



# Intra-breath oscillometry for the evaluation of lung function in children and adolescents with a history of preterm birth

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## ABSTRACT

**Objective:** To assess respiratory system impedance ( $Z_{rs}$ ) and spirometric parameters in children and adolescents with and without a history of preterm birth. **Methods:** We evaluated a sample of 51 subjects between 11 and 14 years of age: 35 who had a history of preterm birth (preterm group) and 16 who had been born at term (full-term group). Lung function was measured by spirometry, spectral oscillometry, and intra-breath oscillometry. **Results:** Neither spirometry nor spectral oscillometry revealed any statistically significant differences between the preterm and full-term groups. However, intra-breath oscillometry demonstrated significant differences between the two groups in terms of the change in resistance, reactance at end-inspiration, and the change in reactance ( $p < 0.05$  for all). **Conclusions:** Our findings suggest that abnormalities in  $Z_{rs}$  persist in children and adolescents with a history of preterm birth and that intra-breath oscillometry is more sensitive than is spectral oscillometry. Larger studies are needed in order to validate these findings and to explore the impact that birth weight and gestational age at birth have on  $Z_{rs}$  later in life.

**Keywords:** Oscillometry; Premature birth; Respiratory function tests; Respiratory mechanics; Spirometry.

## INTRODUCTION

Approximately 15 million children are born prematurely every year, corresponding to 11% of all live births worldwide. Of those 15 million children, approximately 1 million die within the first month of life because of respiratory complications.<sup>(1)</sup> The intrauterine environment plays an essential role in lung growth and in subsequent respiratory health. The interruption of that development resulting from preterm birth may do harm to the respiratory system. Although advances in neonatal intensive therapy have extended the survival of preterm infants, respiratory morbidity is a common complication.<sup>(2)</sup> Monitoring the lung function of such children over the mid- and long-term seems to have great relevance for the continuation of their respiratory development.<sup>(3)</sup> In addition to spirometry and other widely used pulmonary function tests, such monitoring can be performed by oscillometry, a technique that measures the respiratory system impedance ( $Z_{rs}$ ).<sup>(4)</sup> Although much is known about the lung function of children and adolescents who were born preterm, there are few data regarding their  $Z_{rs}$ .

Spirometry can aid in the decision-making process related to the control of the respiratory diseases, facilitating the diagnosis and allowing the quantification of ventilatory defects.<sup>(5)</sup> Previous studies using spirometry to assess preterm neonates throughout childhood have demonstrated that the degree of lung function impairment is inversely proportional to the gestational age (GA) at birth.<sup>(6)</sup>

Many authors have assessed patients who had been extremely preterm infants affected by respiratory diseases, mostly bronchopulmonary dysplasia, and have found lung function to be lower in such patients than in control subjects.<sup>(7-10)</sup> However, there have been few studies analyzing the lung function of individuals who had been moderately to late preterm infants and did or did not have neonatal respiratory diseases.<sup>(11-14)</sup>

Oscillometry is a noninvasive method to assess respiratory mechanics.<sup>(4,15)</sup> In comparison with spirometry, it has greater sensitivity and specificity in the evaluation of the peripheral airways.<sup>(16,17)</sup> Oscillometry measures the  $Z_{rs}$ , which is characterized by the combination of forces that oppose the movement of air in and out of the lungs.<sup>(4)</sup> The  $Z_{rs}$  is composed of respiratory system resistance ( $R_{rs}$ ), which reflects the resistance to friction in the respiratory system, and by respiratory system reactance ( $X_{rs}$ ), which expresses the sum of the elastic and inertial properties of tissues.

A comparative study of the applicability of oscillometry and spirometry in children and adolescents suggested that the former is more precise.<sup>(18)</sup> Previous studies have also demonstrated that oscillometry is more sensitive to the effects of environmental exposure, suggesting that it is ideal for epidemiologic studies.<sup>(18)</sup> A new modality, intra-breath oscillometry, has shown even greater sensitivity in children and adults with respiratory diseases. Intra-breath analysis shows high sensitivity for detecting

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lung function impairment.<sup>(19,20)</sup> Oscillometry applied by the wave-tube technique provides new parameters for the analysis of ventilatory mechanics. Because it requires only passive cooperation from the patient, the technique has increasingly been used in children as a complement to the classic methods of pulmonary assessment.

We hypothesized that oscillometry, particularly the intra-breath technique, would be more sensitive than spirometry for the detection of respiratory abnormalities in children and adolescents with a history of preterm birth. To test that hypothesis, we applied both modalities in a sample of such subjects.

## METHODS

For the purposes of this study, we recruited subjects from a cohort of preterm infants previously evaluated by our group.<sup>(21)</sup> In brief, the cohort consisted of children and adolescents who had been born preterm (at < 37 weeks of GA), consecutively, between June of 2004 and April of 2005, at São Lucas Hospital, operated by the Pontifical Catholic University of Rio Grande do Sul, in the city of Porto Alegre, Brazil. Through telephone contact, we recruited subjects from among the constituents of the cohort. To form a control group, we recruited healthy, age-matched subjects who had been born at  $\geq 37$  weeks of GA from among patients seen at the pediatrics outpatient clinic of the hospital. All of the subjects (in both groups) were between 11 and 14 years of age. Individuals who had been diagnosed with, or had signs and symptoms of, chronic lung disease were excluded from the control group, as were those with a history of recurrent wheezing ( $\geq 3$  episodes ever), thoracic surgery, or heart disease. For both groups, individuals who presented with respiratory symptoms during sampling or who had impediments to performing forced expiratory maneuvers were excluded. After exclusions, there were 35 subjects who had been recruited from the cohort, collectively designated the preterm group, and 16 subjects who had been recruited from the pediatrics outpatient clinic, collectively designated the full-term group.

Because the forced maneuvers employed in spirometry have an impact on the  $R_{rs}$  and  $X_{rs}$ , all of the subjects underwent spectral and intra-breath oscillometry prior to undergoing spirometry. Before starting the examinations, the subjects remained at rest for 5-10 min, during which time we applied a questionnaire designed to collect clinical data. The procedures were carefully explained to the participants and their legal guardians, with an emphasis on the need to avoid leaks around the mouthpiece during the tests. For spirometry and oscillometry, the mouthpiece contained a bacterial/viral filter with minimal dead space. To prevent air leakage (during all procedures), a nose clip was used. All of the tests were carried out in a calm, private environment.

This study was approved by the Scientific and Research Ethics Committees of the Pontifical Catholic University

of Rio Grande do Sul. Written informed consent was obtained from the parents or legal guardians, and all of the participants gave written informed assent. All procedures were performed in accordance with the ethical criteria for research involving human beings established in Brazilian National Health Council Resolution no. 466/2012.

## Oscillometry

Oscillometry was performed in accordance with the European Respiratory Society Task Force guidelines.<sup>(15)</sup> The  $Z_{rs}$  was measured with custom-made equipment incorporating a wave-tube and a loudspeaker.<sup>(22)</sup> The wave-tube technique is a variant of classical oscillometry that allows the measurement of impedance in infants.<sup>(19)</sup> Intra-breath analysis was used because it is reported to be more sensitive than is spectral analysis for detecting lung disease.<sup>(22)</sup> To perform the test, participants remained seated, using a nose clip, with the head in a neutral position and the cheeks firmly supported by the examiner, maintaining spontaneous ventilation for 20 s. The cheeks were supported to reduce the effect of upper airway soft tissue compliance, which could generate mechanical impedance parallel to the  $Z_{rs}$ . As previously noted, the mouthpiece contained a bacterial/viral filter with minimal dead space. The estimated  $Z_{rs}$  was corrected for the filter resistance. The equipment measured the  $Z_{rs}$  in the spectral and intra-breath phases. Spectral oscillometry measures  $Z_{rs}$  throughout a signal of multiple frequencies ranging from 6 Hz to 32 Hz. Multifrequency analyses produce an average of the performance of respiratory mechanics over several respiratory cycles. In both phases, three to six curves were obtained, being considered reproducible if the coefficient of variation for  $R_{rs}$  was  $\leq 10\%$ . If four or more curves were obtained, the three that were most similar to each other were chosen and the results were calculated as the mean of those three. Intra-breath oscillometry uses a single frequency to assess alterations to the respiratory mechanics at different phases of each respiratory cycle. In our subjects, a frequency of 10 Hz was used. Curves in which there were artifacts (cough, glottal noise, swallowing, etc.) were deemed unacceptable. In such cases, the measurement was discarded and another curve was obtained, assuming that the maximum number of attempts was not exceeded.

## Spirometry

Spirometry was performed in accordance with the recommendations of the American Thoracic Society/European Respiratory Society.<sup>(23)</sup> We used a Koko spirometer (PDS Instrumentation, Inc., Louisville, CO, USA) that was calibrated each morning before the tests. The subjects were instructed to perform a maximum inspiration followed by a rapid and sustained expiration, repeating that maneuver until the test was terminated by the examiner.<sup>(5)</sup> Each participant performed the test seated, with the head in a neutral position and using a nose clip. The following spirometric

parameters were assessed: FEV<sub>1</sub>, FVC, the FEV<sub>1</sub>/FVC ratio, and FEV<sub>25-75%</sub>. The spirometric data, presented in Z scores, were normalized to a reference equation.<sup>(24)</sup> It was considered necessary to have three acceptable and two reproducible curves. After acceptable curves ( $\geq 1$  s plateau on the volume-time curve) had been obtained, reproducibility criteria were applied<sup>(24)</sup>: the two highest FEV<sub>1</sub> and FVC values should differ by less than 0.15 L. Tests were repeated until reproducible values were obtained, not exceeding eight attempts. The flow-volume and volume-time curves were analyzed during the test; those that did not meet the acceptance and reproducibility criteria were excluded at the time of sampling.

### Statistical analysis

Statistical analysis was performed with the R Environment for Statistical Computing.<sup>(25)</sup> Values of  $p < 0.05$  on two-tailed tests were considered statistically significant. The main variables of the study were assessed with the Kolmogorov-Smirnov test. Categorical variables are presented as absolute and relative frequencies, whereas numerical variables are presented as mean and standard deviation or as median and interquartile range. Categorical variables were analyzed with Fisher's exact test, and numerical variables were analyzed with a t-test or the Wilcoxon test, as appropriate, depending on the data distribution. Intra-breath values were compared by bootstrap resampling.

## RESULTS

### Sample characteristics

Demographic and anthropometric characteristics of the subjects are shown in Table 1, by group. There were no significant differences between the preterm and full-term groups in terms of those characteristics.

### Perinatal data

Of the 35 subjects in the preterm group, 6 (17.1%) had presented some respiratory disease—defined as bronchopulmonary dysplasia, as hyaline membrane disease, or by the need for mechanical ventilation—in the neonatal period and 17 (48.6%) had subsequently been diagnosed with asthma. None of the subjects in the full-term group had presented neonatal respiratory disease. In terms of birth weight, 33 (94.3%) of the

preterm group subjects were categorized as appropriate for GA, compared with 13 (81.2%) of those in the full-term group (Table 2).

### Spirometry

The spirometry results are presented in Table 3. Although the values were lower in the preterm group than in the full-term group, the differences were not statistically significant.

### Spectral oscillometry

Measures of resistance and reactance at frequencies of 6, 8, and 10 Hz did not differ significantly between the two groups ( $p > 0.05$  for all). The overall mean values of resistance, compliance, inertance, and resonant frequency also did not differ significantly between the groups ( $p > 0.05$  for all). Those data are shown in Table 4.

### Intra-breath oscillometry

We observed differences in reactance at end-inspiration, the change in resistance (i.e., the difference between resistance at end-expiration and resistance at end-inspiration), and the change in reactance (i.e., the difference between reactance at end-expiration and reactance at end-inspiration), all of which were significant ( $p = 0.027$ ,  $p = 0.003$ , and  $p = 0.037$ , respectively). In the intra-breath analysis, differences in resistance at end-inspiration, resistance at end-expiration, and reactance at end-expiration did not reach statistical significance ( $p > 0.05$  for all). Those data are presented in Table 4.

## DISCUSSION

In this study, we have demonstrated that intra-breath oscillometry is able to detect significant differences between children and adolescents with a history of preterm birth and those who were born at term. In contrast, we did not find significant differences between those two groups in terms of the variables obtained with spirometry and spectral oscillometry. Shackleton et al.<sup>(26)</sup> used spectral oscillometry to analyze Z<sub>rs</sub> in preschool children who had been late preterm infants and found that the lung function of such children was comparable to that of preschool children who had been full-term infants. Their findings are in agreement with ours, given that we observed differences only when we used intra-breath oscillometry. This oscillometry

**Table 1.** Demographic and anthropometric characteristics of the subjects.<sup>a</sup>

Characteristic	Group		p
	Full-term (n = 16)	Preterm (n = 35)	
Age, years	12.90 (12.52-13.05)	12.88 (12.80-13.38)	0.167*
Female	13 (81.2)	18 (51.4)	0.041†
White	8 (50)	21 (60)	0.038†
Height, cm	158.5 (152.5-162.0)	158.0 (153.5-163.0)	0.831†
Weight, kg	50.95 (41.78-61.38)	49.50 (40.70-63.45)	0.935†

<sup>a</sup>Values expressed as median (IQR) or n (%). \*Wilcoxon test. †Fisher's exact test.

**Table 2.** Perinatal characteristics of the subjects.<sup>a</sup>

Characteristic	Group		p
	Full-term (n = 16)	Preterm (n = 35)	
Gestational age, weeks	39.3 ± 3.1	33.5 ± 1.5	0.167*
Classification by gestational age			
Extremely preterm (< 28 weeks)	0 (0.0)	4 (11.4)	
Very preterm (28-31 weeks)	0 (0.0)	4 (11.4)	
Moderately preterm (32-33 weeks)	0 (0.0)	6 (17.1)	
Late preterm (34-36 weeks)	0 (0.0)	21 (60.0)	< 0.001†
Early term (37-38 weeks)	7 (43.8)	0 (0.0)	
Term (39-40 weeks)	6 (37.5)	0 (0.0)	
Late term (≥ 41 weeks)	3 (18.8)	0 (0.0)	
Birth weight, g	3,200 (2,795-3,397)	2,100 (1,780-2,530)	< 0.001‡
Classification by birth weight			
Extremely low (< 1,000 g)	0 (0.0)	3 (8.6)	
Very low (< 1,500 g)	0 (0.0)	3 (8.6)	
Low (< 2,500 g)	2 (12.5)	19 (54.3)	0.001†
Normal (≥ 2,500 g)	14 (87.5)	10 (28.6)	

<sup>a</sup>Values expressed as mean ± SD, n (%), or median (IQR). \*t-test. †Fisher exact test. ‡Wilcoxon test.

**Table 3.** Spirometry results.<sup>a</sup>

Variable	Group		p*
	Full-term (n = 16)	Preterm (n = 35)	
FVC (Z score)	0.40 (-0.44 to 1.20)	-0.43 (-0.93 to -0.38)	0.109
FEV <sub>1</sub> (Z score)	0.12 (-0.42 to 0.83)	-0.43 (-1.12 to 0.28)	0.096
FEV <sub>1</sub> /FVC (Z score)	-0.17 (-1.24 to 0.39)	-0.46 (-1.29 to 0.27)	0.670
FEF <sub>75-75%</sub> (Z score)	0.08 (-1.06 to 0.68)	-0.34 (-1.70 to -0.10)	0.256

<sup>a</sup>Values expressed as median (IQR). \*Wilcoxon test.

phase is known as the intra-breath phase because it describes the  $Z_{rs}$  oscillation in each respiratory cycle ( $R_{rs}$  and  $X_{rs}$  are measured at 0.1 s intervals), which makes the intra-breath analysis more sensitive than the spectral analysis.

In the present study, there were three variables for which differences between the preterm and full-term groups were found, all of them being identified by intra-breath oscillometry. One of those variables was the change in resistance. In a study aimed at identifying  $Z_{rs}$  descriptors with high sensitivity and specificity for the detection of airway obstruction in children, Czövek et al.<sup>(22)</sup> found that this same measure of lung function (the change in resistance) detected airway obstruction with 92% sensitivity and 89% specificity in children with acute wheezing.<sup>(22)</sup> Our data support the hypothesis that preterm birth and recurrent wheezing both have abnormal volume-dependent resistance (i.e., tidal changes in  $R_{rs}$  between the beginning and end of inspiration). Previous studies have also shown  $R_{rs}$  to be higher in children and adolescents who had been late preterm infants than in those who had been full-term infants.<sup>(27)</sup>

In the present study, we also found differences between the preterm and full-term groups in terms of reactance at end-inspiration and the change in reactance. Those

variables describe pulmonary compliance, in accordance with previous studies demonstrating that pulmonary complacency tends to be reduced in individuals who were preterm infants, even those who were late preterm infants.<sup>(27,28)</sup> We found that reactance measured in the intra-breath phase was the most impaired oscillometric index in our preterm group subjects. That is in keeping with the findings of Lombardi et al.,<sup>(29)</sup> although those authors analyzed preschool children born very preterm and employed spectral oscillometry. We emphasize that, by using a highly sensitive technique, the effect of preterm birth on respiratory compliance can be detected up through adolescence.

It is noteworthy that nearly half of the subjects in our preterm group had been diagnosed with asthma. Although the diagnosis was reported by parents (or legal guardians), that information is important for the analysis of the results. However, we hypothesize that not all of those subjects actually had asthma; it is possible that they simply had a history of recurrent wheezing due to preterm birth.

Although premature birth may lead to alterations in pulmonary development after the neonatal period,<sup>(30)</sup> previous studies employing spirometry to evaluate subjects with a history of preterm birth have not demonstrated changes in lung function throughout

**Table 4.** Spectral and intra-breath oscillometry results.<sup>a</sup>

Characteristic	Group		p*
	Full-term (n = 16)	Preterm (n = 35)	
<b>Spectral oscillometry</b>			
$R_{rs,6}$ , hPa·s·L <sup>-1</sup>	4.14 (3.38-5.12)	4.49 (3.85-4.78)	0.465
$R_{rs,8}$ , hPa·s·L <sup>-1</sup>	4.14 (3.22-4.83)	4.25 (3.73-4.73)	0.685
$R_{rs,10}$ , hPa·s·L <sup>-1</sup>	4.04 (3.15-4.60)	4.14 (3.58-4.72)	0.556
$X_{rs,6}$ , hPa·s·L <sup>-1</sup>	-0.96 (-1.40 to -0.77)	-0.94 (-1.26 to 0.65)	0.503
$X_{rs,8}$ , hPa·s·L <sup>-1</sup>	-0.61 (-0.92 to -0.41)	-0.64 (-0.87 to -0.35)	0.887
$X_{rs,10}$ , hPa·s·L <sup>-1</sup>	-0.42 (-0.72 to -0.19)	-0.33 (-0.55 to -0.10)	0.477
$R_{rs}$ , hPa·s·L <sup>-1</sup>	3.98 (2.95-4.65)	4.17 (3.61-4.65)	0.383
$C_{rs}$ , mL·hPa <sup>-1</sup>	0.02 (0.02-0.03)	0.02 (0.02-0.03)	0.589
$I_{rs}$ , mL·hPa <sup>-1</sup>	0.01 (0.01-0.01)	0.01 (0.00-0.01)	0.612
$f_{res}$	13.83 (11.01-16.96)	12.82 (11.58-17.45)	0.935
<b>Intra-breath oscillometry</b>			
$R_{ee}$ , hPa·s·L <sup>-1</sup>	3.17 (2.71-4.34)	3.94 (3.16-5.16)	0.118
$R_{ei}$ , hPa·s·L <sup>-1</sup>	3.13 (2.66-4.13)	3.48 (2.72-3.88)	0.823
$\Delta R$ , hPa·s·L <sup>-1</sup>	0.06 (-0.02 to 0.26)	0.46 (0.13-0.84)	0.003
$X_{ee}$ , hPa·s·L <sup>-1</sup>	-0.21 (-0.50 to 0.18)	-0.08 (-0.26 to 0.21)	0.477
$X_{ei}$ , hPa·s·L <sup>-1</sup>	-0.28 (-0.69 to -0.11)	-0.06 (-0.32 to 0.11)	0.027
$\Delta X$ , hPa·s·L <sup>-1</sup>	0.15 (0.01-0.33)	0.04 (-0.11 to 0.16)	0.037

$R_{rs,6}$ : respiratory system resistance at 6 Hz;  $R_{rs,8}$ : respiratory system resistance at 8 Hz;  $R_{rs,10}$ : respiratory system resistance at 10 Hz;  $X_{rs,6}$ : respiratory system reactance at 6 Hz;  $X_{rs,8}$ : respiratory system reactance at 8 Hz;  $X_{rs,10}$ : respiratory system reactance at 10 Hz;  $R_{rs}$ : respiratory system resistance;  $C_{rs}$ : respiratory system compliance;  $I_{rs}$ : respiratory system inductance;  $f_{res}$ : resonant frequency;  $R_{ee}$ : resistance at end-expiration;  $R_{ei}$ : resistance at end-inspiration;  $\Delta R$ : change in resistance;  $X_{ee}$ : reactance at end-expiration;  $X_{ei}$ : reactance at end-inspiration; and  $\Delta X$ : change in reactance. <sup>a</sup>Values expressed as median (IQR). \*Wilcoxon test.

childhood and adolescence,<sup>(31,32)</sup> as was found in the present study. However, in studies evaluating children and adolescents who were born preterm and who had a more severe history, spirometry has shown differences between such subjects and control subjects who were born at term.<sup>(33-37)</sup>

The fact that we found the lung function of the subjects in the preterm group to be comparable to that of those in the full-term group may be related to the preponderance of individuals in the former group who had been late preterm infants. One study that used oscillometry to assess  $Z_{rs}$  in preschool children who had been late preterm infants demonstrated that the lung function of those children was comparable to that of healthy children who had been full-term infants, suggesting that data related to individuals who had been late preterm infants should be included in the normative reference data for oscillometry.<sup>(26)</sup> However, other studies analyzing children and adolescents who had been late preterm infants, in comparison with control subjects who had been full-term infants, have demonstrated that the former show lower lung function on spirometry<sup>(11,37)</sup> and a higher  $R_{rs}$  on impulse oscillometry.<sup>(37,38)</sup> Another possibility is that, during adolescence, with pulmonary development, adolescents who had been late preterm infants have already achieved lung function similar to that of those who had been full-term infants. One study, comparing the lung function of individuals who had been late or extremely to late preterm infants, at 8-9 years of age and at 14-17 years of age, with that of age-matched control subjects who had been full-term

infants, showed that lung function was lower in those individuals than in the control subjects. However, the preterm group presented better FEV<sub>1</sub> at 14-17 years of age than at 8-9 years, suggesting that lung function improves during adolescence.<sup>(39)</sup>

Our study has some limitations. The main limitation is the sample size, which was smaller than it might have been because the coronavirus pandemic made it necessary to interrupt the data collection. One of the specific objectives initially proposed was to compare oscillometry and spirometry in terms of their accuracy for the detection of pulmonary alterations in adolescents with a history of preterm birth. However, that objective could not be met, because the small sample size prevented us from performing an accuracy analysis. In addition, the fact that the subjects in the preterm group were recruited from an existing cohort could constitute a selection bias, and the sample was relatively heterogeneous, both of which are potential limitations.

In summary, oscillometry is a viable method that is easily applicable in children and adolescents. In the analysis of lung function, the main advantage of the technique seems to be that it includes the intra-breath phase, which is sensitive enough to detect alterations in  $Z_{rs}$ . In the present study, we identified variables that differed significantly between the preterm and full-term groups in the intra-breath phase. These findings suggest that abnormalities in  $Z_{rs}$  persist in adolescents with a history of preterm birth and that intra-breath oscillometry is more sensitive than is spectral oscillometry.

Our findings underscore the need for further studies to investigate the impact that premature birth has on lung function measured by intra-breath oscillometry. Larger studies are needed in order to validate these findings and to explore the impact that birth weight and GA at birth have on  $Z_{rs}$  later in life.

### AUTHOR CONTRIBUTIONS

BFA: study conception and design; data collection and analysis; drafting and revision of the manuscript;

approval of the final version. FOF: data collection and analysis; revision of the manuscript; approval of the final version. ALC: study design; data collection; drafting of the manuscript; approval of the final version. JPR: data collection and analysis. MHJ: study design; data analysis; revision of the manuscript; approval of the final version.

### CONFLICT OF INTEREST

None declared.

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