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Pulmonary function in school-aged children with mild to moderate infant respiratory distress syndrome requiring nasal continuous positive airway pressure

Ocena funkcji płuc u dzieci szkolnych leczonych metodą n-CPAP z powodu łagodnego lub średnio nasilonego noworodkowego zespołu zaburzeń oddychania

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Abstract

Objectives: *The aim of our study was to evaluate whether mild to moderate infant respiratory distress syndrome (RDS) treated with nasal continuous positive airway pressure (NCPAP) might affect the pulmonary function in school-aged children.*

Material and methods: *50 children, aged 10.2±2.8 years, with a history of RDS and 90 controls without a neonatal history of lung diseases, matched for age and gestational age at birth, were studied. Pulmonary function was assessed by spirometry and oxygen saturation measured by pulse oximeter.*

Results: *The incidence of respiratory tract infections within the first 6 years after discharge from the intensive care neonatal unit was higher in the RDS group than in controls (P<0.05). Spirometric parameters of the pulmonary function were comparable in both groups. Oxygen saturation was significantly lower in the RDS group (96.2±7 vs. 97.3±7%; P<0.05). A significant negative correlation between spirometric parameters and the duration of NCPAP application and the duration of oxygen supplementation has been found.*

Conclusions: *Pulmonary function assessed by spirometry was normal in school-aged children with infant RDS. However, spirometric parameters were negatively correlated with the duration of NCPAP and the duration of oxygen supplementation. In comparison with the controls, children with infant RDS had a higher incidence of respiratory tract infections (laryngitis, acute bronchitis and pneumonia) within the first 6 years of life, as well as lower oxygen saturation.*

Key words: **prematurity** / **respiratory distress syndrome** / / **follow-up pulmonary function** /

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Streszczenie

Cel pracy: *Celem pracy była ocena funkcji płuc u dzieci szkolnych leczonych w okresie noworodkowym metodą NCPAP z powodu łagodnych lub średnio nasilonych zaburzeń oddychania.*

Materiał i metody: *Badaniami objęto 50 dzieci w wieku 10,2±2,8 lat z przebytą w okresie noworodkowym niewydolnością oddechową i 90 dzieci w podobnym wieku kalendarzowym i urodzonych w podobnym wieku ciążowym, ale bez objawów niewydolności oddechowej w okresie noworodkowym. Funkcje płuc oceniono poprzez zastosowanie badania spirometrycznego i oceny przezskórnego wysycenia tlenem hemoglobiny.*

Wyniki: *W ciągu pierwszych 6 lat życia dzieci wymagające wsparcia oddechowego metodą NCPAP chorowały istotnie częściej na infekcje układu oddechowego (p <0,05) niż dzieci nie wymagające takiego leczenia. Oceniane parametry spirometryczne były podobne w obu grupach. Przezskórna saturacja była istotnie niższa w grupie dzieci leczonych NCPAP niż w grupie kontrolnej. Stwierdzone występowanie ujemnej korelacji między parametrami spirometrycznymi a czasem trwania leczenia metoda NCAP i liczba dni tlenoterapii.*

Wnioski: *Dzieci szkolne z przebytą łagodną lub umiarkowaną niewydolnością oddechową w okresie noworodkowym nie wykazują różnic w funkcji płuc ocenianych badaniem spirometrycznym. Parametry spirometryczne korelują negatywnie z okresem czasu stosowania NCPAP i suplementacji tlenem. Dzieci z niewydolnością oddechową w wywiadzie częściej chorują na zapalenie krtani, zapalenie oskrzeli i zapalenie płuc w okresie przedszkolnym i mają niższą saturację w wieku szkolnym.*

Key words: **płuca** / **okres noworodkowy** / **zaburzenia oddychania** / / **niewydolność oddechowa** / **układ oddechowy** /

Introduction

Prematurity is frequently complicated by respiratory distress syndrome (RDS) and additional defects in other organ functions [1]. Despite huge advances in neonatal care, RDS remains the most common single cause of death in the first month of neonatal life. RDS is frequently associated with some metabolic disorders, such as acidosis, low blood pressure, patent ductus arteriosus, retinopathy of prematurity, intracranial hemorrhages and lung diseases (pneumothorax, pneumomediastinum, pneumonia, bronchopulmonary dysplasia, bleeding into the lung).

Nasal continuous positive airway pressure (NCPAP) delivered by nasal prongs has been widely applied in neonatal intensive care units for treatment of infant RDS. Early treatment with NCPAP can prevent or temporarily compensate for the increased alveolar-retraction forces that are a consequence of high surface tension caused by a deficiency of surfactant. It has been shown that the application of NCPAP and treatment with surfactant are effective in reducing the mortality and morbidity rates associated with RDS [2-7]. Moreover, early treatment of very preterm infants with RDS using NCPAP is effective in decreasing the need for mechanical ventilation, with its related adverse effects, such as upper airway damage, sepsis and bronchopulmonary dysplasia [8-12]. Although the majority of studies have suggested that NCPAP is a safe way of providing respiratory support to neonates at risk of, or actually experiencing respiratory failure [4-8, 12], Morley et al. have demonstrated in a recent study that, in infants born at 25 to 28-weeks gestation, NCPAP did not significantly reduce the rate of death or bronchopulmonary dysplasia, as compared with intubation [9].

Much less is known about long-term pulmonary functions in infants with RDS receiving NCPAP and it remains unclear whether the well-demonstrated short-term benefits of this treatment translate into significant reductions in chronic lung disease in childhood and adolescence.

Aim

The aim of our study was to evaluate whether mild to moderate infant RDS requiring NCPAP application during the neonatal period would have an impact on pulmonary function, as assessed by spirometry and pulse oximetry, of school-aged children.

Materials and methods

Study Population

The study was performed on 140 Caucasian children aged 5-15 years, born in the Clinic of Pathology of Labour and Delivery in Szczecin, Poland. The study group consisted of 50 children with mild to moderate infant RDS, requiring NCPAP during the neonatal period (Hudson type of nasal prongs, Kwapisz Co., Warsaw, Poland). The RDS was diagnosed by widely accepted criteria [4, 5]. Infants with other respiratory pathologies requiring NCPAP during the neonatal period, such as wet lung, asphyxia, or pneumonia, as well as infants with RDS requiring mechanical ventilation were not included into the study. The control group consisted of 90 healthy, age-matched children. From our medical records we randomly selected children with a similar range of gestational age at birth as in the RDS group, born by uncomplicated delivery and without pulmonary complications during the neonatal period. In all cases, parental written informed consent was obtained for the participation in the study.

By reviewing medical records from the neonatal period, the following data were collected: complications of pregnancy (preeclampsia, pregravid or gestational diabetes mellitus, oral and intravenous tocolysis, infection and premature rupture of membranes), mode of delivery, gestational age at birth, birth weight and body length, Apgar score at 5 minutes, as well as respiratory complications (air leak syndrome, pulmonary hemorrhage and nasal mucosal damage) and infections during the neonatal period (pneumonia, meningitis or sepsis).

Additionally, other complications in the neonatal period, such as retinopathy of prematurity, intraventricular hemorrhage, patent ductus arteriosus, anemia and hyperbilirubinemia, were recorded. Using other available medical records, we also collected data on respiratory tract infections (acute laryngitis, acute bronchiolitis and pneumonia) after discharge from the neonatal intensive care unit until the day of the spirometric assessment.

Anthropometric Measurements and Assessment of Oxygen Saturation

Weight was measured on a standard medical balance for children and height was measured by a fixed stadiometer. Before spirometry, after a 10-minute rest, heart rate and oxygenation were measured by a pulse oximeter (Dräger Pulse Oximeter; Medical System IT GmbH, Freiburg, Germany).

Pulmonary Function Studies (Spirometry)

The pulmonary function was assessed by spirometry (Lungtest 500; MES, Cracow, Poland). The spirometry was performed in children without cough or wheezing for more than two weeks within a year before the spirometric evaluation, and known chronic pulmonary disease. All measurements were performed at the same time each day, between 4 and 6 pm. The spirometer was calibrated before each test, and current values of atmospheric pressure, temperature and relative humidity were included for correction of the pulmonary function parameters. The results of the measurements were also corrected for body temperature and saturation. Spirometry was performed in a seated position with the head tilted back. The pulmonary function testing and its duration were performed according to the standards recommended by the American Thoracic Society [13]. The results were calculated from three comparable values of parameters, which did not differ by more than 5% (or 0.1 liter) and were determined from the best forced vital capacity (FVC) result [14].

The following pulmonary function parameters were measured: 1-second forced expiratory volume (FEV_1), forced expiratory vital capacity (FVC_{EX}), forced inspiratory vital capacity (FVC_{IN}), peak inspiratory flow (PIF), vital capacity (VC), inspiratory capacity (IC), total lung capacity (TLC), and peak expiratory flow (PEF).

The protocol and parental informed consent form were approved by the institutional review board.

Statistical Analysis

The distribution of continuous variables was tested for normality by the Shapiro-Wilk test. The differences between children with a history of RDS and healthy controls were tested by the Wilcoxon test or Mann-Whitney nonparametric U test as appropriate. Linear correlation and regression or non-parametric regression analyses were used to test for associations between spirometric parameters, duration of NCPAP and duration of oxygen therapy after weaning from NCPAP.

Results

Baseline characteristics of the studied population at birth are provided in Table I. In comparison with the controls, children receiving NCPAP during the neonatal period had significantly lower birth weight and height. In the NCPAP group, the gestational age ranged from 29 to 39 weeks and was <37 weeks in 62% of newborn infants.

In this group 7 infants were born at 29-32 weeks gestation (mean birth weight 1629.0±170g), 24 infants at 33-36 weeks (birth weight 2455±232g) and 19 infants at 37-39 weeks (birth weight 3235±301g). In the control group, 12 infants were born at 28-32 weeks gestation (mean birth weight 1721±201g), 45 at 33-36 weeks (birth weight 2501 ± 280 g) and 33 at 37-39 weeks (birth weight 3299±312g), respectively. All newborn infants from the control group had normal Apgar scores at birth, whereas in the NCPAP group, normal score were found in only 60% of the cases.

Table I. Baseline characteristic at birth of the studied population.

	NCPAP N=50	Controls N=90
Gestational age at birth (weeks)	35.7 ± 2.1	36.2 ± 1.1
28–32 weeks (N)	7 (14%)	12 (13%)
33–36 weeks (N)	24 (48%)	45 (50%)
37–39 weeks (N)	19 (38%)	33 (37%)
Birth weight (g)	2735.8 ± 221	3371.6 ± 310 **
Birth height (cm)	51.6 ± 0.5	55.2 ± 0.6 **
Apgar score (N)		
0–3	5 (10%)	0 *
4–7	15 (30%)	0 **
8–10	30 (60%)	90 (100%) **
Male (N)	24 (48%)	45 (50%)
Female (N)	26 (52%)	45 (50%)
Cesarean section (N)	24 (48%)	24 (27%)
Spontaneous vaginal delivery (N)	26 (52%)	66 (73%)

Data are presented as mean ± SD
* P<0.01; ** P<0.0001

Table II. Complications during the neonatal period.

	NCPAP N=50	Controls N=90
Pneumonia (N)	3 (6%)	0 (0%)
Respiratory distress syndrome (N)	50 (100%)	0 (0%)
Intraventricular hemorrhage (N)		
Grade I-II	23 (46%)	0 (0%)
Grade III-IV	1 (2%)	
Sepsis (N)	4 (8%)	0 (0%)
Abdominal distension (N)	33 (66%)	0 (0%)
Patent ductus arteriosus (N)	1 (2%)	0 (0%)
Anemia (N)	6 (12%)	1 (1%)
Hyperbilirubinemia (N)	19 (38%)	8 (9%)

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

	NCPAP (n=50)	Controls (N=90)
Laryngitis (N)		
0-2 years	18 (36%) *	25 (28%)
3-6 years	24 (48%) *	27 (30%)
7-15 years	8 (16%)	13 (14%)
Bronchitis (N)		
0-2 years	19 (38%) *	18 (20%)
3-6 years	24 (48%)	39 (43%)
7-15 years	9 (18%)	15 (17%)
Pneumonia (N)		
0-2 years	16 (32%) *	10 (11%)
3-6 years	10 (20%)	13 (14%)
7-15 years	1 (2%)	4 (4%)

* P<0.005 versus controls

As summarized in Table II, abdominal distension, intraventricular hemorrhage and hyperbilirubinemia were frequent complications in the NCPAP group (overall, in 44 of 50 infants). Similarly, the incidence of respiratory tract infections (laryngitis, acute bronchitis and pneumonia) within the first 6 years after discharge from the intensive care neonatal unit was higher in the NCPAP group than in healthy controls. (Table III).

The highest incidence of acute bronchitis and pneumonia that occurred within the first 2 years after discharge was in NCPAP infants born at 33-36 weeks gestation (OR=2.85, 95% CI: 1.09-7.5; P<0.05 and OR=3.29, 95%CI: 1.1-9.88; P<0.05, respectively). Children from the control group were heavier, taller and had higher oxygen saturation as compared to the NCPAP group. (Table IV). However, after adjustment for weight and height, spirometric parameters of the pulmonary function were comparable in both groups. (Table V).

In the NCPAP group, the duration of respiratory support ranged from 23 to 238 hours (median: 54 hours) and the fraction of inspired oxygen was 0.40-0.89% (median: 0.53%). The duration of oxygen supplementation after weaning from NCPAP ranged from 2 to 25 days (median: 8.3 days), and was the longest in infants born at 28-32 weeks gestation (median: 10.4 days), as compared with those born at 33-36 weeks gestation (median: 3.4 days; P<0.001) or 37-39 weeks gestation (median: 2.6 days; P<0.001).

There were weak but significant negative correlations found between the duration of NCPAP or oxygen supplementation after weaning from respiratory support and all the spirometric parameters of the pulmonary function. (Table VI).

Discussion

Chronic lung diseases in infants is a heterogeneous group of diseases that usually evolves from an acute, prematurity-associated newborn respiratory disorder. These disorders, such as RDS, and their subsequent treatments may predispose infants to the development of chronic lung disease. It has been suggested that in mid-childhood (5-12 years of age), prematurity is associated with an excess of various respiratory symptoms, such as chronic cough, wheezing, asthma or upper respiratory tract infections [12, 15-17].

This has been reported both in low and very low birth weight babies, mainly in those who required prolonged respiratory support, or developed bronchopulmonary dysplasia. In the present study, we found a history of higher incidences of laryngitis, bronchitis and bronchopneumonia during the first two years of life in school-aged children who were treated with NCPAP due to the RDS. However, in older children, aged 3 to 15 years, the incidence of respiratory tract infections was similar to that of the healthy controls. 62% of our patients in the infant RDS group were born <37 weeks gestation.

Both prematurity per se as well as low birth weight have been suggested as independent risk factors for impairment of pulmonary functions in childhood [15, 17, 18, 19] .

Furthermore, we found that school-aged children (5-15 years of age) with infant RDS had normal pulmonary function, as assessed by spirometric measurements, which may suggest an improvement in pulmonary function over a longer period. Several factors might contribute to this improvement. The damage of respiratory bronchioles in survivors of RDS during the first year of life may be counteracted by later catch-up growth [17]. Parenchymal lung growth in the first years of life is associated with the addition of new alveoli and by the formation of alveolar ducts. As alveolar development is generally completed before 8 years of age [20], pulmonary abnormalities documented after this age would suggest a long-standing impairment of pulmonary function.

Low arterial oxygen pressure and decreased functional residual capacity have been demonstrated in the early recovery phase of RDS [19]. Some studies reported normal total airway resistance at discharge from the neonatal unit in survivors of RDS who were ventilated with the subsequent increase of the airway resistance in a 1-year follow-up [21]. In contrast, Ben-Abraham et al. [22] observed normal lung volumes, flow rates and PaO_2 in survivors of RDS after 5 years. In our study, children with infant RDS had lower pulse oximeter oxygen saturation than the control subjects at 5-15 years of age. However, average oxygen saturation was within normal range in both groups (96.2% and 97.3%, respectively).

We found weak but statistically significant negative correlations between spirometric parameters of pulmonary function, duration of NCPAP and duration of oxygen supplementation in the neonatal period. There have been no previous reports testing for such associations in RDS survivors treated with NCPAP. However, the negative correlations found in our study probably reflect only the severity of the underlying disease and the NCPAP duration is probably only a marker of this severity. Similar impairment of pulmonary function has been reported in very low birth weight children with and without bronchopulmonary dysplasia [19]. In very low birth weight children (<1500g), the FEV1 to FVC ratio was <70% and was inversely associated with the duration of NCPAP >28 days, prolonged use of oxygen therapy and RDS [23]. In contrast, Kitchen et al. [24] found that FEV1 and FVC were unrelated to bronchopulmonary dysplasia or NCPAP per se, and that abnormalities of flow rates were only seen in those with asthma or recurrent bronchitis at 8 years of age. Despite these discrepancies, there is a general agreement that, in the case of very low birth weight children, a significant reduction in the incidence of chronic lung diseases detected in childhood can be achieved by using a quality improvement process that includes avoidance of intubation, adoption of new pulse oximeter limits and early use of NCPAP [12, 19].

Our study has several limitations. First, our study population was comprised of patients with mild to moderate RDS, treated with NCPAP at a gestational age of 28 to 39 weeks (average 35.7 weeks).

Table IV. Anthropometric measurements and oxygen saturation.

	NCPAP (N=50)	Controls (N=90)
Age (years)	10.2 ± 2.8	10.6 ± 2.9
Weight (kg)	35.9 ± 3.6 *	40.2 ± 4.1
Height (cm)	142.1 ± 14 *	148.0 ± 15
Heart rate (beats/min)	90.0 ± 10	90.2 ± 11
Oxygen saturation (%)	96.2 ± 7.1 *	97.3 ± 6.9

* P<0.05 versus controls

Table V. Parameters of pulmonary function in children treated with NCPAP and healthy controls.

	NCPAP N=50	Controls N=90
FEV_1 %	96.5 ± 9.1	98.3 ± 9.3
FVC_{EX} %	85.7 ± 8.6	87.7 ± 8.8
FVC_{IN} %	82.3 ± 8.1	83.7 ± 9.6
PIF %	2.65 ± 0.4	2.75 ± 0.6
VC %	85.1 ± 7.9	88.3 ± 9.1
IC %	86.1 ± 8.4	91.1 ± 9.9
TLC %	124.0 ± 12.8	138.9 ± 14.6
PEF %	86.1 ± 8.0	86.5 ± 8.8

Data are presented as mean ± SD
FEV_1 – 1-sec forced expiratory volume;
FVC_{EX} – forced expiratory vital capacity;
FVC_{IN} – forced inspiratory vital capacity;
PIF – peak inspiratory flow; VC – vital capacity;
IC – inspiratory capacity; TLC – total lung capacity;
PEF – peak expiratory flow

Table VI. Correlations between parameters of pulmonary function, duration of NCPAP and duration of oxygen supplementation.

	Duration of NCPAP	Duration of oxygen saturation
FEV %	-0.16 *	-0.15 *
FVC_{EX} %	-0.16 *	-0.19 *
FVC_{IN} %	-0.17 *	-0.18 *
PIF %	-0.16 *	-0.17 *
VC %	-0.23 **	-0.23 **
IC %	-0.22 **	-0.25 **
PEF %	-0.26 **	-0.26 **

* P<0.05; ** P<0.01

Therefore, our findings may not apply to the population of very low birth weight infants (<32 weeks of gestation; birth weight <1500g) with RDS. Second, we did not assess bronchial airway reactivity and our assessment of pulmonary function was based solely on the spirometric results. An important consideration is whether our findings describing apparent normalization of pulmonary function in childhood truly reflect a catch-up of lung growth. Some studies reported a decreased sensitivity of spirometry in this age group [19]. Further, spirometry has long been known to be insensitive to distal airway obstruction until the very late phases [19]. Thus, the use of other methods of evaluating lung ventilation and lung growth might provide more accurate information. These methods include measurements of indices of overall ventilation inhomogeneity, such as the lung clearance index, the noninvasive assessment of lung growth with the use of labeled carbon monoxide, and hyperpolarized gases in magnetic resonance or pulmonary high-resolution computed tomography [19, 25].

In conclusion, pulmonary function assessed by spirometry was normal in school-aged children with mild to moderate RDS treated with NCPAP in the neonatal period. However, spirometric parameters were negatively correlated with the duration of NCPAP and the duration of oxygen supplementation.

The incidence of respiratory tract infections (laryngitis, acute bronchitis and pneumonia) within the first 6 years after discharge from the intensive care neonatal unit was higher in the infant RDS group than in controls.

Conflict of interest

The authors declare they have no conflicts of interest.

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