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Lung function at term in extremely preterm-born infants: a regional prospective cohort study

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ABSTRACT

Objectives To compare lung function of extremely preterm (EP)-born infants with and without bronchopulmonary dysplasia (BPD) with that of healthy term-born infants, and to determine which perinatal characteristics were associated with lung function at term and how predictive these measurements were for later respiratory health in EP-born infants.

Methods Perinatal variables were recorded prospectively, and tidal breathing parameters were measured at term-equivalent age using electromagnetic inductance plethysmography. Respiratory morbidity was defined by hospital readmissions and/or treatment with asthma medications during the first year of life.

Results Fifty-two EP-born infants (mean gestational age 26^1, range 22^6–27^6 weeks) and 45 term-born infants were included. There was evidence of significant airway obstruction, higher tidal volumes and increased minute ventilation in the EP-born infants with and without BPD, although generally more pronounced for those with BPD. Male gender, antenatal steroids and number of days on continuous positive airway pressure were associated with lung function outcomes at term. A prediction model incorporating two unrelated tidal breathing parameters, BPD, birth weight z-score and gender, predicted respiratory morbidity in the first year of life with good accuracy (area under the curve 0.818, sensitivity and specificity 81.8% and 75.0%, respectively).

Conclusion Lung function measured at term-equivalent age was strikingly abnormal in EP-born infants, irrespective of BPD. Tidal breathing parameters may be of value in predicting future pulmonary health in infants born premature.

Trial registration number NCT01150396; Results.

Strengths and limitations of this study

- ► This is one of very few studies from this decade comparing lung function in infants born extremely preterm and healthy term-born infants using tidal breathing parameters.
- ► The data reflect infants' natural breathing pattern, with no disturbances from sedation or a face mask, which has been applied in most previous studies.
- ► The applied measuring device is relatively new and the number of participants is relatively low, and the results should therefore be tested in larger studies.

INTRODUCTION

Survival after extremely preterm (EP) birth, that is, before 28 weeks' gestational age (GA), has steadily increased since the 1970s, and most infants born after 24–25 weeks' GA are now discharged alive from well-equipped neonatal intensive care units (NICUs). When born EP, the normal in utero pulmonary development is disrupted in a vulnerable phase,[1–4] and gas exchange must take place in developmentally fetal lungs. Combined effects from pulmonary immaturity and the trauma inflicted by life-saving neonatal interventions lead to inflammatory responses that disturb lung growth and development. The result is altered lung structure with alveolar hypoplasia, disrupted pulmonary vasculature and interstitial cell proliferation.[5]

Respiratory outcome in EP-born neonates is heterogeneous and insufficiently understood, and predictors for later respiratory health are poorly defined. Bronchopulmonary dysplasia (BPD) is defined by the use of oxygen supplementation at specific time points, and has long been used as a predictor of subsequent increased risk of respiratory disease.[6] However, it is now increasingly recognised that BPD is a relatively poor measure of neonatal lung injury.[7–11] Thus, new and feasible diagnostic methods are needed to improve our understanding of lung injury in these vulnerable infants and to enhance our ability to predict their later respiratory health. Such knowledge is also needed to objectively assess interventions aimed at early prevention and treatment of lung disease.

In this study we compared lung function at term-equivalent age in EP-born and healthy term-born infants using tidal breathing parameters obtained with electromagnetic inductance plethysmography (EIP). The aim was to investigate if, in what way, and to what extent, survivors of EP birth exhibit lung function abnormalities, and if infants with and without BPD differ in that respect. Additionally, we explored if lung function at term was associated with perinatal clinical characteristics or with respiratory morbidity during the first year of life.

METHODS

Subjects and study design

This study was part of a larger, prospective, population-based cohort study (project extreme prematurity; BabyPEP) that has been ongoing since 2011 in two tertiary referral hospitals in Western Norway (Haukeland University Hospital and Stavanger University Hospital). Women with threatening preterm delivery before 28 weeks' gestation are invited, and the infants are included if they are born before 28 weeks' GA. Detailed prenatal, perinatal and neonatal history, examinations and treatments are consecutively recorded in a database during the hospital stay. At discharge or term age, whatever comes first, the lung function is assessed by EIP. Follow-up at 3, 6 and 12 months' corrected age, that is, age calculated from expected term birth, includes clinical examinations and parental questionnaires addressing various problems, including respiratory symptoms and treatments.

Additionally, 45 healthy infants born at term (37–41 weeks' GA) at Haukeland University Hospital in the period of November 2015–March 2016 were recruited as controls. Infants returning to the maternity outpatient clinic for routine metabolic screening or weight control on days when our study nurse was available were asked to participate, provided they appeared healthy and breathed without efforts. Exclusion criteria were significant perinatal disease, malformations or syndromes.

Definitions

BPD was defined as being dependent on oxygen supplementation at 36 weeks' GA.[6] Oxygen supplementation was provided according to similar algorithms in the two participating NICUs, and usually by low-flow nasal cannulas guided by pulse oximetry targeting 90%–95% saturation at 36 weeks' GA.

Small for gestational age (SGA) was defined as birth weight (BW) <10th percentile for GA according to Norwegian growth curves.[12] z-Scores for BW were calculated with reference to the 2013 Fenton growth charts.[13]

Respiratory morbidity during the first year of life was defined by need for hospital readmission because of respiratory symptoms and/or parental report of treatment with inhaled asthma medications.

Lung function measurements

Lung function was measured using EIP, made commercially available by VoluSense (Bergen, Norway). The EIP system basically consists of an electromagnet and a patient vest encircling the torso in order to quantify chest and abdominal volume changes. EIP does not require sedation and allows continuous and prolonged recording of respiratory data without using a face mask. Data were obtained as described previously,[14] partly (in the period from 2011 to 2013) by using the first released version from VoluSense (FloRight),[15–20] and partly by using the upgraded version released in 2015 (VoluSense Pediatrics, VSP).

The infants were dressed in the appropriate-sized vest selected according to their armpit–hip length. All measurements were performed with the baby quietly awake or asleep and in supine position in a cot. No sedation was used, but some of the infants were given oral sucrose for relaxation. Tidal breathing was recorded for 5–10 min.

Analysis of flow volume loops

The traces were inspected visually to select a minimum of 50 stable breaths based on the following criteria: (1) no obvious artefacts, (2) no sighs and (3) no obvious changes in the depth of breathing or baseline. The following tidal breathing parameters were calculated and averaged by the computer software: tidal volume (Vt), minute ventilation (V'E), respiratory rate (RR), peak tidal expiratory flow (PTEF), time to peak tidal expiratory flow as a ratio of total expiratory time (Tptef/Te), ratio of tidal expiratory flow at 50% of expired volume to peak tidal expiratory flow (TEF_{50}/PTEF), ratio of tidal expiratory flow at 75% of expired volume to peak tidal expiratory flow (TEF_{75}/PTEF) and flow volume gravity (FVg), described in details previously.[20] Weight at measurement differed between groups, and hence data for volume and flow parameters were related to body weight.

Statistical methods

Data were analysed and graphs created with SPSS V.22 and MedCalc V.13.1 (MedCalc Software, Mariakerke, Belgium). Power calculations were based on the tidal breathing parameter Vt/kg, with data on distribution obtained from a previous study.[20] It was estimated that 44 infants were needed in each group to provide a power of 80% to show a 20% difference (0.6 SD) between the EP and term-born groups. After testing for normal distribution, groups were compared by independent samples t-tests or Mann-Whitney U tests, as appropriate. Categorical data were analysed with the X^2 test. Differences between the EP-born and term-born control group in terms of gender, GA at the time of measurement as well as body weight at the time of measurement were adjusted for in multiple regression analyses. We used linear regression analyses to assess if perinatal variables were associated with lung function at term. The following tidal breathing parameters were tested as outcomes: Vt/kg, RR, V'E/kg, PTEF/kg, TEF_{50}/PTEF and Tptef/Te. Potential explanatory variables were first entered into univariate models, and those associated with outcome with p<0.10 were entered into multivariate backward stepwise linear regression analyses. Receiver-operator characteristic (ROC) analyses were used to assess the ability of tidal breathing parameters and selected clinical variables to discriminate between groups, and to predict respiratory morbidity during the first year of life. To create the best possible prediction model of later respiratory morbidity, we estimated a prognostic score (predicted probabilities) using multiple logistic regression incorporating two unrelated tidal breathing parameters (TEF_{50}/PTEF and Vt/kg), BPD, BW z-score and gender. This prognostic score was subsequently used as the independent variable in an ROC analysis, while respiratory morbidity in the first year of life was used as the dependent variable.

Approvals

The study was approved by the Regional Committee on Medical Research Ethics of Western Norway (REC West) and reported to the ClinicalTrials.com (ID NCT01150396).

RESULTS

Subjects

All EP-born infants born during the time periods we had the EIP method available (FloRight or VSP) and survived to be discharged were included: 41 at Haukeland University Hospital and 11 at Stavanger University Hospital. Clinical characteristics and perinatal data are provided in table 1. FloRight was used in 33 (63%) and VSP in the remaining 19 EP-born infants and all the 45 term-born controls. There were no differences between test results obtained using FloRight and VSP in comparable preterm-born groups (see online supplementary table S1).

Comparisons of tidal breathing parameters and discrimination between groups

All EP-born versus term-born control infants

Mean GA and body weight at the time of lung function assessment and the proportion of male were lower in the EP-born than the term-born group, and thus adjusted for in the regression analyses (table 2). Vt/kg, RR, V'E/kg and PTEF/kg were higher while the variables indicating airway obstruction (TEF_{50}/PTEF, TEF_{75}/PTEF, Tptef/Te and FVg) were all lower in the EP-born compared with the term-born control group (table 2). ROC analyses

Table 1 Perinatal data* of the infants studied (n=52)

	All preterm-born infants	Preterm-born infants without BPD	Preterm-born infants with BPD	p Value†
Number of subjects	52	20 (38%)	32 (62%)	
Male gender	18 (35%)	8 (40%)	10 (31%)	p=0.73
Gestational age at birth, weeks	26* (22–27)	26† (24‡–27)	25 (22–27§)	p=0.33
Birth weight, g	788 (370–12 809)	909 (650–1280)	713 (370–1045)	p<0.0005
Birth weight z-score	−0.17 (−2.58 to 1.88)	0.40 (−0.53 to 1.80)	−0.53 (−2.58 to 1.88)	p=0.004
Small for gestational age§	12 (23%)	0	12 (38%)	p=0.005
Antenatal steroids	48 (92%)	18 (90%)	30 (94%)	p=0.99
Chorioamnionitis	10/18 (56%)	12/30 (40%)	22/48 (45.8%)	p=0.79
Latency, days§	3.4 (0–55)	5.1 (0–55)	2.3 (0–21)	p=0.28
Caesarean section	27 (52%)	8 (40%)	19 (59%)	p=0.29
Apgar score 1 min	4.4 (1–9)	4.5 (1–9)	4.4 (1–9)	p=0.87
Apgar score 5 min	6.0 (1–9)	6.0 (2–9)	6.0 (1–9)	p=0.97
Surfactant, treated	48 (92%)	16 (80%)	32 (100%)	p=0.036
Patent ductus arteriosus, treated	17 (33%)	8 (40%)	9 (28%)	p=0.55
Septicaemia, verified or suspected	22 (42%)	5 (25%)	17 (53%)	p=0.089
Mechanical ventilation, days	6.6 (0–33)	2.7 (0–11)	9.1 (0.5–33)	p=0.004
CPAP or HFNC, days	48.7 (13–75)	38 (13–62)	55.4 (31–75)	p<0.0005
Supplementary oxygen, days	75.6 (0–127)	53.5 (0–79)	89.4 (61–127)	p<0.0005
Postnatal steroids	14 (26.9%)	0	14 (44%)	p=0.0016
Pathological chest X-ray at PMA 36 weeks	21/42 (50%)	7/18 (39%)	14/24 (58%)	p=0.36

*Means with ranges, or numbers (%).
†Independent samples t-tests, Mann-Whitney U test or X^2 test.
‡Days from rupture of membranes to delivery.
§Birth weight <10th percentile for gestational age.
BPD, bronchopulmonary dysplasia; CPAP, continuous positive airway pressure; HFNC, high-flow nasal cannulae; PMA, postmenstrual age.

Table 2 Lung function at term-equivalent age in all infants

	Healthy term-born controls (n=45)	All extremely preterm-born infants* (n=52)	Preterm-born infants without BPD* (n=20)	Preterm-born infants with BPD† (n=32)
Male gender	24 (53.3%)	18 (34.6%) p=0.035	8 (40%) p=0.28	10 (31.3%) p=0.73
Gestational age at time of measurement, weeks (ranges)	40.6 (37.3–43.1)	38.8 (36.0–42.9) p<0.001	38.7 (36.1–41.3) p<0.0001	38.9 (36.0–42.9) p=0.50
Postnatal age in days (ranges)	6.5 (3–21)	88.9 (60–115) p<0.001	86.9 (62–103) p<0.0001	90.2 (60–115) p=0.42
Body weight at time of measurement, g (ranges)	3494 (2465–4700)	2768 (1900–3800) p<0.001	2862 (2177–3800) p<0.0001	2709 (1900–3500) p=0.22
Vt (mL)/kg	4.6 (4.3 to 4.9)	6.0 (5.5 to 6.5) p=0.019	5.8 (5.0 to 6.6) p=0.026	6.1 (5.3 to 6.8) p=0.63
RR (/min)	58.2 (54.6, 61.9)	67.8 (63.4, 72.2) p=0.012	71.1 (62.8, 79.4) p=0.002	65.7 (60.7, 70.8) p=0.23
V’E (mL)/kg	258.5 (236.4 to 280.6)	394.0 (358.1 to 429.8) p<0.0001	405.0 (336.7 to 473.3) p<0.0001	387.1 (344.3 to 429.9) p=0.63
PTEF (mL/s)/kg	14.2 (12.5 to 15.9)	27.5 (24.6 to 30.5) p<0.0001	25.6 (21.3 to 30.0) p<0.0001	28.7 (24.6 to 32.8) p=0.31
TEF_{50}/PTEF (%)	84.1 (82.2 to 86.0)	78.2 (75.9 to 80.4) p=0.008	81.6 (78.7 to 84.4) p=0.51	76.1 (73.0 to 79.1) p=0.015
TEF_{75}/PTEF (%)	67.6 (64.5 to 70.7)	53.1 (48.7 to 57.5) p<0.0001	59.9 (53.8 to 66.1) p=0.026	48.8 (43.1 to 54.5) p=0.012
Tptef/Te (%)	40.9 (37.6 to 44.3)	30.1 (26.4 to 33.8) p<0.0001	35.1 (29.2 to 41.1) p=0.056	26.9 (22.2 to 31.6) p=0.029
FVg	0.48 (0.47 to 0.49)	0.44 (0.43 to 0.45) p<0.0001	0.46 (0.44 to 0.48) p=0.019	0.43 (0.42 to 0.45) p=0.013

Data are presented as means with 95% CIs, unless stated otherwise.
*Significance tested versus the term-born control group and adjusted for differences in terms of GA and body weight at the time of measurement.
†Significance tested versus the EP-born group without BPD.
BPD, bronchopulmonary dysplasia; EP, extremely preterm; FVg, expiratory flow volume loop centre of gravity (dimensionless); GA, gestational age; PTEF, peak tidal expiratory flow; RR, respiratory rate; TEF_{50}/PTEF, flow at 50% expired volume as a per cent of PTEF; TEF_{75}/PTEF, flow at 75% expired volume as a per cent of PTEF; Tptef/Te, time to peak tidal expiratory flow as a ratio of total expiratory time; V’E, minute ventilation; Vt/kg, tidal volume per kilogram body weight.

showed that most tidal breathing parameters discriminated between the EP-born and term-born control groups (figure 1).

Non-BPD versus term-born control infants

As for the complete EP-born group, Vt/kg, RR, V’E/kg and PTEF/kg were significantly higher and TEF_{75}/PTEF and FVg were significantly lower in the non-BPD group when compared with the term-born control group; however, they were numerically less pronounced (table 2). TEF_{50}/PTEF and Tptef/Te did not differ significantly.

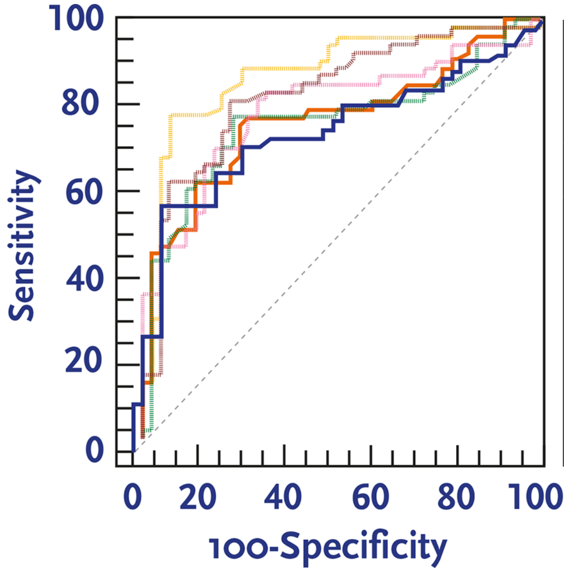
BPD versus non-BPD infants

Thirty-two (62%) of the 52 EP-born infants had BPD (table 1). The BPD infants had lower mean BW, and higher proportions were SGA and treated with surfactant and postnatal corticosteroids compared with infants without BPD. The BPD infants also required more days on mechanical ventilation, continuous positive airway pressure (CPAP) or high-flow nasal cannulas (HFNC), and supplementary oxygen.

TEF_{50}/PTEF, TEF_{75}/PTEF, Tptef/Te and FVg were all lower in the infants with BPD (table 2), but on ROC analyses none of these tidal breathing parameters could distinguish better between infants with and without BPD than the clinical variables ‘days on mechanical ventilation’, ‘days on CPAP/HFNC’ and ‘BW z-scores’ (figure 2).

Perinatal clinical determinants of tidal breathing parameters in EP-born infants

Explanatory variables associated with one or more of the tidal breathing outcome parameters in univariate linear regression analyses are provided in the online supplementary table S2. In the multivariate regression model, male gender was related to lower (more obstructive)



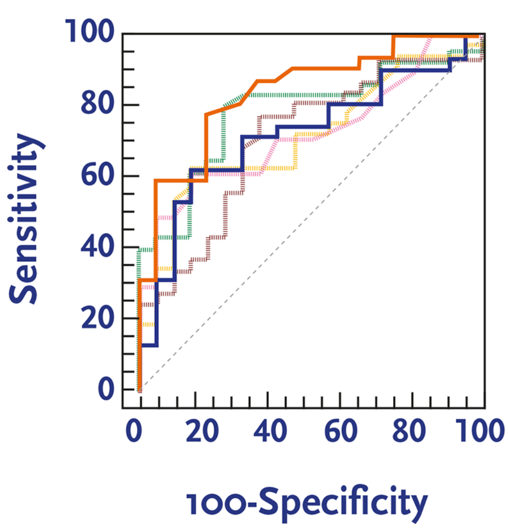
	Tidal breathing parameter	AUC with 95% CI	Optimal cut-off point	Sensitivity	Specificity
	Vt/kg	0.742 (0.643, 0.825)	5.64	57.7	93.3
	V'E/kg	0.829 (0. 739, 0.898)	282.7	80.8	77.8
	PTEF/kg	0.881 (0.800, 0.938)	19.98	76.9	93.3
	Tptef/Te	0.760 (0.663, 0.841)	34.4	76.9	77.8
	TEF_{75}/PTEF	0. 790 (0.696, 0.866)	64.7	80.8	71.1
	FVg	0.767 (0.671, 0.847)	0.463	75.0	75.6

Figure 1 Receiver-operator characteristic (ROC) curves comparing the ability of different tidal breathing parameters to discriminate between extremely preterm-born infants (n=52) and healthy term-born controls (n=45). If the 95% CI of the area under the ROC curve (AUC) includes 0.5 (no discrimination), the tested variable does not distinguish between the two groups. The optimal cut-off point is the point for which sensitivity+specificity is maximal. For abbreviations of lung function variables, please see list in table 2.

TEF_{50}/PTEF and Tptef/Te, as well as lower RR, whereas number of days on CPAP/HFNC was related to lower RR and lower TEF_{50}/PTEF. Antenatal treatment with steroids was related to lower (more normal) Vt/kg. The results from the multivariate regression model are shown in table 3. Neither SGA nor BW z-score influenced the lung function measures (see online supplementary table S2 and table S3).

Prediction of later respiratory morbidity

At the time of data analysis, 35 of the 52 EP-born children had reached a corrected age of 1 year, and 11 (31%) of them had either been hospitalised and/or treated with asthma medication. Mean TEF_{50}/PTEF was significantly lower and TEF_{75}/PTEF, Tptef/Te and FVg tended to be lower in the group with respiratory morbidity (table 4). The ROC analyses showed that the tidal breathing variable TEF_{50}/PTEF, but not BPD, predicted respiratory morbidity during the first year of life (figure 3). The prediction model that incorporated TEF_{50}/PTEF, Vt/kg, BPD, BW z-score and gender gave an area under the curve (AUC) of 0.818 (95% CI 0.651 to 0.928), predicting respiratory morbidity in the first year of life with a sensitivity and specificity of 81.8% and 75.0%, respectively.



		AUCwith 95% CI	Optimal cut-off point	Sensitivity	Specificity
	Tptef/Te	0. 727 (0.585, 0.841)	25.7	62.5	85.0
	TEF_{50}/PTEF	0. 715 (0.573, 0.831)	82.0	78.1	65.0
	FVg	0. 710 (0.568, 0.828)	0.426	59.4	85.0
	BWz-score	0. 793 (0.658, 0.893)	0.04	81.2	75.0
	Ventilation days	0. 736 (0.595, 0.848)	4.0	62.5	85.0
	CPAP/HFNC days	0.840 (0. 712, 0.927)	44	78.1	80.0

Figure 2 Receiver-operator characteristic (ROC) curves comparing the ability of tidal breathing parameters and clinical variables to discriminate between extremely preterm-born infants with and without bronchopulmonary dysplasia. If the 95% CI of the area under the ROC curve (AUC) includes 0.5 (no discrimination), the tested variable does not distinguish between the two groups. The optimal cut-off point is the point for which sensitivity+specificity is maximal. For abbreviations of lung function variables, please see list in table 2.

Table 3 Final multivariate regression model* testing relations between perinatal variables and lung function parameters at term in extremely preterm-born infants (n=52)

	Multivariable model			
	Coefficient	95% CI	p Value	
Vt/kg (mL)				
Antenatal steroids	−2.4	−4.3 to 0.5	0.014	Adjusted R^2=10%
RR (/min)				
Male gender	−7.6	−15.9 to 0.65	0.070	Adjusted R^2=19%
Days of CPAP/HFNC	−0.45	−0.72 to 0.19	0.001	
Tptef/Te (%)				
Male gender	−7.1	−14.7 to 0.5	0.07	Adjusted R^2=5%
TEF_{50}/PTEF (%)				
Male gender	−5.8	−9.9 to 1.6	0.007	Adjusted R^2=23%
Days of CPAP/HFNC	−0.22	−0.35 to 0.09	0.002	

*Explanatory variables that were associated with a p<0.10 in univariable analyses were included in the final multivariate regression model (ie, male gender, birth weight z-score, antenatal steroids, days of CPAP/HFNC and days of oxygen). Only variables associated with one or more of the tidal breathing outcome parameters in the final model (p<0.10) are presented in the table.
CPAP, continuous positive airway pressure; HFNC, high-flow nasal cannulas; PTEF, peak tidal expiratory flow; RR, respiratory rate; TEF_{50}/PTEF, flow at 50% expired volume as a per cent of PTEF; Tptef/Te, time to peak tidal expiratory flow as a ratio of total expiratory time; Vt/kg, tidal volume per kilogram body weight.

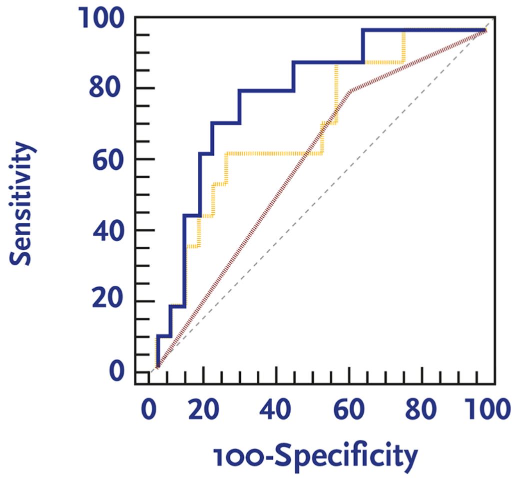
DISCUSSION

The EP-born infants had primarily obstructive pulmonary abnormalities at term-equivalent age when compared with healthy term-born controls. Lung function abnormalities were present irrespective of BPD, although more pronounced within the BPD group. Male gender and days on CPAP/HFNC were associated with airway obstruction at term, while treatment with antenatal steroids was associated with lower Vt, that is, more similar to the control group. The parameter TEF_{50}/PTEF, which reflects airway obstruction, showed a promising ability to predict respiratory morbidity during the first year of life in infants born EP. A compound prediction model, incorporating TEF_{50}/PTEF, Vt/kg, BPD, BW z-score and gender, showed the best accuracy to predict respiratory morbidity in the first year of life (AUC=0.818, 95% CI 0.651 to 0.928).

Table 4 Presence or absence of respiratory morbidity during the first year of life* dependent on early clinical characteristics and lung function data obtained at near-term gestational age after extremely preterm birth

	Respiratory morbidity (n=11)	No respiratory morbidity (n=24)	p Value†
Gestational age at birth	25.6 (24.5 to 26.7)	25.9 (25.4 to 26.4)	0.53
Birth weight z-score	−0.21 (−1.11 to 0.70)	−0.29 (−0.60 to 0.02)	0.81
Male gender	4 (36.4%)	8 (33.3%)	0.84
Pathological chest X-ray at term	3/8 (37.5%)	12/19 (63.2%)	0.42
Diagnosis of BPD	8/11 (72.7%)	15/24 (62.5%)	0.84
Vt/kg (mL/kg)	5.5 (4.4 to 6.6)	5.9 (4.9 to 6.8)	0.63
RR (/min)	67.7 (58.7 to 76.8)	66.2 (59.2 to 73.2)	0.79
V'E/kg (mL/kg/min)	366.2 (286.3 to 446.0)	378.6 (318.0 to 439.2)	0.80
PTEF/kg (mL/s/kg)	26.8 (19.0 to 34.6)	27.2 (22.3 to 32.1)	0.93
Tptef/Te (%)	25.8 (19.2 to 32.5)	34.2 (27.2 to 41.2)	0.13
TEF_{50}/PTEF (%)	73.5 (68.5 to 78.6)	79.9 (76.6 to 83.1)	0.03
TEF_{75}/PTEF (%)	47.9 (40.5 to 55.2)	56.5 (48.5 to 64.5)	0.17
FVg	0.43 (0.41 to 0.46)	0.45 (0.43 to 0.47)	0.21

*Defined by the need for hospital readmission because of respiratory symptoms and/or a parental report of treatment with inhaled asthma medications. Data are given as means with 95% CIs or numbers (% in brackets).
†Independent sample t-tests or the X^2 test.
BPD, bronchopulmonary dysplasia; RR, respiratory rate; V'E, minute ventilation; Vt/kg, tidal volume per kilogram body weight.



		AUC with 95% CI
	Compound model	0.818 (0.651, 0.928)
	BPD	0.617 (0.438, 0.776)
	TEF_{50}/PTEF	0. 723 (0.547, 0.861)

Figure 3 Receiver-operator characteristic (ROC) curves comparing the ability of TEF_{50}/PTEF and BPD, and additionally a compound model incorporating TEF_{50}/PTEF, Vt/kg, BPD, birth weight z-score and gender, used to predict development of respiratory distress requiring readmission or treatment with asthma medication during the first year of life of extremely preterm-born individuals (n=35). The compound model achieved the best sensitivity and specificity, that is, respectively, 81.8% and 75.0% at a cut-off value of 0.34. If the 95% CI of the AUC includes 0.5 (no discrimination), the parameter does not predict later respiratory distress. The optimal cut-off point is where the sensitivity and specificity are maximal. This value corresponds with the point on the ROC curve farthest from the diagonal line. AUC values for other breathing parameters and clinical variables are given in (online supplementary table S4). AUC, area under the curve; BPD, bronchopulmonary dysplasia; TEF_{50}/PTEF, ratio of tidal expiratory flow at 50% of expired volume to peak tidal expiratory flow; Vt/kg, tidal volume per kilogram body weight.

Strengths and limitations

This is one of few studies comparing lung function in EP and healthy term-born infants using tidal breathing parameters obtained with a non-invasive method that does not involve sedation and/or the application of a face mask. In our opinion, the use of this method is an important strength of this study, since a face mask inevitably adds dead space and alters the breathing pattern of the baby, possibly in different ways in health and disease.[21–24] None of the participants in this study were sedated, and the data reflect the infant's natural breathing pattern. As few studies have applied comparable methods, our data cannot easily be compared with those of others. The mean GA and body weight at the time of the measurements and the gender ratio differed slightly between the EP and term-born groups, characteristics that may have influenced the findings, although adjustments did not influence statistical conclusions. Unfortunately, the manufacturer upgraded the equipment during the study and we were forced to comply. However, we found no systematic differences between the two models for any of the tidal breathing parameters, suggesting that bias was not introduced. A relatively low number of participants made the study vulnerable to type II statistical errors, possibly explaining some of the non-significant differences, for example, no difference in respiratory morbidity in the first year of life between infants with and without a neonatal diagnosis of BPD (table 4 and figure 3). Finally, differences regarding birth year between the EP and term-born infants (2011–2013 and 2015–2016 vs 2015–2016, respectively) and the use of a convenience sample as control group were weaknesses that possibly may have influenced outcome.

Comparisons of tidal breathing parameters and discrimination between groups

Vt and V'E were higher in the EP than in the term-born group. This corresponds with the findings of Olden *et al*,[15] who also used EIP and found the mean Vt/kg was 5.4 mL in healthy term-born infants and 7.0 mL in prematurely born infants with BPD. Increased Vt is also consistent with results from studies using the multiple-breath washout method.[10 25] However, it contrasts the findings of studies where tidal breathing parameters were assessed with mask-based methods, such as the studies by Schmalisch *et al*[26] and Hjalmarson and Sandberg.[27] They found that preterm-born infants with chronic lung disease had *lower* Vt compared with term-born controls, and that a higher V'E was instead related to a substantially higher RR. Higher V'E in EP-born infants is compatible with the histological picture of BPD with few but large alveoli and a cell-rich interstitial space,[5] and thus presumably a greater physiological dead space ventilation that necessitates larger exchanges of volumes to maintain adequate gas exchange. To conclude on this issue, our data suggest that a *combination* of increased Vt and RR is the most likely adapted breathing pattern in EP-born infants. Increased Vt may not be captured by mask-based measurements as the face mask alters the breathing pattern.

Evidence of small airway obstruction has been found in most studies comparing EP-born infants at term-equivalent age with term-born controls, especially for infants with BPD. This applies to studies using EIP as well as mask-based methods.[15 26 28] This is consistent with our findings, and also with long-term follow-up studies that show persistent airway obstruction in older EP-born children.[9]

Clinical determinants of lung function at term in EP-born infants

Our findings suggest that antenatal steroids have a positive effect on Vt measured at term-equivalent age. Thus, antenatal steroids might possibly improve later respiratory mechanics. Male gender and prolonged respiratory support were negatively associated with the tidal breathing parameters reflecting airway obstruction. This is plausible considering what is known from studies on causes and prevention of BPD.[1 29] Contrasting some recent studies,[9 25 28] GA at birth, SGA status and BW z-score were unrelated to the assessed tidal breathing parameters, findings for which we have no good explanation.

Prediction of later respiratory morbidity

The proportion of EP-born infants readmitted to hospital or treated for asthma-like symptoms during their first year of life corresponds with data from other studies.[11 30 31] Infants with tidal breathing parameters compatible with airway obstruction were more likely to develop respiratory symptoms perceived to require treatment in their first year of life, significantly so for the parameter TEF_{50}/PTEF. This is in agreement with Proietti *et al*,[30] who found that reduced Tptef/Te in preterm infants assessed near term was associated with wheezing during the first year of life. It is also consistent with Drysdale *et al*,[32] who used the single-breath occlusion technique and found higher airway resistance (Rrs) at 36 weeks' GA in preterm-born infants who were later hospitalised because of viral lower respiratory tract infections. A compound prediction model consisting of easily accessible variables including two tidal breathing parameters could predict respiratory morbidity in the first year of life with high accuracy.

Data from several studies have suggested a lifelong tracking of lung function, also in people born EP.[33–36] We suggest that non-invasive and clinically acceptable methods of assessing lung function in infants will facilitate large-scale early assessment of lung function after preterm birth. Hopefully, such measurements may prove to be so closely related to future lung function that they can be used as a proxy of long-term pulmonary outcome in intervention studies aiming at prevention or treatment of neonatal lung disease.

CONCLUSIONS

EP-born infants exposed to contemporary advanced NICU care had strikingly abnormal lung function at term age. Lung disease of prematurity appears to represent a continuum, and classifying lung morbidity simply by BPD or not seems too imprecise when predicting future pulmonary health. Tidal breathing measurements at term-equivalent age using the EIP method gave important additional information about later respiratory morbidity in EP-born infants. A prediction model combining tidal breathing parameters, a diagnosis of BPD and readily available clinical parameters could predict later respiratory morbidity with good accuracy. EIP emerges as a feasible method to obtain lung function data of value for targeted follow-up and also for objective assessment of effects of interventions aimed to prevent or treat lung disease associated with prematurity.

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