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Respiratory Function in Healthy Late Preterm Infants Delivered at 33-36 Weeks of Gestation

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Abstract

Objective—To compare pulmonary function testing including respiratory compliance (Crs) and time to peak tidal expiratory flow: expiratory time ($T_{PEF}:T_E$) at term corrected age in healthy infants born at 33-36 weeks of gestation versus healthy infants delivered at term.

Study design—We performed a prospective cohort study of late preterm infants born at 33-36 weeks without clinical respiratory disease (<12 hours of >0.21 FiO_2) and studied at term corrected age. The comparison group was term infants matched for race and sex to the preterm infants and studied within 72 hours of delivery. Crs was measured with the single breath occlusion technique. A minimum of 50 flow-volume loops were collected to estimate $T_{PEF}:T_E$.

Results—Late preterm infants ($n=31$; mean gestational age 34.1 weeks, birth weight 2150 g) and 31 term infants were studied at term corrected age. The late preterm infants had decreased Crs (1.14 vs 1.32 mL/cm H₂O/kg; $p<0.02$) and decreased $T_{PEF}:T_E$ (0.308 vs 0.423; $p<0.01$) when compared with the term infants. Late preterm infants also had an increased respiratory resistance (0.064 vs 0.043 cm H₂O/mL/sec; $p<0.01$).

Conclusions—Healthy late preterm infants (33-36 weeks of gestation) studied at term corrected age have altered pulmonary function when compared with healthy term infants.

Keywords

Expiratory flow ratio; late preterm infants; pulmonary function; respiratory compliance

Human lung development is a vulnerable process that can be significantly affected by multiple factors, particularly premature delivery. The rate of preterm births in the United States has increased over the last 20 years. Of these preterm births, about 70% are born late preterm (34 0/7 to 36 6/7 weeks' gestation) with the rate of late preterm births increasing at a faster pace than the overall rate of preterm birth (1-3). Infants born at late preterm gestations are at increased risk for morbidities in the immediate newborn period including a higher rate of respiratory distress syndrome and transient tachypnea of the newborn when compared with term infants (1).

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Alveolarization in the human lung occurs in the third trimester of gestation and therefore preterm delivery, and without any clinical signs of respiratory distress, may affect lung structure and development. Histological studies of the lungs of premature infants, including infants without respiratory disease, have shown pulmonary structural changes with increased bronchial muscle, collagen, and elastin (4). Recent studies examining premature infants born at a wide range of gestational ages (25 weeks to 36 weeks), but without signs of respiratory distress, have demonstrated these infants to have altered airway and alveolar development (5,6) in the first few years of life. Prematurity is considered a risk factor for subsequent airway dysfunction, respiratory morbidity and asthma in childhood. Little is known about the evolution of pulmonary function in the extra-uterine environment of the subgroup of healthy late preterm infants.

Our objective was to measure and compare pulmonary function tests (PFTs) including respiratory compliance (Crs) and flow volume characteristics including time to peak tidal expiratory flow to expiratory time ($T_{PEF:Te}$) in healthy late preterm infants versus healthy term infants matched for race and sex. We hypothesized that the late preterm infants without clinical lung disease would have decreased pulmonary function compared with healthy term infants studied at the same corrected age.

METHODS

This study was conducted in the Neonatal Intensive Care Unit and the normal newborn nursery at Oregon Health & Science University (OHSU). The protocol was reviewed and approved by the Institutional Review Board at OHSU. Informed consent was obtained for all enrolled patients. Infants were enrolled if they met the following inclusion criteria: (1) born at a gestational age 33 0/7 to 36 6/7 weeks for the late preterm infants and 38 0/7 weeks or more in the comparison group (term infants); (2) appropriate for gestational age; (3) without or requiring less than 12 hours of supplemental oxygen (including nasal cannula) or continuous positive airway pressure to maintain an adequate oxygen saturation; and (4) signed informed consent. Exclusion criteria included: (1) infants delivered to mothers who gave a history of smoking; (2) documented sepsis; (3) multiple congenital anomalies; (4) history of oligohydramnios; (5) congenital heart disease; and (6) evidence of respiratory distress syndrome (RDS) by chest radiograph or need for surfactant therapy. Gestational age was calculated using the date of last menstrual period confirmed by first trimester ultrasound, or if unavailable by the Ballard exam of the neonatologist or pediatrician (7). Late preterm infants had to be free of respiratory symptoms for at least four weeks prior to the outpatient testing at term corrected age.

A prospective cohort study design was used. Infants were studied in the supine position while quietly asleep, behaviorally determined by a stable body posture, regular respirations and a lack of eye movements. No sedation was used. The term infants in the comparison group were matched for race and sex to the late preterm infants. Pulmonary function was measured at 40 weeks of corrected age for both groups of infants. Late preterm infants had been discharged prior to this age, so they were tested in the infant pulmonary function laboratory as outpatients. Term infants in the comparison group were studied prior to discharge, within 72 hours of life, in a room designated for pulmonary function testing on the Mother Baby Unit at OHSU. One respiratory therapist performed all of the tests.

Measurements

Pulmonary function tests were measured with computerized infant pulmonary function carts (SensorMedics 2600; SensorMedics Inc, Yorba Linda, CA and Jaeger/Viasys Master Screen BabyBody; Yorba Linda, CA). The measurements were done with the infants breathing through a face mask that was connected to a 3-way valve (8-10). Passive respiratory system

compliance (Crs) was measured with the single-breath occlusion technique. The airway was briefly occluded at end inspiration until an airway pressure plateau was observed and the Hering Breuer reflex was invoked. The linear portion of the passive flow-volume curve was identified, and a regression line was drawn for the best fit. From the intercepts on the flow and volume axes, Crs and respiratory resistance (Rrs) were calculated. Acceptance criteria included: (1) stable end expiratory baseline; (2) plateau pressure lasting >100 milliseconds; (3) plateau pressure varying by ± 0.125 cm H₂O or less; (4) acceptable flow-volume curve by visual inspection, with linear data segment identified; and (5) at least 10 breaths accepted with a coefficient of variation of <20% (9-11).

The functional residual capacity (FRC) was measured by the nitrogen washout technique. Calibration was done with two known volumes, and a calibration line was constructed for the system at the specific flow rate. The infant was switched in at end expiration from his/her baseline fraction of inspired oxygen (21%) to 100% oxygen at the flow rate used for calibration. The calibration curve was then used to correlate the nitrogen washed out to the infant's FRC. The system corrected for dead space the FRC to body temperature, pressure, and water-saturated conditions. Total FRC was also related to body weight. Acceptance criteria included: (1) baby supine and quietly asleep; (2) test initiated at end expiration; (3) no evidence of leak on tracing of the washout; (4) consistent tracings; and (5) at least 3 measurements with a coefficient of variation <10% (8,9,12). A minimum of 50 flow-volume loops with inspiratory and expiratory volumes within 15% were collected to estimate tidal volumes and the expiratory flow ratio of $T_{PEF}:T_E$ (Jaeger/Viasys Master Screen BabyBody, Yorba Linda, CA) (13,14). These loops were collected during behaviorally determined quiet sleep and customarily collected in epochs of 20-30 breaths. Clinical outcome variables including time on continuous positive airway pressure (CPAP) and time on oxygen supplementation were also monitored.

Statistical Analyses

Our primary outcome was the difference in Crs measurements between the late preterm infants and the term infants. Hjalmarson et al (15) reported an approximate 40% difference in Crs between 32 "healthy" preterm infants born at a mean gestational age of 29.5 weeks (range of 25 to 33 weeks) compared with term infants. We hypothesized that the Crs in healthy infants born at 33-36 completed weeks of gestation would be approximately 30% different than the Crs in healthy term infants, when both groups were tested at term corrected age. We estimated a sample size of approximately 30 infants in each group to demonstrate a 30% difference in Crs between the groups with an 80% power and a type I error of 0.05.

The late preterm infants and term infants were matched for race and sex, and studied as closely as possible to 40 weeks of corrected gestational age. Both groups of infants were healthy with no clinical signs of respiratory disease.

Differences in continuous variables between the two groups were analyzed by Student's t-tests (two-tailed) and categorical variables were evaluated by the χ^2 test or Fisher's exact test where appropriate. To account for confounders, the pulmonary function data was further adjusted using general linear modeling (GLM) (16) for: socioeconomic status based on insurance coverage; family history of asthma; the z score for the infant's length at the time of study; and the corrected age of the infant at the time of study. These factors are all well known confounders of lung function and preterm delivery. In addition, the infant's weight at time of study, and important perinatal factors such as gestational age at delivery, birth weight, multiple gestation, antenatal steroid therapy, and preeclampsia were investigated. The infant's Z scores for anthropometric measurements were calculated from 2000 CDC growth charts (Epi Info v3.3.2) for the term group (17) and Fenton's preterm infant growth

charts for the preterm group (18). Data are presented as Mean $\pm$ SD, unless indicated otherwise. Data were analyzed with SPSS for Windows, version 19.0 (Chicago, IL) and SAS 9.2, SAS Institute Inc. (Cary, NC).

RESULTS

Thirty-one late preterm infants and 31 matched term infants were studied (Table I). There was no significant difference in family history of asthma, socioeconomic status, multiple gestation (2 sets of twins in the late preterm group and none in the comparison group), or rupture of membranes between the two groups of infants. As expected, there was a significantly higher incidence of preterm labor, pre-eclampsia, and antenatal steroid administration in the infants born late preterm. Both groups had a mean weight of approximately 3600 g and length of 51 cm at the time of study at 40 weeks (term) corrected age. The infants had comparable z scores for weight, but the late preterm infants had lower z scores for length. Only two of the late preterm infants and none of the term infants required any oxygen or any CPAP.

The healthy late preterm infants studied at term corrected age, had a significantly lower total respiratory compliance and respiratory compliance normalized for weight when compared with the term infants (Table II). There was no significant difference in the respiratory rate between the two groups. Similar to results of previous studies (15), the late preterm infants studied at term had a higher tidal volume during tidal breathing at 7.3 mL/kg versus 6.0 mL/kg in the term infants, as well as a higher total tidal volume at 26.8 mL vs 22.1 mL ($p < 0.05$). The late preterm infants had a significantly lower $T_{PTF}:T_E$ than the term infants and an increased total respiratory resistance ($p < 0.01$) when compared with term infants (Table II). Functional residual capacity was measured in 28 late preterm infants and 24 term patients, and there was no significant difference between the groups.

The analysis by general linear modeling demonstrated that socioeconomic status was significant when added to the model that contained being born late preterm versus being born at term in relation to pulmonary function measurements. Adjusting for socioeconomic status resulted in a larger estimate of the mean Crs difference (from 0.18 to 0.23) between the two groups. A family history of asthma, z score for length at time of study, and corrected age at study were not statistically significant when added to the model (Table III). Also, the infant's weight at study, gestational age at delivery, birth weight, multiple gestation, antenatal steroid therapy and preeclampsia were not significant when added to this model (data not shown).

DISCUSSION

The increased incidence of late preterm births has become a public health problem with epidemiologic data demonstrating their increased respiratory morbidity, particularly when compared with term infants (1-3,19). In contrast to very preterm infants, there is little data available in late preterm infants detailing their pulmonary function at birth and its evolution. Previous studies examining pulmonary function in preterm infants have evaluated a wide range of gestational ages and have included very premature infants, a known risk factor for subsequent respiratory disease (20). In this study, we have shown that a defined group of healthy late preterm infants born at 33 to 36 weeks of gestation and studied at 40 weeks have significantly lower respiratory compliance and expiratory flow ratio ($T_{PTF}:T_E$) when compared with term infants.

The strengths of our study include a well and tightly defined study population of healthy late preterm infants and reproducible, noninvasive testing techniques to document their

pulmonary function. The need for mechanical ventilation is a well known factor for volutrauma/ barotrauma and the subsequent development of bronchopulmonary dysplasia (9). We included only patients who had required less than 12 hours of oxygen or CPAP support, and only two of the late preterm infants and none of the term infants required either of these therapies. In utero smoke exposure also affects fetal lung structure and subsequent pulmonary function with decreased Crs, expiratory flow ratios, and forced expiratory flows (21-24). None of the mothers of our study subjects reported smoking during pregnancy or exposure to second hand smoke in the house. Although we matched the term infants to the late preterm infants for race and sex and studied both groups of infants as close to 40 weeks of age as possible, other important covariates can affect pulmonary function. We adjusted our results for potential confounding by socioeconomic status, family history of asthma, z scores for length at testing, corrected age at testing. A single course of antenatal steroid therapy is the standard of care for infants at risk for preterm delivery (24-34 weeks of gestation) and significantly increases Crs and FRC in treated preterm infants versus term infants when measured within 72 hours of age (8,9). Twenty three percent of the late preterm group received antenatal steroid therapy. However if antenatal steroids have long term structural effects, this would increase the measured Crs and FRC in the late preterm group and thus decrease the difference.

Other investigators have reported abnormal pulmonary function in premature infants delivered at a wide range of gestational ages. Hjalmarson et al (15) studied 32 healthy preterm infants who delivered between 25 to 33 weeks of gestation (mean gestational age of 29.5 weeks) and had required less than three days of oxygen. The premature infants were studied at a mean corrected age of 39.8 weeks and compared with 54 healthy full term infants. These preterm infants had a significantly decreased total respiratory compliance when compared with the term infants at 3.2 vs 5.4 mL/cm H₂O ($p < 0.001$). We found a significant, but less striking, difference in Crs between the late preterm and term infants, likely because our preterm infants were more mature with a mean gestational age at birth of 34.1 weeks. Merth et al (25) studied 26 healthy preterm infants in the first year of life who had been born between 26 and 36 weeks of gestation. They found no difference in static compliance normalized for length between preterm and term infants. However, the patients were studied at a wide range of corrected ages, weights, and lengths which could have introduced variability that likely reduced their ability to detect differences between the groups. Of clinical importance, studies have shown that reduced Crs measured at 1 month of age in infants born at >36 weeks of gestation was associated with persistent wheezing for the first 2 years of life (26) and Crs below the median after delivery was associated with a diagnosis of asthma at 10 years of age (13). Kotecha et al recently reported that former 33-34 week infants have significantly lower lung function at 8-9 years of age compared with children who had delivered at term (27). In this study, the pulmonary function tests in the 33-34 week preterm infants were more similar to former 25-32 weeks infants than in term infants when all were tested at 8-9 years old.

In addition to decreased Crs, the late preterm infants in our study demonstrated a significantly decreased $T_{PTEF}:T_E$, increased Rrs, and a higher tidal volume when compared with the term infants. The expiratory flow ratio of $T_{PTEF}:T_E$ reflects the degree to which expiration is modulated, and a decreased ratio is thought to be a reflection of expiratory airflow limitation. A decrease in this ratio in the newborn period preceded and predicted subsequent wheezing. Martinez et al (28) reported an increased rate of recurrent wheezing at 1 and 3 years age in infants who had reduced $T_{PTEF}:T_E$ at birth. Hoo et al (21) also reported decreased $T_{PTEF}:T_E$ values in infants with family histories of asthma and parental smoking. Most recently, Haland et al (13) found an association between reduced $T_{PTEF}:T_E$ measured shortly after birth in 880 term infants and a significantly increased risk for developing asthma at 10 years of age. $T_{PTEF}:T_E$ was influenced by several factors including postnatal age

(14), thus the decreased flow ratio demonstrated in the group of late preterm infants in the present cohort could represent expiratory airflow limitation and/or the impact of postnatal age when compared with the term infants. The preterm infants could also have comparable peak flows at the same time point after initiating expiration, but may have a longer expiratory time therefore resulting in a lower $T_{PTEF}:T_E$ compared with the term infants. Because the preterm infants had a larger tidal volume, they may have needed additional expiratory time to maintain their functional residual capacity. However, we studied both groups at the same corrected age and they had a comparable respiratory rate. We also found an increased Rrs in our late preterm infants compared with the term infants, which supports our findings of decreased $T_{PTEF}:T_E$ in the late preterm infants. There can be large inpatient variability in the measurement of $T_{PTEF}:T_E$, however our values are comparable with those reported by Hoo et al (21) in preterm infants. The findings of a higher total tidal volume as well as higher tidal volume normalized for body weight in the late preterm infants is similar to the results reported by Hjalmarson et al (15) in more preterm infants (25-33 weeks' gestation). These investigators were also able to measure alveolar ventilation and demonstrated that although the premature infants had larger tidal volumes than the term infants, the two groups had similar alveolar ventilation. They hypothesized that the preterm group had larger tidal volumes because of increased dead space (15). Our findings of decreased pulmonary function at term age support that longitudinal studies in late preterm infants are needed to follow changes in pulmonary function testing and correlate these changes to clinical outcomes.

We acknowledge several limitations to our study. Recently the American Academy of Pediatrics designated late preterm infants as those infants born between the gestational ages of 34 0/7 to 36 6/7 weeks (29). Because pulmonary maturation is a continuum and the gestational age cutoff may be an arbitrary one, we chose to expand the definition of the late preterm infant for this study to include patients down to 33 weeks of gestation. We were able to measure FRC successfully in 52 patients (84%) from the entire cohort due to limited stable sleep state. Because our sample size was based on changes in respiratory compliance, we may lack an adequate sample size to comment conclusively on the apparent lack of significant differences in FRC between the groups.

In conclusion, healthy late preterm infants delivered at 33-36 weeks of gestation have a significantly decreased passive respiratory compliance and expiratory flow ratio ($T_{PTEF}:T_E$), compared with term infants matched for race and sex. These results suggest that late preterm infants may have delayed or abnormal pulmonary development compared with term infants and thus may be at greater risk for later pulmonary problems. The increased incidence of late preterm infant births and their associated increased health care costs raises the question of the need for longitudinal pulmonary function evaluation to assess impact on clinical outcomes, and to provide an opportunity to identify infants who may benefit from intervention to reduce the risk of long term pulmonary morbidity.

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ABBREVIATIONS

CPAP	Continuous positive airway pressure
Crs	Passive respiratory system compliance
FiO ₂	Fractional inspired oxygen concentration

FRC	Functional residual capacity
LPI	Late preterm infants
PFT	Pulmonary function test
RDS	Respiratory distress syndrome
T_{PTEF}:T_E	Time to peak tidal expiratory flow to expiratory time

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Table 1**Maternal and Infant Demographics**

	Preterm (n = 31)	Term (n = 31)	P
Maternal age (y) *	29.6 ± 6.8	28.8 ± 6.0	NS
Caucasian (%)	17 (55)	17 (55)	NS
Maternal smoking (%)	0 (0)	0 (0)	NS
Public insurance (%)	15 (48)	21 (68)	NS
Asthma in immediate family (%) [#]	7/28 (25)	6/29 (21)	NS
Rupture of membranes (hours) **	0 (0-9)	0 (0-7.8)	NS
Preterm labor (%)	16 (52)	1 (3.2)	<0.05
Pre-eclampsia (%)	11 (35)	1 (3.2)	<0.05
Antenatal steroid therapy (%)	7 (23)	1 (3.2)	<0.05
NSVD (%)	12 (39)	18 (58)	NS
1-min Apgar **	8 (7-9)	8 (7-9)	NS
5 min Apgar **	9 (9-9)	9 (8-9)	NS
Birth weight (g) *	2150 ± 400	3561 ± 436	<0.05
Gestational age (wks) *	34.1 ± 1.0	39.3 ± 0.9	<0.05
Female (%)	17 (55)	17 (55)	NS
Corrected age at study (wks) *	40.8 ± 1.6	39.5 ± 1.0	<0.05
Weight at study (g) *	3669 ± 539	3536 ± 465	NS
Z score for weight at study *	0.05 ± 0.99	0.11 ± 0.95	NS
Length at study (cm) *	50.6 ± 2.7	51.1 ± 2.5	NS
Z score for length at study *	-0.09 ± 0.98	0.44 ± 0.95	<0.05
Needing any oxygen or CPAP (%)	2 (6)	0 (0)	NS

* Mean ± SD

[#] Data available on 28 late preterm and 29 term infants

** Median (25th-75th percentiles). NSVD, normal spontaneous vaginal delivery; CPAP, continuous positive airway pressure; NS, not significant.

Table 2**Pulmonary Function Measurements**

	Preterm (n = 31)	Term (n = 31)	95% CI**	P**
Respiratory rate (br/min) *	54 ± 11	54 ± 13	(-5.16, 6.69)	NS
Crs (mL/cmH ₂ O/kg) *	1.14 ± 0.29	1.32 ± 0.36	(0.05, 0.46)	0.0144
Crs (mL/cmH ₂ O) *	4.13 ± 0.96	4.66 ± 1.17	(0.07, 1.43)	0.0306
T _{PTEF} :T _E *	0.308 ± 0.09	0.423 ± 0.11	(0.03, 0.15)	0.0033
FRC (mL/kg) *, #	24.6 ± 5.1	26.1 ± 4.3	(-0.53, 5.86)	NS
FRC (mL) *, #	90.6 ± 22.5	91.0 ± 19.4	(-8.81, 18.71)	NS
Rrs (cmH ₂ O/mL/sec) *	0.064 ± 0.029	0.043 ± 0.011	(-0.04, -0.01)	0.0049

* Mean ± SD

FRC measurements done in 28 late preterm and 24 term infants. Crs, respiratory compliance; T_{PTEF}:T_E, time to peak tidal expiratory flow: expiratory time; FRC, functional residual capacity; Rrs, respiratory resistance; NS, not significant.

** Values for term versus late preterm infants adjusted for socioeconomic status, family history of asthma, corrected age and z score for length at testing.

Table 3

Effect of Individual Covariates on Respiratory Compliance/kg

Model	Covariate slope coefficient			Delivery (<u>Term-Preterm</u>)	
	Estimate	(95% CI)	p	Effect	p
Term vs Premature				0.18	.0304
Term vs Premature + sec ^a	0.20	(0.03 to 0.30)	0.02	0.23	.0072
Term vs Premature + asthma ^b	0.07	(−0.48 to 0.70)	0.52	0.15	.0840
Term vs Premature + length z score ^c	−0.05	(−0.14 to 0.03)	0.27	0.19	.0325
Term vs Premature + corrected age ^c	0.04	(−0.02 to 0.11)	0.20	0.24	.0124

^a is socioeconomic status as portrayed by insurance

^b is family history of asthma

^c refers to length z score and corrected age at time of study