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Pre/Postbronchodilator Interrupter Resistance in Former Preterm Children During Preschool Age

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Abstract

The primary aims of this study were to determine the pulmonary outcome of very low birth weight (VLBW) infants and to use interrupter resistance (Rint) measurements in testing bronchoreactivity at preschool age. The study group (n=15) was composed of preschool children who were born at less than 32 weeks gestation who were all mechanically ventilated during the newborn period. The control group (n=15) consisted of healthy children who were born at term and had not experienced any acute or chronic respiratory problems. A detailed history and physical examination were completed at the time of Rint testing. Rint measurement, reversibility to salbutamol and skin prick tests were performed. Resistance measurements made with the interrupter technique were subdivided into inspiratory (Rint insp) and expiratory (Rint exp) values. Eighty-five percent of all preschool children were able to perform Rint measurement. Median Rint insp value was significantly higher in the study group than the controls (0.74 and 0.53 Kpa.L-1.sec, respectively). Median Rint exp values of the study group (0.64 Kpa.L-1.sec) were not statistically significantly different than those of the control group (0.49 Kpa.L-1.sec). Pre-/post-bronchodilator Rint insp values of the study group were significantly different as well (0.74 and 0.64 Kpa.L-1.sec, respectively, p=0.01). Children born before 32 weeks of gestation had higher Rint insp values at preschool age. The interrupter technique is a noninvasive test and can be used to assess airway obstruction in young children who fail to cooperate with forced expiratory measurements.

Keywords: preterm, pulmonary function test, interrupter resistance, Rint

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INTRODUCTION

Survival rates of very low birth weight (VLBW) preterm infants who require respiratory support during the neonatal period have been improving; however, these infants are at high risk of respiratory morbidity during infancy and childhood [1]. In several studies, former preterm children were reported to have reduced lung functions during childhood and adolescence [2,3].The ability to assess respiratory function is important for evaluation of a child with pulmonary symptoms. Pulmonary function tests (PFT) are helpful in establishing a diagnosis, evaluating the severity of impairment and providing effective care [4]. Children under six years of age cannot reproducibly perform lung function measurements that require active cooperation. The interrupter resistance (Rint) is a non-invasive technique for estimating airflow resistance [5,6]. Respiratory resistance measured by this technique provides objective measurement of lung function during tidal breathing in nonsedated preschool children [7,8,9,10,11]. Rint measurements have been used in asthmatic children for testing bronchoreactivity [7,8,12]. To our knowledge, Rint before and after bronchodilator inhalation has not been determined previously in former preterm children at preschool age. In this study, we aimed to evaluate the respiratory health of preschool children who were born before 32 weeks gestation and received respiratory support during the neonatal period using Rint measurements to test bronchoreactivity in these children.

MATERIALS AND METHODS

Subjects

The study group consisted of children aged 2-5 years who were born before 32 weeks of gestation and received respiratory support during the neonatal period. The median duration of respiratory support was seven days. Respiratory support was defined as continuous positive airway pressure or intermittent positive pressure ventilation. Bronchopulmonary dysplasia (BPD) was defined as oxygen requirement at postmenstrual age of 36 weeks. The control group was composed of preschool children who were born at term and had not had any respiratory or cardiac disease. The study coordinator performed a physical examination on each child on the day of the study including height and weight measurement. A detailed history was obtained regarding the respiratory symptoms and medications. The Rint measurements were postponed to a later date if the

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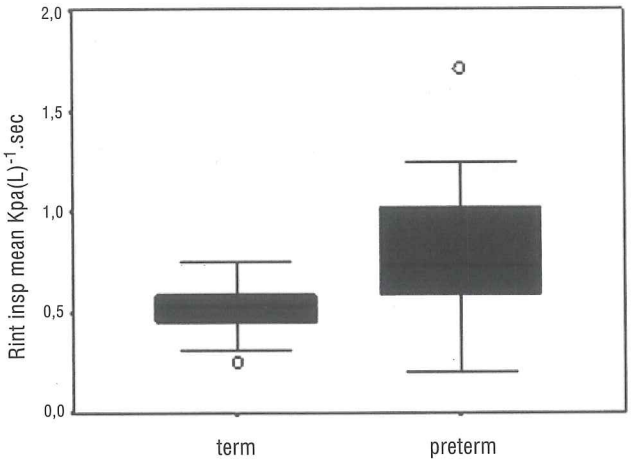

Figure 1: Rint insp values of former term and preterm children at preschool age

children in either the study or control group had a respiratory infection during the last four weeks. Previous hospitalizations due to respiratory illness were recorded. Neonatal data of the former preterm children were obtained from hospital records. Family history for atopic diseases was questioned. Record was made of any children exposed to passive smoke at home. Tobacco smoke exposure was defined as exposure of >2 cigarettes/day [7]. All children had screening skin prick test for pollens, house dust, cat and dog epithelia, and molds. The study was approved by the local ethics committee and informed consent was obtained from the parents of the children in the study.

Rint measurement procedure

All measurements were performed by using a single commercial device (Micro Lab 4000; Micro Medical Ltd, Gillingham, UK) throughout the study. Flow calibration was performed before each measurement. Each child was first familiarized with the measuring instrument. They breathed quietly through a cardboard mouthpiece (2.7 cm diameter) with the nose clipped and neck slightly extended [13]. After a period of quiet breathing, in response to a trigger during respiration at the peak of tidal flow, a single shutter closed automatically within 10 ms and stayed closed for 100 ms. One or two practice attempts were made before starting to record data. Subjects were unable to anticipate the trigger but were able to hear the valve closing.

All Rint values measured during breathing cycles disturbed by a respiratory pause, crying or coughing were discarded. In addition, investigators examined the x/y graph for the mouth pressure (Pm) flow and deleted Rint data for which Pm values were aberrant relative to flow [14]. At least five validated Rint measurements with a coefficient of variation of 20% or less were obtained for calculation of the median Rint value of a child. Rint was measured in former preterm children first during expiration (Rint exp) and then during inspiration (Rint insp) immediately before and 15 minutes after bronchodilator inhalation of 200 mcg of salbutamol administered using a meter dose inhaler and a spacer. Rint was measured in healthy control subjects first during Rint exp and then during inspiration Rint insp.

Statistical analysis

Data were analyzed using SPSS for Windows programs. Differences in dichotomous variables were contrasted by chi-square analysis and differences in continuous variables compared by Mann-Whitney U test. Wilcoxon test was used for paired samples. Coefficients of variation of the measurements in different groups were compared by Mann-Whitney U test.

RESULTS

Table 1 shows the demographic characteristics of the study and control groups. The children in the study group had achieved catch-up growth and did not show any significant difference in anthropometric measurements at preschool age. Of 15 preterm children seen at age 3-5 years, birth weight was less than 1000 g in 20% (n=3); all ex-preterm children were mechanically ventilated in the newborn period. Of the preterm children, 26% (n=4) had BPD, 40% (n=6) received respiratory syncytial virus (RSV) immunoglobulin (palivizumab), 20% (n=3) had lower respiratory tract infections that required emergency room visit or hospitalization in the first two years of life, and 46% (n=7) needed to use bronchodilator or inhalational steroids. There were no children using bronchodilator at the time of the study.

The number of term and preterm children who had a family history of atopic disease was not statistically significantly different between groups [50% (n=6) versus 23.1% (n=3), respectively]. The number of term and preterm children who had smoker in the household was not significantly different between groups [41.7% (n=5) versus 23.1% (n=3), respectively]. None of the children in the study or control groups had positive skin prick test results. The study group did not differ significantly for males (n=9) and females (n=4) with respect to Rint insp (0.80 versus 0.88, respectively) and Rint exp (0.65 versus 0.64, respectively) measurements. The control group did not differ significantly for males (n=4) and females (n=8) with respect to Rint insp (0.50 versus 0.51, respectively) and Rint exp (0.38 versus 0.48, respectively) measurements.

Eighty-five percent (n=25) of all preschool children were able to perform Rint measurement, including two children with mild neuromotor disability. Of five children

Table 1. Demographic values of term and preterm children

	Term		Preterm		p
	Median	25%-75%	Median	25%-75%	
Current age	3.8	3.4-4.7	4.0	3.2-5.3	0.8
Actual height (cm)	104.0	98.5-110.0	102	94-108	0.6
Actual weight (kg)	16.5	15.2 -17.0	15.0	13.7-21.2	0.8
Birth weight (g)	3655	3215-3927	1500	1247-1575	<0.05
Sex (n) (F/M)	8 / 4		4 / 9		

Table 2. Rint insp and Rint exp values of former preterm children (n=13) pre- and post- bronchodilator administration

	Inspiratory	Expiratory
	Median	Median
Pre-bronchodilator	0.742	0.646
Post-bronchodilator	0.646	0.596
p	0.01	0.5

who were not able to perform Rint measurement, two were former preterm. Median coefficient of variation of the Rint insp values were 8.4% (6.6-13.8) and 9.5% (6.0-17.4) in study and control groups, respectively (p=0.5). Median coefficient of variation of the Rint exp values were 16.5% (7.4-27.6) and 7.8% (4.0-14.9) in study and control groups, respectively (p=0.06). Median Rint insp value (0.74 Kpa.$(L)^{-1}$.sec) was significantly higher (p=0.01) in study group than the controls (0.53 Kpa.$(L)^{-1}$.sec). Figure 1 shows the Rint insp values of the term and preterm children. Median Rint exp value of the study group (0.64 Kpa.$(L)^{-1}$.sec) was not significantly different (p=0.08) than that of the control group (0.49 Kpa.$(L)^{-1}$.sec). Figure 1 shows the Rint exp values of the term and preterm children. Pre- and post-bronchodilator Rint insp values of the study group were significantly different as well (0.74 and 0.64 Kpa.$(L)^{-1}$.sec, respectively, p=0.01). Pre- and post-bronchodilator Rint exp values of study group were not significantly different (0.64 and 0.59 Kpa.$(L)^{-1}$.sec, respectively, p=0.5) (Table 2).

DISCUSSION

The aim of this study was to determine pulmonary outcome in former preterm children at preschool age and to use Rint to test bronchoreactivity of former premies. In our study, former preterm children had frequent respiratory symptoms, needed to use bronchodilator treatment, and had frequent hospitalizations due to lower respiratory tract infection in the first two years of life. Children who were born before 32 weeks gestation had significantly higher Rint insp values than the healthy control children at 3-5 years.

The interrupter technique is a non-invasive technique for estimating airflow resistance. This technique requires only quiet breathing and is based on measurements of tidal airflow and mouth pressure before and directly after closure of a fast shutter near a pneumotachograph [12,15]. The ratio between pressure difference and airflow equals the Rint. Rint measurements have been correlated closely with spirometric values [9,16]. In this study, we investigated Rint with a portable device. It was feasible to obtain reliable measurements of Rint in the majority of children older than three years, including two children with mild neuromotor disability.

Rint was reported to be significantly and negatively correlated with age and height, reflecting the increase of airway dimensions with growth [10,11,17]. In our study, the age and height of study and control groups were similar. The numbers of children who had a family history of atopic disease or who had a smoker at home were also not different between study and control groups. Higher Rint insp values of former preterm children in comparison to healthy children were mediated through prematurity rather than differences of growth, especially height, smoke exposure or risk of atopy. In this preliminary study, the sample size was small, thus these findings should be retested in future studies with larger sampling sizes.

Rint is calculated from the ratio of the alveolar pressure (estimated from mouth pressure during occlusion) to flow prior to interruption [13]. The effect of direction of flow before occlusion (inspiration versus expiration) can be assessed as well [18]. It has been reported that Rint insp is higher than Rint exp before five years of age. It was reported that the size of the nasopharyngeal airway decreased between 3 and 5 years of age because the surface area of the soft tissues grew faster than that of the nasopharyngeal airway. At the oropharyngeal level, a faster increase in the surface area of soft tissues as compared with that of the pharyngeal airway may result in an increase in upper airway resistance. If this is the case, the reduction in glottal opening during expiration may not exceed that of the pharyngeal lumen, thus explaining the lower Rint exp than Rint insp in young children [7]. The difference between Rint insp and Rint exp decreases with age [7,8,19]. Similar to these reports, in our study, Rint insp was higher than Rint exp in all preschool children. This indicates that Rint insp data and Rint exp data should be reported separately in young children as done in our study. In previous studies, Rint insp and Rint exp did not differ significantly in boys and girls [10,11,20]. We also found no difference in Rint measurements between sexes in the present study.

In each subject, five sequentially obtained technically satisfactory measurements were done, and intra-measurement variability was satisfactory in both groups. In our study, Rint was measured immediately before and 15 minutes after bronchodilator inhalation in former preterm children using a meter dose inhaler and a spacer. Bridge et al. [18] have suggested an absolute change in Rint that exceeded 0.21 Kpa.$(L)^{-1}$.sec as reflection of significant reversibility of airway obstruction. Nielsen et al. [21] found that an absolute change of >0.34 Kpa.$(L)^{-1}$.sec indicates reversibility of airway obstruction by bronchodilators in asthmatic children. In our study, Rint insp values after short acting bronchodilator inhalation were significantly lower than pre-bronchodilator Rint insp values, but the absolute change in Rint insp was smaller than 0.21 Kpa.$(L)^{-1}$.sec. Pre-post bronchodilator Rint exp values were not significantly different in our study. Bronchodilator response was expected to be larger in Rint exp measurements since bronchial obstruction increases more in the expiratory phase of respiration. As inadequate absolute change in Rint insp and no statistical difference in Rint exp in response to bronchodilator were achieved in our study, we concluded that the ex-preterm children clinically did not respond to the bronchodilators.

Whole body plethysmography (WBP) is a sensitive method in assessing bronchodilator responsiveness in preschool children [21]. The sensitivity of WBP was reported to be similar to spirometry and higher than interrupter technique [21,22]. Although WBP has been successfully applied to young children, some limitations exist. To measure specific airway resistance (sRaw) by this technique, the child must sit inside a closed, constant volume WBP for several minutes and breathe quietly through a pneumotachograph [13,23,24]. The limitations of using WBP include the expense required in purchasing the necessary equipment as well as the patience needed to complete the test if the child refuses to sit inside the equipment.

The forced oscillation technique (FOT) is a non-invasive method for measuring respiratory mechanics. FOT employs small-amplitude pressure oscillations on the normal breathing and does not require the performance of respiratory manoeuvres. Values of respiratory resistance have proven sensitive to bronchodilation in healthy and asthmatic children, although the reported cut-off levels remain to be confirmed in future studies. Limitations of FOT in preschool children include poor tolerance of the dead space of the test instruments and impaired discriminative power [25]. Malmberg et al. [26] described higher airway resistance and lower reactance in preterm children with chronic lung disease (CLD) than in preterms without CLD and healthy controls at school age. More studies are needed to characterize the changes in airway resistance during growth in these children [25].

Premature infants are at high risk for long-term pulmonary morbidity [27]. There are reports of respiratory function of preterm children born during the 1980's from the pre-surfactant era. Anand et al. [2] have reported that there was a reduction in adolescent lung function indices reflecting medium- and small-sized airway obstruction in former preterm children. There was no association between respiratory support in the neonatal period and reduced lung function indices during adolescence. Rona et al. [3] found a significant association with low birth weight and poor forced expiratory function at 5-11 years. Respiratory symptoms, especially wheezing, were significantly associated with prematurity. Every extra week of gestation decreased the risk by 10%. In this study, we found that respiratory symptoms, especially wheezing and the need for bronchodilator therapy, were frequent in former preterm children at preschool age. In our preliminary study, we did not perform subgroup analysis according to birth weight, presence of BPD, corticosteroid treatment for BPD or smoke exposure among former preterm children because of the small sample size. Future studies with larger sample sizes are necessary to provide this information.

In conclusion, children born before 32 weeks of gestation have frequent respiratory problems at preschool age and require long-term follow-up. Interrupter technique is a non-invasive test and is useful in assessing airway obstruction in former preterm children at preschool age. Future trials with interrupter technique with larger sample sizes would provide information about the airway resistance and reactivity of former preterm children at preschool age.

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