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Original Article

Evaluation of lung function on impulse oscillometry in preschool children born late preterm

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Abstract ***Background:*** There is a paucity of data on lung physiology in late-preterm children, who may be exposed to a risk of decline in lung function during childhood. In this study, we evaluated lung function in preschool children born late preterm using impulse oscillometry (IOS), and compared the results with those obtained in healthy term-born children.

Methods: Children between 3 and 7 years of age who were born late preterm and who were being followed up at the outpatient clinic were included as the late-preterm group. Age-matched healthy term-born children served as controls. A total of 90 late-preterm and 75 healthy children were included in the study. At 5–20 Hz, resistance (R5–R20), reactance (X5–X20), impedans (Z5) and resonant frequency were measured on IOS.

Results: Mean IOS R5 and R10 were significantly higher in the late-preterm group than in the control group ($P < 0.05$). Mean R5, R10 and Z5 were statistically higher in late-preterm children who had been hospitalized for pulmonary infection compared with the control group ($P < 0.05$). Mean R5, R10, R15, R20 and Z5 were significantly higher, and mean X10 and X15 significantly lower in late-preterm children with passive smoking compared with late-preterm children without passive smoking and controls ($P < 0.05$).

Conclusion: Children born late preterm had signs of peripheral airway obstruction on IOS-based comparison with healthy term-born controls. Besides the inherent disadvantages of premature birth, hospitalization for pulmonary infection and passive smoking also seemed to adversely affect lung function in children born late preterm.

Key words impulse oscillometry, late preterm, lung function.

Late preterm is defined as birth at 34 0/7–36 6/7 weeks of gestation in the late saccular stage, when lung development is still proceeding. Given that lung development is a programmed process, its interruption may render the lungs less effective and more susceptible to infection.[1,2] Late-preterm subjects are a growing population and account for approximately 60% and 74% of all preterm births in Turkey[3] and in the USA,[4] respectively. Despite the well-defined immediate neonatal respiratory risks,[5,6] the impact of late-preterm delivery on long-term respiratory outcome in children and the association between the occurrence of asthma and late prematurity have only recently been recognized.[7,8] Furthermore, there is a paucity of data on lung physiology in late-preterm children, who may be exposed to the risk of decline in lung function during childhood.[9,10] Impulse oscillometry (IOS), is a non-invasive, rapid and feasible methodology that is used as an indicator of lung function. IOS requires minimum cooperation from the patients and can be used easily in preschool children.[11]

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In this study, we evaluated lung function using IOS in preschool children born late preterm who were being followed up at the outpatient clinic, and compared the results with those of a group of healthy term-born children.

Methods

Participants and study design

This prospective study was designed by the Kocaeli University Department of Neonatology between 2013 and 2014. Children between 3 and 7 years of age born at 34 0/7–36 6/7 weeks of gestation who had been admitted to the neonatal intensive care unit for any reason after delivery and who were being followed up at the outpatient clinic represented the target sample for this study. Due to the known association between asthma and change in IOS parameters,[11] late-preterm children with physician-diagnosed asthma were excluded from the study. Patients with a diagnosis of congenital cardiac, pulmonary and/or muscle diseases were excluded also. For the remaining late-preterm children, information was collected on the following three areas of interest: (i) perinatal history; (ii) asthma status as defined by the International Study of Allergy and Asthma in Children[12] for children older than 6 years of age and as defined by the modified Asthma Predictive Index[13] for children younger than 6 years of age; and (iii) history of

hospitalization for lung infection and passive smoking. Age-matched healthy controls were chosen for the study according to criteria proposed by the American Thoracic Society (ATS). Premature birth, low birthweight, obesity, previous mechanical ventilation, presence of congenital cardiac or muscle disease, exposure to environmental cigarette smoking and diagnosis of asthma were used as exclusion criteria in healthy controls.[14] In addition, children with a respiratory tract infection in the preceding 2 weeks before the study were excluded both from the study and control groups.

Impulse oscillometry

Impulse oscillometry was performed while the child was in a sitting position, holding his/her head in a neutral position, and breathing quietly through a mouthpiece. A nose-clip was used and the cheeks were supported by the hands. Testing is performed at 30 s intervals. While the patient is breathing normally, the IOS apparatus generates small pressure oscillations that are transmitted into the lungs to determine the impedance (Z) of the respiratory system. Pulmonary resistance (R) and reactance (X) are the components of Z. Pulmonary R is the energy required to propagate the pressure wave through the airways and is a measure of central and peripheral airway caliber. X is the amount of recoil generated against that pressure wave and indicates the elastic recoil properties of the lung tissue.[11,15,16] IOS measures R and X over a range of frequencies (5–20 Hz). A lower-frequency oscillation, generally is transmitted into the peripheral lung and is an index of the airway status in the entire pulmonary system. Therefore, when either proximal or distal airway obstruction occurs, R5 may be increased. Disease limited to distal airway, however, is associated with a greater increase in R5 than in R20, while disease limited to the proximal airway will be reflected as a similar increase in R5 and R20. The difference between R5 and R20 (R5 minus R20) as an index of frequency dependence of resistance is also reported to be a sensitive index of peripheral airway obstruction. Higher frequency oscillations provide information regarding the central airways. Reactance is equal to zero at the point where frequency transitions from passive distention to active stretch in the lungs; this point is referred to as the resonant frequency (F_{res}). It is dependent on physical properties of chest size and tissue components.[11] Coherence is the correlation between airflow and pressure, and reflects the reliability of the IOS measurements. For 30 s of testing, acceptable coherence values are $\geq$0.6 at 5 Hz and $\geq$0.8 at 10 Hz.[17]

In the present study, a Jaeger Master screen IOS system (Wurzburg, Germany) was used. The system was calibrated each day for room temperature and humidity prior to measurement. Gender, height and weight for each child were recorded on IOS data. Mean R and X were calculated in the frequency range of 5–20 Hz. A series of three measurements was performed at each test time-point. The best measurement with a regular breathing process was analyzed.

The study was approved by the ethics committee of Kocaeli University (2013/138), and informed consent was obtained from the parents prior to participation in the study.

Statistical analysis

IBM SPSS 20 (SPSS, Chicago, IL, USA) was used to analyze data. The results are expressed as mean ± SD and as n (%). Normality was tested using Kolmogorov–Smirnov test. Between-group differences were analyzed using Mann–Whitney *U*-test and Kruskal–Wallis test. Categorical variables were assessed with Pearson chi-squared test and Fisher's exact test. $P < 0.05$ was considered statistically significant.

Results

Participants

Database search identified a total of 150 late-preterm children between 3 and 7 years of age who were currently being followed up at the outpatient clinic. Of these, 11 were excluded from the study due to established diagnosis of congenital cardiac, pulmonary or muscular disease. Of the remaining 139 late-preterm children, 48 (34.5%) were excluded due to diagnosis of asthma. One patient was not able to cooperate during IOS test. Thus, a total of 90 non-asthmatic late-preterm children and 75 healthy controls were included in the study. The mean age of late-preterm and control children was 67.4 ± 15.8 and 68.3 ± 16.5 months, respectively. Weight and height percentiles in both groups were within normal limits and there were no statistically significant differences between the groups in terms of anthropometric measurements.

Late-preterm subject characteristics

During the postnatal period, diagnosis at first admission in late-preterm children included respiratory disorder (RD; 60%), transient tachypnea of the newborn (30.6%), neonatal pneumonia (28.1%) and meconium aspiration syndrome (1.3%). The remaining patients had been diagnosed with non-RD. A total of 14.4% of the late-preterm patients with RD received surfactant for respiratory distress.

A history of passive smoking and at least one hospitalization for bronchiolitis or pneumonia were present in 58.9% and in 30% of the late-preterm children, respectively. Other characteristics of these subjects are listed in Table 1.

Table 1 Late-preterm subject characteristics

Late preterm n = 90	Mean ± SD or n(%)
Gestational weeks	35.27 ± 0.90
Birthweight (g)	2429.62 ± 514.71
Male	57 (63.3)
Caesarean section	75 (83.3)
APGAR score at 5 min	9.32 ± 0.72
Diagnosis	
Respiratory disorder	54(60)
Non-respiratory disorder	36 (40)
Respiratory support	37 (41.1)
Surfactant treatment	13 (14.4)
Duration of hospitalization (days)	6.64 ± 5.13
Maternal asthma during pregnancy	5 (5.6)
Passive smoking	53 (58.9)
Hospitalization for pulmonary infection	27 (30)

IOS results

A total of 90 late-preterm children and 75 healthy controls underwent IOS. Mean R5, R10, R5–R20 and Z5 were significantly higher in late-preterm children than in controls ($P < 0.05$). Other IOS parameters did not differ significantly between the two groups ($P > 0.05$). Mean IOS results are listed in Table 2.

The late-preterm children and controls were also compared with regard to a number of clinical factors that may affect IOS results, including the following.

Gestational age and IOS

The late-preterm children were divided into 34, 35 and 36 week gestation groups, respectively. Each of these subgroups and controls were also compared with regard to IOS results. No statistical differences were found between the groups ($P > 0.05$; data not shown).

Diagnosis of RD during the neonatal period and IOS parameters

The late-preterm patients were classified according to presence of RD during the neonatal period. Those with a history of neonatal RD were referred to as the RD group, and those without as the non-RD group. On comparison of IOS results between the RD group, non-RD group and controls, there were no significant differences ($P > 0.05$; data not shown).

Also, there were no significant differences in IOS results among the late-preterm patients in terms of surfactant therapy in the postnatal period ($P > 0.05$; data not shown).

Hospitalization for pulmonary infection and IOS results

Similarly, late-preterm children were subgrouped according to history of hospitalization for pulmonary infection. Those who had been hospitalized for pulmonary infection were termed the HPI group, and those who had not were termed the non-HPI group. On comparison between the HPI group, non-HPI group, and controls there was a significantly higher R5, R10 and Z5 in the HPI subjects compared with the controls ($P < 0.05$). There were no significant differences between the three groups for other IOS parameters (Table 3).

Passive smoking and IOS results

The late-preterm children were also subcategorized according to passive smoking exposure. Those with and without exposure to passive smoking were referred to as the PS group and the non-PS group, respectively. One comparison of the PS, non-PS and controls there were significant differences in mean R5, R10, R15, R20, Z5 and X10, X15 ($P < 0.05$). Accordingly, mean R5, R10, R15, R20 and Z5 were significantly higher and, conversely, mean X10 and X15 were significantly lower in the PS group compared with the non-PS group and controls ($P < 0.05$; Table 4).

Table 2 IOS results

IOS	Late-preterm children (n = 90)		Controls (n = 75)		*P*
	Mean	SD	Mean	SD	
R5 kPa/(L/s)	0.96	0.29	0.88	0.25	**0.028**
R10 kPa/(L/s)	0.82	0.20	0.75	0.19	**0.037**
R15 kPa/(L/s)	0.76	0.18	0.72	0.18	0.158
R20 kPa/(L/s)	0.70	0.17	0.67	0.17	0.197
R5-R20 kPa/(L/s)	0.25	0.17	0.20	0.12	**0.018**
X5 kPa/(L/s)	–0.27	0.11	–0.26	0.11	0.719
X10 kPa/(L/s)	–0.15	0.09	–0.12	0.07	0.079
X15 kPa/(L/s)	–0.09	0.08	–0.07	0.06	0.091
X20 kPa/(L/s)	–0.00	0.08	0.01	0.05	0.337
F_{res} (1/s)	19.57	3.72	18.52	4.69	0.240
Z5 kPa/(L/s)	1.00	0.28	0.91	0.27	**0.030**

F_{res}, resonant frequency; IOS, impulse oscillometry; R, pulmonary resistance; X, pulmonary reactance; Z, pulmonary impedance.

Discussion

In this study, lung function in preschool children born late preterm who were currently being followed up at the neonatal outpatient clinic was compared with that in healthy term children in terms of IOS results. Significantly increased distal airways resistance, as reflected by the differences in mean R5, R10 and R5–R20,was noted in children born late preterm compared with controls. This is indicative of peripheral airway obstruction in these children.

Preterm delivery is known to be associated with potential adverse effects on lung development and may result in alterations of pulmonary function.[18,19] These effects are generally different to those observed in infants born before 32 week of gestation,[10,20]

Table 3 IOS results vs presence of hospitalization for pulmonary infection

IOS	HPI (n = 27)		Non-HPI (n = 63)		Control (n = 75)		*P*
	Mean	SD	Mean	SD	Mean	SD	
R5 kPa/(L/s)	1.00	0.22	0.94	0.31	0.88	0.25	**0.019**†
R10 kPa/(L/s)	0.86	0.19	0.79	0.19	0.75	0.19	**0.036**†
R15 kPa/(L/s)	0.81	0.17	0.74	0.18	0.72	0.18	0.065
R20 kPa/(L/s)	0.74	0.16	0.68	0.17	0.67	0.17	0.128
X5 kPa/(L/s)	–0.28	0.08	–0.26	0.11	–0.26	0.11	0.702
X10 kPa/(L/s)	–0.15	0.07	–0.14	0.10	–0.12	0.07	0.149
X15 kPa/(L/s)	–0.10	0.08	–0.09	0.08	–0.07	0.06	0.120
X20 kPa/(L/s)	–0.02	0.11	–0.00	0.07	0.01	0.05	0.222
F_{res} (1/s)	20.46	4.01	19.18	3.50	18.52	4.69	0.149
Z5 kPa/(L/s)	1.05	0.22	0.98	0.30	0.91	0.27	**0.020**†

†HPI group vs controls. F_{res}, resonant frequency; HPI, hospitalized for pulmonary infection; IOS, impulse oscillometry; R, pulmonary resistance; X, pulmonary reactance; Z, pulmonary impedance.

Table 4 IOS parameters vs passive smoking status

IOS	PS (n = 53)		Non-PS (n = 37)		Controls (n = 75)		*P*
	Mean	SD	Mean	SD	Mean	SD	
R5 kPa/(L/s)	1.03	0.30	0.86	0.22	0.88	0.25	**0.002**[§,†]
R10 kPa/(L/s)	0.86	0.19	0.74	0.16	0.75	0.19	**0.003**[§,†]
R15 kPa/(L/s)	0.80	0.18	0.70	0.17	0.72	0.18	**0.020**[§,†]
R20 kPa/(L/s)	0.73	0.17	0.65	0.16	0.67	0.17	**0.027**[§,†]
X5 kPa/(L/s)	–0.28	0.10	–0.24	0.10	–0.26	0.11	0.058
X10 kPa/(L/s)	–0.17	0.11	–0.11	0.05	–0.12	0.07	**0.003**[§,†]
X15 kPa/(L/s)	–0.11	0.10	–0.06	0.06	–0.07	0.06	**0.015**[§,†]
X20 kPa/(L/s)	–0.01	0.08	–0.00	0.09	0.01	0.05	0.134
F_{res} (1/s)	20.28	3.59	18.51	3.59	18.52	4.69	0.077
Z5 kPa/(L/s)	1.07	0.30	0.89	0.20	0.91	0.27	**0.001**[§,†]

[†]PS group vs controls; [§]PS group vs non-PS. F_{res}, resonant frequency; IOS, impulse oscillometry; PS, passive smoking; R, pulmonary resistance; X, pulmonary reactance; Z, pulmonary impedance.

and the data suggest that children born late preterm could have a risk of declining lung function later in life.[9]

There is a paucity of data on the long-term outcome of lung function in children born late preterm.[9,10] In a study by Todisco *et al*., a group of children with a mean age of 11.6 years who were born at 34–36 weeks of gestation and who had no history of respiratory distress or mechanical ventilation were compared with their siblings born at term. The authors found that the mean residual volume and the residual volume/total lung capacity in both late-preterm children and their siblings were within the upper limit of normal.[21] Kotecha *et al*. found similar lung function in children born at 35 or 36 weeks of gestation and in healthy controls born at term, both at 8–9 and at 14–17 years of age.[22] In the present study on IOS measurements in children between 3 and 7 years of age who were born late preterm, a higher distal airway resistance was observed as compared with healthy age-matched controls. This is in contrast to the two aforementioned studies, which involved older children and spirometry. Given that the present hospital is a reference center for the district, the outpatient unit is attended by children born late preterm for the follow up of a variety of medical problems. Also, the fact that the control group was chosen on the basis of strict ATS criteria rather than randomized community-based sampling might also have influenced the present results. The main limitation of this study is that airway obstruction may have been overestimated. Therefore a longitudinal study is currently being planned to identify any improvement in lung function with age in this same patient group.

Most of the studies using IOS in preterm children had small sample sizes and involved very low-birthweight infants (VLBW) with chronic lung disease.[23,24] In a study by Malmberg *et al*. involving children between 5 and 10 years of age who were VLBW and healthy children born at full term, the correlation between oscillometry and conventional lung function tests was assessed. In children who were born prematurely, oscillometry yielded concordant information on the severity of lung function deficit obtained using other conventional methods, especially spirometry, leading to the conclusion that oscillometry may serve as an alternative method for the assessment of lung function in preschool children.[23] In contrast to other methods, IOS requires passive cooperation and can easily be carried out for young children. It can be used to diagnose, evaluate, and determine the treatment response in asthma and certain other pulmonary diseases.[11,23,25]

In the Malmberg *et al*. study, oscillometry in children born prematurely was characterized by significantly higher R5 and R10, lower X5 and X10, and higher F_{res} than in healthy children.[23] In the present study, significantly higher R5 and R10 were found in late-preterm children than in controls. There were no statistically significant differences in other parameters. Literature search did not identify any studies on IOS parameters in children with a history of late-preterm birth.

In late-preterm infants born at the late saccular stage of lung development, the volume and surface area of the lung are in a state of rapid increase.[1,26,27] It has been hypothesized that inadequate lung volume and the physiological instability of the chest wall are likely to be corrected subsequently due to the rapid growth rate in the first to second years of life, and thus should not lead to long-term pulmonary defects.[10] Being born with immature lungs, however, renders late-preterm children more susceptible to injury and infection.[2,10] It has been suggested that late-preterm delivery is a risk factor for increased incidence of respiratory disease in infancy or early childhood, especially due to viruses such as the respiratory syncytial virus.[27,28]

In the present study, there were no significant differences in IOS parameters between control and subgroups according to gestational age and history of neonatal RD. In contrast, history of hospitalization for pulmonary infection was a significant factor in IOS results. Significantly higher distal airway resistance was found in late-preterm children who had been hospitalized for pulmonary infection compared with healthy term controls. Two cohort studies also suggested that early respiratory infection in late-preterm infants may lead to reduced lung function in later life.[29,30] In the Broström *et al*. study, oscillometry showed higher resistance and more negative reactance in school children with a history of passive smoking.[31] Similarly, in the present study late-preterm children with passive smoking had significantly higher resistance and significantly lower reactance in airways as compared with healthy term controls and the late-preterm children without passive smoking.

In conclusion, the present findings suggest the presence of peripheral airway obstruction in late-preterm children as compared

with healthy term-born controls. Also, hospitalization for pulmonary infection and passive smoking were factors that had a negative impact on IOS parameters in children born at late preterm. In addition to late-premature birth, previous hospitalization for pulmonary infection and passive smoking are also likely to cause alterations in lung function in children born at late preterm. Therefore, lung function should be monitored in these children.

Disclosure

The authors declare no conflict of interest.

Ethics approval

The study was approved by the ethics committee of Kocaeli University.

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