideal index because it is much more prone to be affected by illness in infancy than length. *C*rs is conventionally expressed per unit lung volume. However, this ratio was negatively correlated with both FRCHe and length, precluding its use as a size-independent index of respiratory system elasticity. Also, disease may affect both *C*rs and FRCHe, and this might be masked in their ratio. Log *C*rs and FRCHe correlated satisfactorily with crown-heel length (r^2=0.48 and 0.85, respectively), (table 2, figs. 1 and 2). Hence, comparisons of

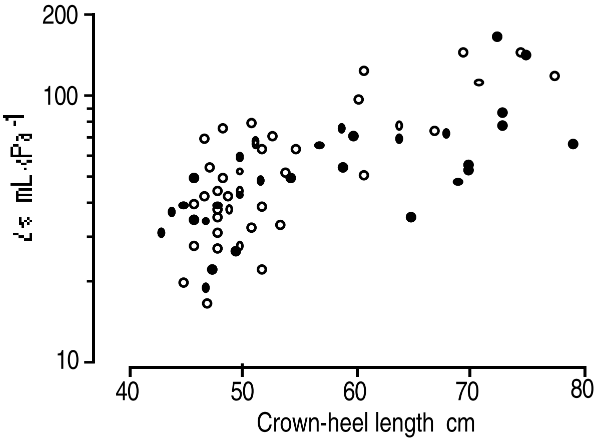

Fig. 1. – Relationship between respiratory system compliance (*C*rs) and crown-heel length in infants born prematurely (●) and full-term (○). *C*rs was smaller in prematurely born infants than in those born full-term; differences are accounted for by gestational age. Note log scale for Crs.

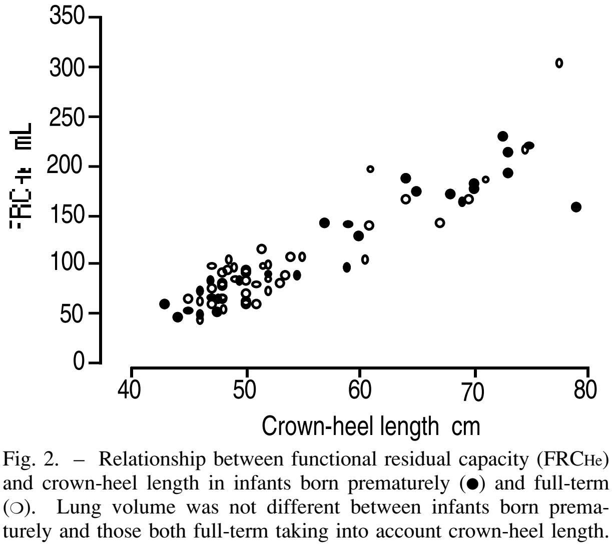

Fig. 2. – Relationship between functional residual capacity (FRCHe) and crown-heel length in infants born prematurely (●) and full-term (○). Lung volume was not different between infants born prematurely and those both full-term taking into account crown-heel length.

FRCHe and log *C*rs between groups were made using crown-heel length as a covariate.

Log *C*rs was smaller in PT than in FT infants (p=0.035), but differences disappeared when account was taken of gestational age as a continuous instead of a dichotomous variable (p=0.18). Differences were unrelated to gender (p=0.65). The interaction term of gender and premature or mature delivery was not significant (p=0.16). Therefore, FT and PT infants were combined as a single group to predict log *C*rs from crown-heel length (table 2).

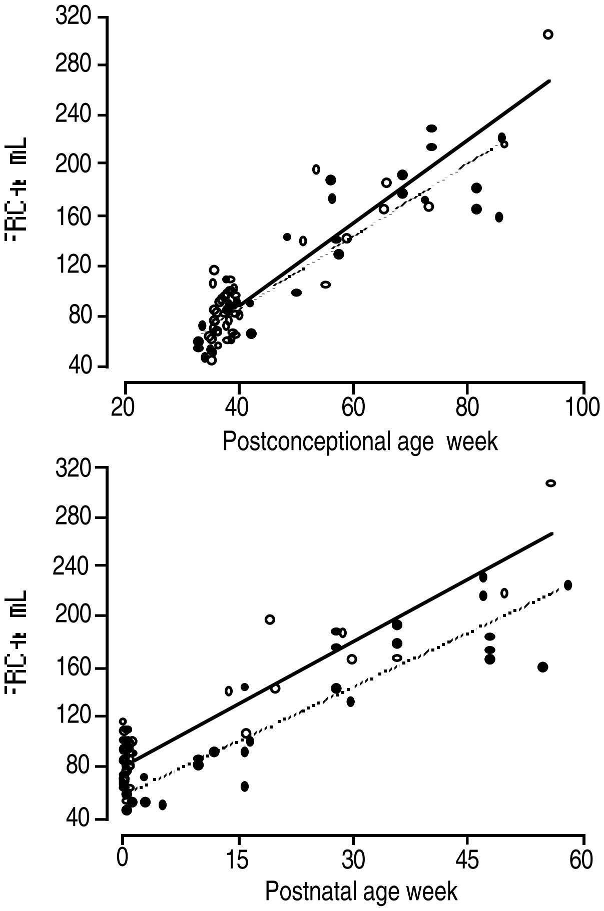

Fig. 3. – Relationship between age and lung volume. Functional residual capacity by closed circuit helium dilution (FRCHe) was not different for any postconceptional age between full-term (○) and premature (●) infants (p=0.21). At any postnatal age the FRCHe was lower in infants born prematurely (p<0.0001). ---------: born prematurely; ———: born full-term.

Table 3. – Prediction of FRCHe (mL) from age in the first year of life according to duration of gestation

FT/PT	Slope (±SE)	Intercept (±SE)	±RSD	r^2
		Postconceptional age		
FT	3.31 (±0.23)*A	-44.3 (±10.7)	21.0	0.83
PT	2.89 (±0.29)*A	-31.5 (±17.1)	27.4	0.80
		Postnatal age		
FT	3.33 (±0.23)*A	78.4 (±3.5)	20.9	0.83
PT	2.87 (±0.27)*A	55.3 (±8.5)	25.9	0.82

A: age in weeks. For further abbreviations see legend to tables 1 and 2.

Lung volume corrected for crown-heel length was not different between FT and PT, or between girls and boys. A prediction equation for FRCHe based on length, therefore, relates to the whole group (table 2); predictions are very similar to those reported by others [23, 24]. Analysis of covariance showed that lung volume in infants born full-term did not differ from those born prematurely at any postconceptional age (p=0.21) (fig. 3). However, at any postnatal age prematurely born infants had a significantly smaller FRCHe (p<0.0001) (fig. 3, table 3).

Mixing index

The study was not initially set up to study the mixing index. Therefore, not all registrations were suitable for evaluation (too slow paper speed during a measurement, making breath count inaccurate); thus, MI was available in 36 infants. MI was unrelated to crown-heel length (r^2=0.10). Analysis of covariance showed no difference between boys and girls (p=0.39); MI was unrelated to PT or FT birth (p=0.55), to gestational age (p=0.44) or gender-age interaction (p=0.27). The median value was 64% (95% confidence interval (95% CI) 36–80%) for FT infants, 57% (95% CI 48–64%) for PT infants and 57% (95% CI 48–65%) for the whole group.

Body size

The distributions of crown-heel length and body weight were very similar in FT and PT infants. Of the 69 infants, four had birth weights less than 10% predicted for their gestational age. As the expected frequency is seven, there is no evidence for inappropriate growth which could have biased the results. Crown-heel length was nonlinearly related to postconceptional as well as postnatal age both in FT and PT infants. It could be satisfactorily described as a second degree polynomial of age (fig. 4). The relationship was independent of postconceptional age (p=0.40), but different for postnatal age (p<0.0001). Obviously, if crown-heel length is depicted as a function of postconceptional age, there is normal growth (fig. 4). However, when length is related to postnatal age, preterm infants are on average smaller (fig. 4).

Repeatability

Functional residual capacity. In 10 infants, measurements of FRCHe could not be repeated because the infant woke up. The SDSD of the difference between two measurements of FRCHe was 0.076 on a logarithmic scale (table 4); this comes to about 7.9% on a linear scale. One-way ANOVA for the group with up to four measurements in the same subject gave comparable reproducibility (residual standard deviation (RSD) 0.083).

*Respiratory system compliance. C*rs measurements could be repeated in 23 infants (table 4). The difference between two measurements was unrelated to their mean; the median difference came to -6.38 mL·kPa^{-1} (95% CI -10.32–0.24%).

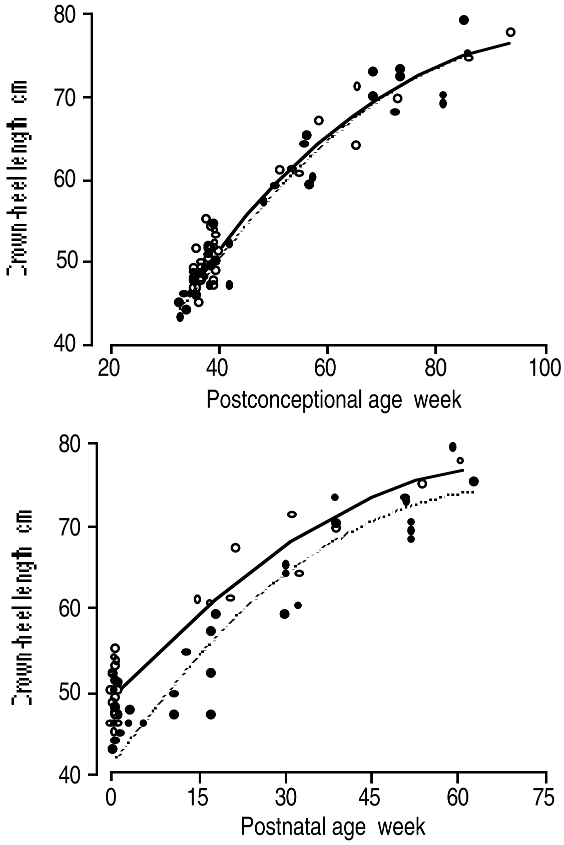

Fig. 4. – Relationship between age and crown-heel length. Crown-heel length was comparable for any postconceptional age for full-term (○) and premature (●) infants. Prematurely born infants were shorter at any given time after birth, especially during the first 30 postnatal weeks. --------- : born prematurely; ———: born full-term.

Table 4. – Repeatability of pulmonary function tests

	Mean of two repeated measurements ±SD		Single determination standard deviation (SDSD)		
FT/PT	*C*rs mL·kPa^{-1}	MI %	log FRCHe	*C*rs mL·kPa^{-1}	MI %
FT	72.6±26.2	66±20	0.073 n=36	6.6 n=11	12.5 n=11
PT	81.6±42.6	53±9	0.079 n=23	17.7 n=12	4.9 n=12
All	72.3±35.2	59±17	0.076 n=59	13.5 n=23	9.3 n=23

MI: mixing index; n: number of infants in whom index could be measured repeatedly; for FRCHe repeatability is exp(*a*), where *a* is the figure in the column. For further abbreviation see legends to tables 1 and 2.

Mixing index. The difference between two repeated measurements of MI in 23 infants was independent of their mean; the median difference came to -1.38% (95% CI -5.19–5.21%).

Analysis of data on respiratory system compliance

We have added the 69 infants of the present study to the 128 from the literature in whom static respiratory system compliance had been assessed (table 5). With few exceptions, they were studied during the first year of life. The methods applied varied: weighted spirometry [14], multiple occlusion technique [25, 26], and measurement of chord compliance from a single inflation in curarized infants [27]. In the ANOVA, we regressed log compliance on crown-heel length. The geometric means, adjusted for differences in length, and their 95% CI are given in table 5. There were systematic differences between authors (p<0.001), which were due to the data by THOMPSON *et al.* [25]: when these data were excluded, the remaining data did not differ systematically (p=0.1348).

Discussion

Decreased perinatal mortality of prematurely born infants has led to increased morbidity in this population, especially during the first year of life [28–30]. Rehospitalization may be twice as frequent as in infants born at term [7], respiratory problems being the cause in 30–50% of cases [8, 31]. We hypothesized that respiratory problems might be related to lung development lagging behind in preterm infants compared to their term counterparts; this should then be reflected in the mechanical properties of the respiratory system. Indeed, respiratory system compliance appeared to be smaller in the infants born prematurely, consistent with this hypothesis. However, it would be logical to expect that the more premature the neonate at birth, the more pronounced the effect on respiratory compliance. This was not borne out by the facts, as differences disappeared when biological (gestational) age was used in the analysis. Also, a stiffer respiratory system would give rise to a smaller lung volume, but again, using gestational age for the analysis, there was no evidence for this. Hence, we believe that this study provides no evidence that lung volumes and respiratory compliance in healthy infants

Table 5. – Static respiratory system compliance, adjusted for crown-heel length, in infancy assessed by different methods

Method	PT/FT	Subject n	Median age months	Median length cm	*C*rs mL·kPa^{-1}	95% CI	[Ref.]
Chord	NS	34	2.3	59.5	52.0	46.9–57.8	NIGHTINGALE [27]
MOT	23/11	34	0.75	45.7	38.1	34.3–42.4	THOMSPON [25]
MOT	24/0	24	0.16	44.0	46.6	41.2–52.9	GAPPA [26]
WS	NS	36	12.5	72.5	46.1	41.7–51.1	TEPPER [14]
WS	26/43	69	0.3	51.5	52.0	48.3–55.9	This study

*C*rs: respiratory system compliance, geometric mean; 95% CI: 95% confidence interval of the geometric mean; NS: not stated; Chord: chord compliance at 0.66 kPa inflation pressure assessed in curarized infants; MOT: multiple occlusion technique; WS: weighted spirometry. For further abbreviations see legend to table 1.

born at term or prematurely are materially different after taking into account crown-heel length.

Although the preterm infants were older than their full-term counterparts at the time they were studied (table 1), crown-heel lengths were comparable for postconceptional age in both groups of infants (fig. 4); this rules out the possibility that different anthropometry explains these findings. Consequently, because of the strong relationship between length and lung volume, PT and FT infants are indistinguishable, as far as their lung volume is concerned, at any postconceptional age (fig. 3). Hence, omitting biological age from the analysis of the pulmonary function results can easily lead to spurious conclusions. This obviously also holds when biological age is simply categorized by either full-term or premature birth. This is illustrated in figures 3 and 4. For the same postnatal age, PT infants were smaller (fig. 4), consequently their lung volume was less (fig. 3) than of those born at term, falsely suggesting that lung development lags behind in infants born prematurely.

The normal mechanical properties of the respiratory system might be a fortuitous finding, as *e.g.* abnormally stiff areas might be compensated by more compliant lung regions. This would then show up in abnormal distribution of ventilation [12]. Indeed, the mixing index has been shown to be affected early in the clinical course in infants with cystic fibrosis prior to respiratory symptoms [14]. Nevertheless, the MI was not different between FT and PT infants. The median value of MI in the group of FT infants (63%) was similar to that (68%) obtained by measuring pulmonary clearance delay of N_2 in healthy neonates [13, 32], and the same as found in healthy infants born at term using helium wash-in [23]. This suggests that the distribution of ventilation attained by the end of the first day [32] remains constant during the first year of life. These data would suggest a somewhat lower mixing efficiency in healthy infants than in healthy adults, in whom it approaches 80% [18]; this may be attributable to more extensive airway closure in infants compared to adults [33].

Our findings disclose no differences in lung mechanics, lung volume and distribution of ventilation attributable to gender, premature birth, or their interaction. Thus, in terms of ventilatory function, the lungs of infants born prematurely are comparable to those of infants born at term at any postconceptional age. These findings are consistent with earlier studies on dynamic lung compliance and lung volume, applying oesophageal manometry and whole body plethysmography [10, 11]. They are also compatible with the studies of HISLOP and coworkers [34, 35], who did not find that preterm delivery *per se* was associated with altered postnatal lung growth. Thus, the severity of subsequent respiratory trouble following premature birth is not necessarily attributable to abnormal lung development.

Weighted spirometry is not applied routinely because of the theoretical possibility that infants fail to relax their respiratory muscles upon positive end-expiratory pressure. However, the remarkable agreement between our data and those where muscle relaxation is achieved either by reflex stimulation (multiple occlusion technique (MOT)) [26], or by pharmacological means [27] (table 5), suggests that respiratory muscle activity does not play an important role when weighted spirometry is applied. To some extent, the interpretation of respiratory system compliance is hampered by the fact that it comprises both chest wall and lung compliance; unlike oesophageal manometry, which exclusively provides an estimate of lung compliance. In theory, it is possible that the progressive stiffening of the chest wall in infancy obscures the more subtle alterations which might have occurred in the lung parenchyma of infants born prematurely. However, the normal lung volumes and the normal mixing index provide no clue whatsoever that the lungs of prematurely born infants differ from those born at full-term.

The close relationship between lung size and body length in infants born at full-term [23, 24] appears to be maintained in healthy infants born prematurely without cardiorespiratory problems after birth, as well. Lung dimensions, however, are an important determinant of airway patency: the smaller the lung the narrower the airway. According to Poiseuille's law, a diminished airway diameter due to an increase in the thickness of mucosa and submucosa as a result of inflammation may result in a dramatic increase of flow resistance in terminal airways, easily leading to respiratory problems. Consequently, diseases affecting the terminal air passages, such as acute viral bronchiolitis, predispose PT infants to clinically more severe lower respiratory tract illness with more frequent hospitalization than infants of the same postnatal age but born at full-term [7, 30]. This is compatible with the observation that clinical problems are more likely to occur in infants having the narrowest airways prior to any respiratory illness [36, 37].

A measurement is only valuable if it is repeatable [22]. The reproducibility of FRC_{He} was fair: 7.9% for duplicate measurements and 8.5% for up to four measurements. The repeatability of respiratory compliance and the mixing index was somewhat less satisfactory. These indices are preferably reported as the mean of two measurements. Each of the techniques is easily applicable provided the infant remains in quiet sleep and the investigator is endowed with much patience.

In conclusion, premature birth does not affect the mechanical properties of the respiratory system given body dimensions, neither does it influence the distribution of ventilation during the first year of life. However, prematurely born infants are smaller at any postnatal age compared to those born at term, leaving them with smaller lungs and narrower airways, and thus more vulnerable to developing clinically more severe respiratory disease.

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