PRACE ORYGINALNE
neonatologia

School-age spirometry in survivors of chronic lung disease of prematurity in the surfactant era

Spirometria w wieku szkolnym u dzieci urodzonych przedwcześnie w erze surfaktantu z przebytą przewlekłą chorobą płuc

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Abstract

Objective: *To assess whether school-age spirometry and lung volume outcomes of preterm infants with history of moderate to severe respiratory distress syndrome (RDS), born in the surfactant era and treated with conventional mechanical ventilation (IMV) and discharged home with or without the diagnosis of BPD (hronic lung disease of prematurity), differ from those of term neonates (controls).*

Participants: *The study included 148 Caucasian school-aged children (38 preterm infants without BPD, 20 preterm infants with BPD and 90 term infants). All infants were born at the Department of Pathology of Pregnancy and Labor, Pomeranian Medical University, Szczecin, Poland.*

Methods: *Respiratory outcome in school-aged children was assessed using spirometry with the evaluation of flow and volume parameters, adjusted for age, weight and gender. The differences in spirometry were tested by the Wilcoxon or Mann-Whitney tests. Linear correlation and regression were also used.*

Results: *No statistically significant differences between the spirometric parameters in preterm infants with and without BPD were found. All investigated parameters were significantly lower in both ventilated groups compared to term controls, with the exception of ERV%, which was significantly higher.*

Conclusions: *The necessity to use assisted ventilation in preterm infants without neurological disorders most probably had an adverse effect on the lung function, assessed by spirometry at the age of 9-10 years, in the groups of children discharged home with or without BPD. Regardless of BPD, lung function parameters in prematurely born children with respiratory distress syndrome are always worse than in term controls.*

Key words: **prematurity** / **mechanical ventilation** / **spirometry** / / **pulmonary function follow-up** /

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Otrzymano: **19.10.2012**
Zaakceptowano do druku: **15.03.2013**

Streszczenie

Cel pracy: *Celem pracy była ocena, czy wskaźniki spirometrii u dzieci urodzonych przedwcześnie z objawami łagodnego do ciężkiego zespołu zaburzeń oddychania (RDS) leczonych w erze surfaktantu metodą konwencjonalnej mechanicznej wentylacji i wypisanych do domu z lub bez objawów przewlekłej choroby płuc (BPD – chronic lung disease of prematurity) różnią się od stwierdzonych u dzieci urodzonych jako zdrowe donoszone.*

Materiał i metoda: *Badania przeprowadzono wśród 148 dzieci rasy kaukaskiej w wieku szkolnym. 58 dzieci urodziło się przedwcześnie; wśród nich 38 wypisano z oddziału intensywnej terapii noworodka bez objawów BPD, a 20 z objawami BPD. Pozostałe 90 dzieci urodzonych o czasie bez objawów niewydolności oddechowej w okresie noworodkowym stanowiło grupę kontrolną. Wszystkie dzieci urodziły się w Klinice Patologii Ciąży i Porodu, Pomorskiego Uniwersytetu Medycznego w Szczecinie.*

Czynność płuc została oceniona za pomocą spirometrii z oceną wskaźników przepływu i objętości skorygowanych według wieku, masy ciała i płci badanych dzieci będących w wieku szkolnym. Różnice badano za pomocą testu Wilcoxona lub Mann-Whitney, zastosowano również regresję liniową i korelację.

Wyniki: *Żaden z ocenianych parametrów spirometrycznych nie różnił się istotnie między grupą przedwcześnie urodzonych dzieci wypisanych z oddziału z objawami bądź bez objawów BPD. Wszystkie oceniane wskaźniki spirometryczne w obu grupach wentylowanych dzieci były istotnie niższe niż w grupie kontrolnej donoszonych dzieci, z wyjątkiem ERV%, który był istotnie wyższy w porównaniu z wartościami stwierdzonymi wśród dzieci donoszonych.*

Wnioski: *Konieczność stosowania mechanicznej wentylacji u przedwcześnie urodzonych dzieci rozwijających się bez poważnych zaburzeń neurologicznych miała podobnie negatywny wpływ na wskaźniki spirometryczne oceniane w wieku 9-10 lat w grupie wypisanych zarówno z, jak i bez BPD. Niezależnie od BPD, parametry funkcji płuc u dzieci urodzonych przedwcześnie są gorsze niż uzyskane wśród dzieci urodzonych z ciąży donoszonej.*

Słowa kluczowe: **wcześniactwo** / **mechaniczna wentylacja** / **spirometria** / / **dzieci szkolne** /

Introduction

Chronic lung disease of prematurity (BPD) is a common cause of respiratory insufficiency during infancy in children born with very low birth weight [1]. The highest rates of BPD are observed in neonates with birth weight less than 1000g and those born at less than 28 weeks of gestation. The use of prenatal corticosteroid therapy and surfactant treatment, in addition to gentle ventilation techniques, are believed to reduce the risk of BPD and later respiratory problems among very low birth weight (VLBW) children [2].

At the beginning of the surfactant era, most neonates with RDS had birth weights above 1000 grams, with infrequent occurrence of BPD, and were successfully treated with surfactant and conventional mechanical ventilation (IMV). However, very low birth weight has been shown to be associated with reduced lung function at school age, both independent of [2, 3, 4] and related to neonatal respiratory illnesses [5, 6, 7]. Furthermore, VLBW school-aged children with BPD show evidence of lower expiratory volumes and flows compared to those without BPD [5, 6, 7] and those born at term [5, 6] .

Moreover, in addition to BPD, gestational age and birth weight were found to be important determinants of lung function in late childhood [3, 7]. In the present study we hypothesized that neonatal lung injury associated with requiring mechanical ventilation is one of the important factors for developing decreased pulmonary outcome in late childhood, irrespectively of BPD.

The aim of our study was to assess whether school-aged spirometry and lung volume outcomes of children born prematurely in the surfactant era, with history of moderate to severe RDS treated with IMV and discharged home with or without the diagnosis of BPD, differ from term infants (controls).

Methods

Study population

All preterm children who were treated for RDS [8] with IMV in the NICU of the Department of Neonatology, Pomeranian Medical University, and discharged home with or without the diagnosis of BPD between 1995-1999, were invited to participate in the study. The inclusion criteria were as follows: preterm delivery (up to 36 weeks of pregnancy), intubation, conventional mechanical ventilation, RDS diagnosed on the basis of clinical and typical radiological findings. The exclusion criteria were as follows: preterm delivery but without the need for intubation and IMV.

For the purpose of the study BPD was defined as requiring supplemental oxygen beyond 36 weeks postmenstrual age or discharge home to maintain oxygen saturation in the 88-95% range by pulse oximetry measurement [9].

In all cases, parental written informed consent to participate in the study was obtained. Research protocols and parent informed consent procedures were approved by the institutional review board of the Pomeranian Medical University.

By reviewing medical records from the neonatal period, the following data were collected: complications of pregnancy (pre-eclampsia, diabetes mellitus, oral and intravenous tocolysis, infection and premature rupture of membranes, maternal tobacco smoking history), mode of delivery, gestational age, birthweight and body length, Apgar score at 5 minutes, as well as acute and chronic respiratory complications and infections during the

neonatal period. Additionally, other complications of the neonatal period, such as retinopathy of prematurity (ROP), intraventricular hemorrhage, patent ductus arteriosus, were recorded. We also collected data on respiratory tract infections after discharge from the NICU until the day of the spirometric assessment on the basis of chart review. Both pneumonia or bronchitis were diagnosed on the basis of an examination performed by a clinical pediatrician and the result of a chest x-ray.

Anthropometric Measurements and Assessment of Oxygen Saturation

Weight was measured with standard growth charts for children and the height was measured with a fixed stadiometer. Before spirometry, after a 10-minute rest, heart rate and oxygenation were measured by pulse oximetry (Dräger Pulse Oximeter; Medical System IT GmbH, Germany).

Pulmonary Function Studies

The pulmonary function was assessed by spirometry (Lungtest 500; MES, Cracow, Poland). The pulmonary function testing and its duration were compliant with the standards recommended by the American Thoracic Society [10]. The results were calculated from three comparable values of parameters that did not differ by more than 5% (or 0.1 liter), and were determined from the best of three forced vital capacity (FVC) results [11]. Standard reference equations (variables included gender, height, and weight) were used for all lung parameters in order to obtain the percentage of predicted normal values. Results were expressed as percentage predicted, with generally accepted reference ranges of 80% to 120% [12, 13].

Statistical Analysis

The distribution of continuous variables was tested for normality by the Shapiro-Wilk test. The differences between the groups were tested by the Wilcoxon test or the Mann-Whitney nonparametric U test. Linear correlation and regression or non-parametric regression analyses were used to test for associations between spirometric parameters and duration of IMV, FiO2 concentration during IMV, and duration of oxygen therapy after weaning from IMV.

Results

Responses were received from 100 families (65 preterm children without BPD and 35 with BPD), representing 47.1% of the total cohort available. A cohort of 150 term infants without history of respiratory problems during the neonatal period, matched for age, gender and ethnic group, were recruited from a local primary school as controls. Responses were received from 110 families.

Testing was performed for 148 children. Technically acceptable spirometric measurements were obtained from 58 preterm children treated with IMV (38 without and 20 with BPD) and 90 term controls (Table I).

Mean gestational age and mean birth weight were significantly lower in the group with BPD ($p<0.0001$; $p< 0.001$) when compared to the group without BPD, and significantly lower in both ventilated groups than in term controls ($p< 0.000001$). Apgar score results were significantly lower in both ventilated groups compared to term controls ($p<0.0001$). No significant differences in relationship to gender or mode of delivery among all compared groups were found (Table I).

As expected, prematurely born infants who required respiratory support, and especially those with chronic lung disease of prematurity, were substantially more often ill during the neonatal period than the healthy control group as far as the occurrence and stage of RDS, incidence of pulmonary interstitial emphysema and ROP were concerned (Table II).

Postnatal steroids were not administered to the children during the neonatal period.

Table I. Baseline characteristics at birth of the study population.

	Preterm with BPD[1] N=20	Preterm without BPD[2] N=38	Term Control[3] N = 90
Gestational age (weeks)* mean ± SD	29.2 ± 3.12	34.3 ± 3.3	39.2 ± 1.36
Birthweight (g)** mean ± SD	1291 ± 598	2184 ± 788	3371.6 ± 310
5' Apgar score # (N, %) 0–3 4–7 8–10	 0 (0.0%) 20 (100.0 %) 0 (0.0%)	 0 (0.0%) 38 (100.0%) 0 (0.0%)	 0 0 90 (100%)
Male (N, %)	12 (60%)	19 (50%)	45 (50%)
Female (N, %)	8 (40%)	19 (50%)	45 (50%)
Cesarean section (N, %) ##	18 (90.0%)	31 (81.6%)	24 (27%)
Spontaneous vaginal delivery (N, %)	2 (10.0%)	7 (18.4%)	66 (73%)
Prenatal corticosteroids (N, %)	18 (90.0%)	36 (94.7%)	0 (0.0%)

* 1/2 $p<0.0001$, 1/3 and 2/3 $p < 0.000001$; ** 1/2 $p < 0.001$, 1/3 and 2/3 $p < 0.000001$;
# 1/3 and 2/3 $p < 0.0001$; ## 1/3 and 2/3 $p <0.001$

Table II. Complications during the neonatal period.

Type of complications	Preterm with BPD[1] N=20	Preterm without BPD[2] N=38	Term Control[3] N = 90
Respiratory distress syndrome (RDS) (N, %)	20 (100%)	38 (100%)	0 (0%)
Grade of RDS * Grade 1 Grade 2 Grade 3 Grade 4	 0 (0.0%) 4 (20.0%) 14 (70.0%) 2 (10.0%)	 6 (15.8%) 22 (57.9%) 10 (26.3%) 0 (0.0%)	 0 (0.0%) 0 (0.0%) 0 (0.0%) 0 (0.0%)
Pneumothorax	2 (10.0%)	1 (2.63%)	0 (0%)
PIE#	5 (40%)	1 (2.63%)	0 (0%)
Surfactant therapy**	9 (45%)	6 (15.8%)	0 (0%)
Pulmonary hemorrhage	1 (5.0%)	0 (0.0%)	0 (0%)
Pneumonia (N, %)	20 (100%)	31 (81,6%)	0 (0%)
Sepsis	7 (35.0%)	13 (34.2%)	0 (0%)
Patent ductus arteriosus (N, %)	1 (5.0%)	0 (0.0%)	0 (0%)
Intraventricular hemorrhage (N, %)	19 (95%)	27 (71.05%)	0 (0%)
ROP***	16 (80%)	9 (23.7%)	0 (0%)

* 1/2 p<0.05; ** 1/2 p <0.05; *** p<0.05; # 1/2 p<0.05; PIE – pulmonary interstitial emphysema; ROP – retinopathy of prematurity;

Table III. Incidence of respiratory tract infections after discharge from the neonatal intensive care unit.

	Preterm with BPD[1] N=20	Preterm without BPD[2] N=38	Term Control[3] N = 90
Bronchitis (N, %) 0-2 years 3-6 years	 7 (35%) 6 (30%)	 17 (44.7%) 17 (44.7%)	 18 (20%) 39 (43%)
Pneumonia (N, %) 0-2 years 3-6 years	 8 (40%) 6 (30%)	 13 (34.2%) 13 (34.2%)	 10 (11%) 13 (14%)

Table IV. Anthropometric measurements, heart rate and oxygen saturation on the day of spirometry.

	Preterm with BPD[1] N=20	Preterm without BPD[2] N=38	Term Control[3] N = 90
Age (years)	10.25 ± 2.7	9.22 ± 2.8	10.6 ± 2.9
Weight* (kg)	35.1 ± 16.8	31.6 ± 12.2	40.2 ± 4.1
Height **(cm)	137.3 ± 17.1	132.3 ± 15.5	148.0 ± 15
Heart rate (beats/min)	94.6 ± 4.1	90.7 ± 6.0	90.2 ± 11
Oxygen saturation# (%)	95.5 ± 1.0	95.9 ± 1.0	97.3 ± 6.9

* 1/3 and 2/3 p<0.001; ** 1/3 and 2/3 p< 0.0001; # 1/3 and 2/3 p< 0.05

Table V. Parameters of pulmonary function in preterm children treated with mechanical ventilation and recovered with or without BPD and in controls subjects.

	Preterm with BPD[1] N=20 Median [95 CI]	Preterm without BPD[2] N=38 Median [95 CI]	Term Control[3] N = 90 Median [95 CI]
FEV_1	1.70 [0.60 – 4.08]	1.71 [0.60 – 5.03]	2.29 [0.93 – 5.26]
FVC_{EX}	1.92 [0.69-4.33]	1.88 [0.69 – 5.41]	2.47 [1.17 – 5.56]
FVC_{IN}	1.82 [0.86-3.79]	1.77 [0.86 – 5.14]	2.36 [1.18 – 5.45]
PIF	2.23 [1.23 – 4.19]	1.81 [1.04 – 4.95]	2.75 [1.09 – 6.08]
VC	1.91 [0.86 – 4.24]	1.87 [0.86 – 5.37]	2.49 [1.28 - 5.52]
IC	1.14 [0.19-2.54]	1.10 [0.05 – 3.43]	1.72 [0.25 – 3.47]
TV	0.58 [0.19-1.71]	0.48 [0.15 - 1.26]	0.63 [0.23 – 1.38]
PEF	3.69 [1.56-8.49]	3.62 [1.56 – 8.83]	4.62 [2.17 – 9.96]
ERV	0.85 [0.08 – 2.58]	0.75[0.31– 1.94]	0.78 [0.02 – 2.97]

FEV1 – 1-sec forced expiratory volume; FVCEX – forced expiratory vital capacity; FVCIN – forced inspiratory vital capacity; PIF – peak inspiratory flow; VC – vital capacity; IC – inspiratory capacity; TV – tidal volume; PEF – peak expiratory flow ; ERV- functional residual capacity;
Comparison of a percentage of the predicted values: all differences between preterm infants with and without BPD were not significant; FEV1 - */# p<0.0001, **/# p<0.05; FVCEX – *,**/# p<0.002; FVCIN – *,**/# p<0.0001; PIF – *,**/# p<0.001; VC - *,**/# p<0.001; IC - *,**/# - p<0.0001; TV - *,**/# p<0.01; ERV- *,**/# p<0.05

Respiratory morbidity was compared in all of the groups of children with ranges: up to 2 years of age and between 3-6 years of age (Table III).

There were no significant differences in the rate of children with bronchitis and pneumonia up to 6 years of age between both ventilated groups, with and without BPD. However, the incidence of bronchitis with more than 2 episodes per year per child was found to be significantly higher in preterm infants with BPD (40% children up to 2 years of age and 45% up to 6 years of age) than in preterm infants without BPD (0.0%) ($p<0.05$). In the control group, bronchitis up to 2 years of age and pneumonia up to 6 years of age were recognized significantly less frequently ($p<0.05$) than in both ventilated groups.

There were no significant differences in relation to age, body size, heart rate and oxygen saturation between the preterm infants with and without BPD on the day of spirometry (Table IV). Mean weight, height and oxygen saturation in the control group were significantly higher than in both ventilated groups ($p<0.001$; $p<0.0001$; $p< 0.05$).

On the day of spirometry all preterm and control children had clear breath sounds on auscultation immediately before the lung function assessment.

After adjustment for age, gender and body size by using a percentage of the predicted values, both groups of preterm children who were treated with IMV turned out to have significantly lower spirometry parameters than controls, except for ERV%, which was lower ($p<0.05$) in the control group. There were no significant differences in relation to all of the evaluated spirometry parameters between preterm children with and without BPD (Table V).

In both groups of preterm children treated with IMV decreased values of most measurement parameters were recorded significantly more frequently than in term controls. Furthermore, elevated values of ERV% were found to be significantly more frequent in both ventilated groups than in the control subjects.

No significant correlation between spirometry parameters and duration of IMV, FiO2 concentration during IMV and duration of oxygen supplementation after weaning from IMV was found in the group of preterm children with BPD. The only significant correlation was observed between inspiratory capacity % (IC%) and duration of IMV ($r=0.72$; $p<0.0007$), as well as the duration of oxygen supplementation ($r=0.57$; $p<0.02$) in the group without BPD.

The percentage of maternal smoking was 45% in the group with BPD, 57.8% in the preterm children without BPD, and 40% in the control group. Incidence of smoking more than 30 cigarettes every day was significantly higher in both IMV groups than in controls ($p<0.01$). However, there was no statistically significant relationship between maternal smoking and values of spirometric parameters.

Discussion

In our study no significant differences in lung function assessed by spirometry in school-aged children, born prematurely with and without BPD, were found but in both these groups spirometric parameters were significantly worse than in full-term infants who never received IMV.

Similar to other previous studies, healthy, full-term, age-matched children were selected as control subjects to compare pulmonary outcomes [3, 12, 14-17]. Children born prematurely and treated with IMV during the neonatal period and term children were compared.

Preterm children treated with IMV during infancy showed an increased respiratory morbidity during early childhood [14, 15, 18]. Especially children with BPD are considered a high-risk group [6, 19, 20, 21]. In our study the percentage of children affected by respiratory morbidity was not significantly different in both ventilated groups. However, the incidence of bronchitis per child/per year in the group of preterm infants with BPD was significantly higher than in preterm children without BPD. Furthermore, the control subjects were less affected by bronchitis and pneumonia than children treated with IMV during infancy.

Pulmonary outcome in school-aged children was assessed using spirometry with evaluation flow and volume parameters adjusted for age, weight and gender. We used percent predicted values (PPVs) for comparison between various spirometry measurements because PPVs are more widely reported and allow for a comparison between various studies, notwithstanding the limitations involved when different prediction equations are used [12, 13 16, 22].

Various studies demonstrated early impairment of lung function in preterm infants, that may vary in severity during follow-up to adulthood [19, 22, 23, 24, 25]. In children with BPD, bronchial obstruction and hyper-responsiveness may persist until school age [14, 16, 26, 27].

In our study no significant differences in the lung function assessed by spirometry in school-aged children, ventilated during infancy, regardless of BPD, were found.

In contrast to our findings, numerous studies report more or less normal lung volumes in healthy preterm children, but slightly lower forced volumes in those with BPD [3, 21]. Korhonen et al., found an inverse relationship between duration of O_2 therapy and FEV_1. These observations support the theory of a continuous course in BPD [3]. Such a correlation was not confirmed in our study.

Broström at al., found significantly lower values of FEV_1 among children (aged 6-8 years) with BPD [21]. Half of the children with BPD had FEV_1 below the normal range, compared with only one-sixth of those without BPD [21]. In our study, 25% of subjects with BPD and 18.42% without BPD had decreased FEV_1. Our findings are in agreement with a study of Blayney at al., who reported improvement in the lung function between 7-10 years of age [28].

The study of Blayney demonstrates that children with evidence of mild to moderate lung disease in the infancy, have continued lung growth or repair during their school years. Similar to these findings, Narang et al., found no differences in spirometric values between former-preterm infants and healthy term controls, 21 years after birth [14]. They suggest that there was some recovery of lung function over time. However, at the mean age of 9-10, we found significantly lower spirometry flow and volume parameters in both groups of ventilated children, compared to healthy full-term non-ventilated controls. Similar to our findings, Doyle et al., reported children at the age of 8-9 years who were born extremely prematurely to have lung function in the reference range, although significantly lower than term controls [23].

In our study, children ventilated during the neonatal period, regardless of BPD, had lower spirometry parameters when compared to controls, except for ERV%. Indeed, mean ERV% values were found to be in normal ranges in both ventilated groups. However, 40% of patients from the group with BPD and 43.2% of patients from the group without BPD had increased values of ERV% compared to 7.78% of control subjects, what probably reflects obstruction in both ventilated groups. Higher mean ERV% in children born prematurely compared to term controls at mean age of 10 years has also described by Smith et al., [12].

The ongoing debate about what factors are more important in determining lung function in late childhood continuous to gain momentum. In various studies, apart from BPD, gestational age and birth weight have been shown to be important [3, 7, 29].

In our study there was a significant difference in birth weight and gestational age between the two groups of preterm children treated with IMV. However, no differences in the respiratory outcomes of these two groups were found. Furthermore, in both ventilated groups most of the assessed spirometric parameters were significantly lower than in term controls who were never treated with IMV. We hypothesize that neonatal lung injury was associated with mechanical ventilation upon birth. Probably this is a more important factor for developing decreased pulmonary outcome in late childhood than either birth weight or gestational age. Moreover, our findings indicate that not only ELBW neonates but also ventilated preterm babies with birth weights over 1250 grams and born after 29 weeks gestation, regardless of BPD, may have lower pulmonary outcome later in life.

Naturally, there are some limitations to our study. Although all NICU preterm RDS survivors, treated with IMV and discharged home between 1995-1999, were invited to participate, only 47.1% responded to our invitation. Except for those who changed their home address (20% of the non-responders), some parents probably ignored the invitation because of severe developmental disability of the child. It is not possible to compare the characteristics of the neonatal period of the non-responders due to lack of written consent of their parents. Similar problems have been observed by others authors in pulmonary follow-up retrospective studies [12, 14]. Only in prospective studies has the percentages of participants been higher [15, 22].

It is conceivable that those who participated in the study represent the 'better' survivors. Unfortunately in the examined population technically acceptable spirometry measurements were obtained only from 57.1% of the preterm children who were treated with IMV and discharged home with BPD and from 58.5% of preterm infants without BPD. Also, 11.8% of the children from the control group were unable to produce acceptable spirometry testing as a result of an inability to understand the required technique, despite repeated attempts. Lack of technically satisfactory spirometry results from a part of the examined children has been also reported in other studies [15, 22].

Despite these limitations, we conclude that adverse outcomes of lung function at the ages of 9-10 years were similar in those premature infants without significant developmental disability who needed assisted ventilation and met the criteria for BPD, and those who did not. In addition, regardless of the BPD status, spirometry parameters in prematurely born children with RDS are not as good as in term controls.

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