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Pulmonary function in former very low birth weight preterm infants in the first year of life

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ABSTRACT

Background: Pulmonary function in former preterm infants may be compromised during childhood.
Objectives: To assess pulmonary function in very-low-birth-weight preterm infants at 6–12 months of corrected age and analyze the factors associated with abnormal pulmonary function.
Methods: Cross-sectional study with preterm infants at 6–12 months of corrected age with birth weight < 1500 g. Children with malformations or affected by neuromuscular and respiratory diseases were excluded. Forced expiratory flows were assessed using the chest compression technique, and volumes were measured by total body plethysmography. Pulmonary function parameters in preterm infants were compared to a control group of same-aged children born at term.
Results: We studied 51 preterm and 37 infants born at term. Preterm infants had: gestational age at birth (30.0 ± 2.5 weeks), birth weight (1179 ± 247 g), 27.5% had bronchopulmonary dysplasia, and 45% received mechanical ventilation. Preterm infants had lower median z-scores in comparison to term infants for the following parameters ($p < 0.05$): FVC (−0.3 vs. 0.7), $FEV_{0.5}$ (−0.5 vs. 0.9), $FEV_{0.5}$/FVC (−0.6 vs. −0.5), FEF_{50} (−0.4 vs. 0.9), FEF_{75} (−0.3 vs. 0.8), FEF_{85} (−0.1 vs. 0.6) and FEF_{25-75} (−0.5 vs. 1.1). No term child had abnormal lung function, compared to 39.2% of preterm infants ($p = 0.001$). Factors associated with abnormal pulmonary function were lower gestational age at birth, small for gestational age, need for mechanical ventilation and presence of recurrent wheezing.
Conclusions: Preterms had a high prevalence of abnormal pulmonary function and lower pulmonary function in comparison to term infants. Prematurity, intrauterine growth restriction, respiratory support and recurrent wheezing were associated with abnormal pulmonary function.

1. Introduction

The pulmonary function of infants born prematurely may be compromised during childhood and adolescence, especially for extremely preterm infants, infants with intrauterine growth restriction or those who develop bronchopulmonary dysplasia or have been subjected to mechanical ventilation in the neonatal period [1–3]. As the pulmonary parenchyma grows, there may be a progressive improvement in parameters related to pulmonary volume due to alveolar multiplication. However, alterations in pulmonary flow may persist until adolescence or adulthood [4,5].

One study comparing very low birth weight preterm infants with and without a history of bronchopulmonary dysplasia at 9.5 years average age showed a significant difference between groups in z-score values for FEV_1 (1.27 vs. 0.40; $p = 0.008$), FVC (1.39 vs. 0.71; $p = 0.022$), and FEF_{50} (2.21 vs. 1.04; $p = 0.048$) [2].

Even with the advent of exogenous surfactant for treating respiratory distress syndrome, the impairment of pulmonary function in extremely preterm infants persists [6,7]. Hacking et al. [7] compared two cohorts of extremely preterm infants with gestational age at birth below 28 weeks at an age of 8 years old; one group was born between 1991 and 1992, the other between 1997 and 1998, finding similar results for both groups, including a significant reduction in the values of FEV_1 and FEF_{25-75} in extremely preterm children.

However, even preterm infants who had no serious respiratory diseases during the neonatal period may later develop impairments in

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their pulmonary function. Friedrich et al. [8] compared the pulmonary function of 62 healthy preterm infants who needed mechanical ventilation for at most 48 h with 27 term newborns during the first month of life, and observed that 31% of preterm infants had a pulmonary flow lower than the 50th percentile, 32% had a flow between the 25th and 75th percentiles, and 10% had a flow below the reference 5th percentile.

Within this context, the objective of this study was to assess pulmonary function in very low birth weight preterm children with corrected ages between 6 months and 1 year and analyze the factors associated with impairment of pulmonary function in these infants.

2. Methods

A cross-sectional study was conducted on infants with corrected ages between 6 months and 1 year, after approval by the Ethics Committee of the Federal University of São Paulo, SP, Brazil (CEP UNIFESP: 1864-08) and signature of a Declaration of Consent by the parents of all children included in the study.

The study included infants aged 6 months to 1 year of corrected age, born at gestational age < 37 weeks and birth weight < 1500 g and followed up at the institution's premature outpatient clinic. Infants with congenital malformations or affected by neuromuscular diseases were excluded from the study, as well as those with respiratory symptoms during the 15 days preceding the pulmonary function test.

The demographic and clinical background of all children included in the study were assessed by consulting their medical records; history of wheezing was assessed using the questionnaire developed by the International Study of Wheezing in Infants (EISL) [9].

Pulmonary function tests were performed after sedation with chloral hydrate (60–80 mg/kg); patients' heart rate and peripheral oxygen saturation were continuously monitored during the tests.

Pulmonary volumes were measured by total body plethysmography using a 90-L plethysmograph (Infant Pulmonary Lab, Collins-nSpire, USA). Measurements were performed according to existing recommendations [10], after daily calibration. In brief, functional residual capacity (FRC) was calculated using the variations in mouth pressure and plethysmograph pressure measured during spontaneous respiratory movements against the occluded airway. At least 3 technically acceptable sequences were obtained for each patient, each with 3 inspirations; the FRC was registered using the average values of the technically acceptable curves obtained.

Forced expiratory flows were obtained using the raised volume rapid thoracic compression technique with Infant Pulmonary Lab equipment, following international recommendations [11]. In short, flow-volume curves were obtained by compression of an inflatable jacket positioned around the thorax and abdomen. Positive pressure inflation of the lungs (30 cm H_2O) was done prior to compression. Thoracic and abdominal compression continued until the end of expiration (identified visually), or for 4 s at most. The thoracic and abdominal compression pressure was raised until no further increase was noted in flow and forced volume values (flow limitation). The best curve among those considered technically acceptable was chosen based on the sum of forced vital capacity (FVC) and forced expiratory flows between 25% and 75% of the FVC (FEF_{25-75}) [11]. The following parameters were registered: FVC, forced expiratory volume during the first half second ($FEV_{0.5}$), forced expiratory flow (FEF) at 50% of the FVC (FEF_{50}), FEF at 75% of the FVC (FEF_{75}), FEF at 85% of the FVC (FEF_{85}), and FEF_{25-75}.

Given that thoracic and abdominal compression continued until the residual volume (RV) was reached, the expiratory reserve volume (ERV) was calculated as the volume difference between the FRC and the volume at the end of thoracic compression. RV was calculated as the difference between FRC and ERV, and total lung capacity (TLC) was calculated as the sum of FVC and RV [12].

Pulmonary function parameters were registered as their z-scores or as the percentage of predicted values according to available reference values [12,13]. Values were considered altered when they were < 80% of predicted values, or when their z-score was < −2 [12,14]. Patients with z-scores < −2 for $FEV_{0.5}$, $FEV_{0.5}$/FVC or FEF were considered to have obstructive pulmonary disease, while patients with TLC < 80% the predicted value were considered to have restrictive pulmonary disease [12,14].

3. Data and statistical analysis

This study used a convenience sample of very low birth weight preterm infants monitored in the institution's preterm outpatient clinic whose parents accepted their participation in the study.

Preterm infants were compared to a control group of same-aged children born at term, without chronic or respiratory disease and having had at most one episode of wheezing prior to their inclusion in the study. Control infants were subjected to pulmonary function tests carried out by the same team, in the same laboratory and using the same methodology and equipment employed for the preterm infants included in this study. Pulmonary function was performed after approval of the Ethic Committee of the Institution and signature of the Informed Consent Form by the parents of all children included in the study (CEP 1345/09).

Numerical variables were initially analyzed using Kolmogorov-Smirnov test. Normal distributed variables were expressed as mean and standard deviation and compared by t-student tests. Numerical variables with non-normal distribution were expressed as median and minimum – maximum values an compared by Mann-Whitney tests. Categorical variables were compared with χ^2 tests or Fisher's exact tests. Linear regressions were used to analyze the factors associated with reduced percentages of predicted values or reduced z-score values for pulmonary function parameters. Statistical analyses were performed using the software *SPSS for Windows/v.17.0* (*IBM SPSS Statistics, Somers, NY, USA*), considering p-values < 0.05 as significant.

4. Results

We studied 51 preterm infants and 37 infants born at term for which adequate pulmonary function curves were obtained. At birth, the preterm infants included in the study had a gestational age of 30.0 ± 2.5 (25–34 weeks), weighed 1179 ± 247 (605–1495 g), measured 36.5 ± 2.5 (31–42 cm) and had 5 min Apgar scores of 9 (3–10); 18 of them (35.3%) were small for their gestational age. Thirty-eight (38, or 74.5%) of the preterm infants were delivered via caesarean section, and 24 (47.1%) were male. During the time spent in the neonatal ICU, 26 infants (51.0%) presented with respiratory distress syndrome, 1 (2.0%) with pneumonia, 13 (25.5%) had patent ductus arteriosus, 10 (19.6%) had early-onset sepsis, 10 (19.6%) had late-onset sepsis, 20 (39.2%) presented with peri-intraventricular hemorrhage, 9 (17.6%) had retinopathy of prematurity, 14 (27.5%) were oxygen dependent 28 days after birth, while 7 (13.7%) were oxygen dependent at a corrected age of 36 weeks, and 23 (45.1%) were subjected to mechanical ventilation for a median period of 5 days (range: 1–35 days). The median time of hospitalization in the neonatal unit was 55 days (range: 25–128 days).

After discharge from the neonatal unit, 34 preterms (66.7%) had at least one wheezing episode, 18 term infants (46.6%) had one wheezing episode. The number of wheezing episodes was higher in preterm infants [median 2 (0–4) vs. 0.0 (0–1), Mann-Whitney test p < 0.001]. Moreover, 10 (19.6%) preterm infants had recurrent wheezing, with three or more episodes, 18 (35.3%) presented with bronchiolitis, and 9 (17.6%) with pneumonia. While no infant born at term was hospitalized, 20 (39.2%) preterms needed hospitalization and the median number of hospitalizations varied between 1 and 5 for these infants.

Both groups (preterm and term infants) were similar in their familial history of asthma (33.3 vs. 43.2%, χ^2 test, p = 0.343), rhinitis (58.8 vs. 62.2%, χ^2 test, p = 0.752) and atopic dermatitis (15.7 vs. 13.5%, χ^2

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