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ORIGINAL ARTICLE: NEONATAL LUNG DISEASE

WILEY PEDIATRIC PULMONOLOGY

Lung function in a cohort of 5-year-old children born very preterm

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Abstract

Objective: We assessed lung function and respiratory health in an area-based prospective cohort of preschool children born very preterm.

Design: Lung function was measured by interrupter respiratory resistance (Rint) and forced oscillation technique (FOT) (respiratory resistance (Rrs8), reactance (Xrs8), and area under the reactance curve (AX)) at a median age of 5.2 years in a cohort of 194 children born at 22-31 weeks of gestational age (GA) in Tuscany, Italy. Respiratory symptoms and hospitalizations were also assessed.

Results: Mean (SD) lung function Z-scores were impaired in preterm children for Rint (0.72 (1.13)), Xrs8 (-0.28 (1.34)), and AX (0.29 (1.41)). However, only a relatively small proportion of children (14.5-17.4%) had values beyond the 95th centile or below the 5th. Children with bronchopulmonary dysplasia (BPD) ($n = 24$) had slightly but not significantly impaired lung function indices in comparison with those without BPD ($n = 170$). In a multivariable analysis, lower GA was associated with worse lung function indices. Fifty-five percent of children had a history of wheezing ever and 21% had been hospitalized in their lifetime because of lower respiratory infections; 31% had wheezing in the last 12 months and this was associated with increased Rrs8 ($P = 0.04$) and AX ($P = 0.08$), and with decreased Xrs8 ($P = 0.04$) Z-scores.

Conclusions: Irrespectively of BPD preschool children born very preterm had impaired lung function indices, as measured by Rint and FOT, and a slightly higher burden of respiratory problems than the general population. GA seems to be crucial for lung development.

KEYWORDS
bronchopulmonary dysplasia, forced oscillation technique, infant, interrupter technique, premature, wheezing

Enrico Lombardi and Valentina Fainardi are joint first authors and contributed equally to this work.

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1 | INTRODUCTION

Thanks to the advances of perinatal medicine, both survival rate and severe neuro-motor and sensory morbidities of children born very preterm (<32 weeks of gestation) have improved. However, respiratory morbidity remains a frequent complication and may have long-term health consequences.[1]

Lung development may be disrupted by several perinatal factors related to preterm birth.[2] The landmark paper by Barker on the foetal origins of diseases[3] has highlighted the role played by the intrauterine environment on lung growth and the subsequent respiratory health from infancy to adulthood.[4]

Previous studies assessing pulmonary function in very preterm children at preschool age were mainly focused on those with bronchopulmonary dysplasia (BPD),[5–7] and the general population of these children has been considered only recently.[8] Studies investigating lung function and its perinatal determinants in area-based prospective cohorts of very preterm children are scarce.[9,10]

This study was based on the data collected in the Tuscany region within the ACTION (ACcess To Intensive Obstetrical and Neonatal care) project, a prospective area-based cohort study of very preterm infants born in Italy.[11] We assessed the respiratory health of these children at preschool age, including measurements of lung function using the interrupter (Rint) and the forced oscillation (FOT) techniques, and explored the association between lung function and perinatal variables.

2 | METHODS

2.1 | Study population and data collection

The ACTION project is a prospective area-based study that recruited all births occurred at 22-31 completed weeks of gestational age (GA) in 2003-2005 in several regions in Italy.[12] In Tuscany only, a respiratory follow-up was carried out at preschool age, including all the surviving children born from July 2003 to June 2004 (June 2005 for those with GA <28 weeks, with the aim of increasing the sample size of the extremely preterm cohort).

Information on maternal characteristics, pregnancy complications, infant's morbidities, and treatments in neonatal intensive care units (NICUs) and health status at 36 weeks of post-menstrual age and at discharge were abstracted from medical records using a standardized form with pre-agreed definitions. When the children reached 4.5-5 years of age, we invited the families to participate in the respiratory follow-up that included a postal questionnaire and a hospital visit for clinical examination and lung function assessment. To ascertain lifetime and previous year prevalence of wheezing we used the International Study of Asthma and Allergy in Childhood (ISAAC) core questionnaire.[13] Additional questions on the child respiratory health were derived from the Italian Studies on Respiratory Diseases in Childhood and the Environment (SIDRIA) phase 2 study.[14]

Among the 382 infants admitted to Tuscany NICUs, 290 were discharged alive. Of these, 204 (70.3%) participated in the respiratory follow-up at age 5. Five children were not included in the study because of severe neurologic impairment and inability to perform lung function tests. Other reasons for loss to follow-up were lack of valid postal and telephone contacts (n = 58), distance from the hospital (n = 18), and explicit parental refusal (n = 5).

2.2 | Lung function tests

Lung function assessments were carried out at the outpatient pulmonary clinic of the Meyer Children's University Hospital (Florence, Italy). We used Rint, an indicator of airway resistance plus a small component of lung tissue and chest wall resistance, and FOT at 8 Hz, which measures airway resistance (Rrs8) and reactance (Xrs8).[15,16] While resistance reflects the frictional losses of the respiratory system, reactance reflects its elastic properties at low frequencies, and the inertial forces of the air columns at higher frequencies.[15,16] In other words, at low frequencies reactance can be thought of as the compliance (ie, the distensibility) of the respiratory system. We chose the 8 Hz frequency because it is the most representative of total airway resistance and compliance, while lower frequencies are considered to also include the mechanic properties of lung tissue and chest wall.[15] We also calculated the area under the reactance curve (AX), which has been shown to be more sensitive than other FOT indices in detecting changes in airway mechanics.[17] AX was calculated as previously described.[18] In every child the tests were performed in random order and according to the European Respiratory Society and American Thoracic Society recommendations,[16] using commercially available devices ("MicroRint," Micromedical, UK; "i2m," Cosmed, Italy). Children were seating and breathing quietly through a bacterial filter while wearing a nose clip, with the head slightly extended and the cheeks and mouth floor supported by an investigator. Measurements were excluded if leak, mouth, or tongue movement, swallowing, talking, or audible noises were detected during the test. To ensure repeatability, measurement sets with a coefficient of variation >20% for Rint or Rrs8 were also excluded. For Rint, 10 measurements were recorded to obtain at least five technically acceptable and repeatable values, and the median value was reported[16]; each interruption was considered to be acceptable if evidence of air leakage around the mouthpiece or an altered ventilator pattern was not present in the trace of mouth pressure versus time.[16] For FOT, between 3 and 5 data epochs lasting 8 s each were recorded to obtain at least three acceptable and repeatable measurements and their mean value was used[16]; individual frequencies that had a coherence function of <0.95 were excluded and the entire measurement was discarded if three or more individual frequencies were unacceptable.[18]

Lung function indices were expressed as Z-scores derived from published reference data from a healthy Italian population for Rint, Rrs8, and Xrs8[19,20] and from a healthy Italian and Australian population for AX.[18]

Lung function measurements were repeated in the same order 15 min after the administration of 200 μg of inhaled salbutamol at tidal breathing via a metered dose inhaler with a spacer ("AeroChamber Plus," Trudell Medical International, Canada). As previously reported, bronchodilation was considered positive: for Rint, when it decreased more than 0.25 $kPa.L^{-1}.s$[21]; for Rrs8, when it decreased more than

1.88 Z-scores[19]; for Xrs8, when it increased more than 2.48 Z-scores[19]; and for AX, when it decreased more than 2.04 Z-scores.[18]

At the time of assessment, all children were clinically stable and free from respiratory tract infections. None had received any systemic corticosteroids or bronchodilators in the previous 48 h. In case of respiratory symptoms or pharmacological treatment, lung function was rescheduled 2-4 weeks later.

2.3 | Data analysis

We computed descriptive statistics and chi-square tests for differences in proportions. The association between perinatal variables (maternal preeclampsia or eclampsia or obstetrical report of intrauterine growth restriction (IUGR), gender, GA as a continuous variable in weeks, birth weight (BW) in classes (< and ≥1500 g), BW Z-score,[22] days of mechanical ventilation) and Rint, Rrs8, Xrs8, and AX Z-scores were assessed by Student's *t*-test, analysis of variance or linear regression analysis, as appropriate. Finally, we carried out multivariable linear regression analyses using as predictors the variables associated with the outcome at univariable analysis with a $P < 0.10$. To remove the collinearity of BW with GA, we used BW Z-score for GA. To account for a nonlinear relationship between Rint, Rrs8, Xrs8, and AX Z-scores and GA (E Figure 1A-D) we added a quadratic term for GA.

The analyses were carried out with the Stata package ("Stata Statistical Software: Release 14," Stata Corporation, Texas).

The ACTION study was approved by the Institutional Review Board of the Bambino Gesù Pediatric Hospital in Rome, national coordinator of the project, and the respiratory follow-up protocol was approved by the Ethics Committee of the Meyer Children's University Hospital in Florence. Parental informed consent was obtained at birth and at the time of follow-up.

3 | RESULTS

Among the 204 recruited children (median age 5.2 years; range: 4.5-6.3), 185 (90.7%) were able to perform both lung function tests, while nine (4.4%) performed only Rint because of poor cooperation. The perinatal characteristics of these children are shown in Table 1.

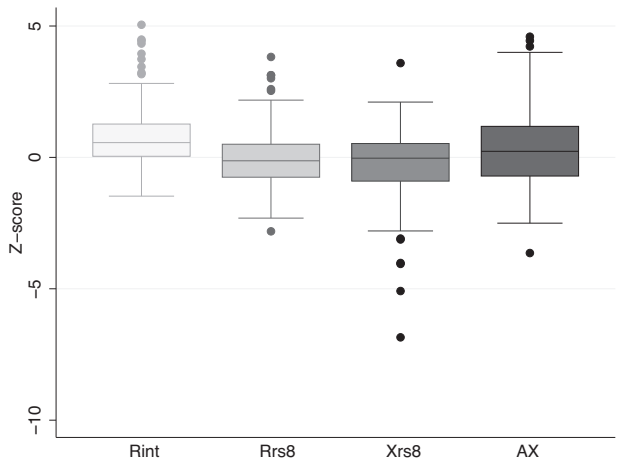

FIGURE 1 Box plots showing the distribution of Rint, Rrs8, Xrs8, and AX Z-scores

Box plots of distribution of Rint, Rrs8, Xrs8, and AX Z-scores are shown in Figure 1. Only 17.5% (*n* = 34), 16.5% (*n* = 32), and 16.5% (32) of the children had Z-scores values above the 95th centile for Rint, Rrs8, and AX, respectively, while 14.4% (*n* = 28) had values below the 5th centile for Xrs8.

Mean raw and Z-score values for lung function indices at baseline and post bronchodilator are reported in Table 2. Lung function results changed significantly after bronchodilation; however, when values were categorized according to reference cut-offs[18–20] only 18.4% of children showed a positive bronchodilator response in Rint, 3% in Rrs8, 1.7% in Xrs8, and 9.9% in AX. Rint and FOT measurements after bronchodilation were not performed in 9 and 7 children, respectively, due to poor cooperation.

Children with BPD (*n* = 24) had a slightly but not significantly lower lung function in comparison with those without BPD (*n* = 170) (mean (SD) Rint Z-score: 0.74 (1.17) vs 0.53 (0.79), $P = 0.379$; Rrs8 Z-score: −0.02 (1.10) vs −0.13 (0.93) $P = 0.65$; Xrs8 Z-score: −0.50

TABLE 1 Characteristics of the cohort of 194 children for which data on lung function were available

Characteristics	No of subjects (%)[a]
Male	104 (53.6%)
Gestational age, weeks	
< 28	65 (33.5%)
28-29	63 (32.5%)
30-31	66 (34%)
Median (10-90th centile)	28 (25–31)
Birth weight, *g*	
<1500	151 (77.8%)
≥1500	43 (22.2%)
median (10-90th centile)	1150 (740–1680)
SGA (< 10th centile)	15 (7.7%)
Maternal preeclampsia/eclampsia or IUGR	43 (23.2%)
Prenatal maternal steroids	154 (80.6%)
Surfactant administration	118 (67.5%)
Mechanical ventilation	93 (47.9%)
Days on mechanical ventilation:	
median (10-90th centile)	3 (0–21)
RDS	121 (70.6%)
BPD	24 (12.4%)
Oxygen at 40 weeks of postmenstrual age	2 (1.0%)
Days on oxygen therapy:	
median (10-90th centile)	3.0 (0–55)

[a]unless otherwise specified; SGA, small for gestational age[20]; IUGR, intrauterine growth restriction based on obstetric ultrasounds; RDS, respiratory distress syndrome; BPD, bronchopulmonary dysplasia, defined as supplemental oxygen dependency at 36 weeks of postmenstrual age.

TABLE 2 Baseline and post-bronchodilator interrupter technique and forced oscillation technique measurements in the 194 studied children

	Measured values baseline	Predicted values	P[a]	Measured values post-bronchodilator	P[a]
Rint	*n* = 194			*n* = 185	
kPa.L^{-1}.s	0.90 (0.23)	0.76 (0.07)	<0.001	0.77 (0.20)	<0.001
Z-score	0.72 (1.13)			0.08 (1.02)	<0.001
Rrs8	*n* = 185			*n* = 178	
hPa.L^{-1}.s	8.20 (1.85)	8.26 (0.73)	0.663	7.31 (1.73)	<0.001
Z-score	−0.03 (1.08)			−0.54 (0.96)	<0.001
Xrs8	*n* = 185			*n* = 178	
hPa.L^{-1}.s	−2.62 (1.25)	−2.37 (0.36)	0.005	−2.06 (0.99)	<0.001
Z-score	−0.28 (1.34)			0.35 (1.04)	<0.01
AX	*n* = 185			*n* = 178	
hPa.L^{-1}	41.41 (27.81)	32.49 (0.14)	<0.001	27.34 (20.27)	<0.001
Z-score	0.29 (1.41)			−0.54 (1.21)	<0.001

Data are expressed as mean (SD). Values measured at baseline were compared with predicted values,[18–20] and with values measured post-bronchodilator administration.

[a]paired Student's *t* test; Rint: interrupter resistance; Rrs8: respiratory resistance at 8 Hz; Xrs8: respiratory reactance at 8 Hz; AX: area under the reactance curve.

(1.24) vs −0.24(0.11), $P = 0.379$; AX Z-score: 0.25 (1.43) vs 0.53 (1.28), $P = 0.357$).

The relationships between perinatal variables and lung function indices expressed as Z-scores are shown in Tables 3 and 4. At multivariable analysis, only GA and GA squared were significantly associated with lung function. Males had significantly lower AX Z-scores than females.

Based on the questionnaire on respiratory health, 106 children (54.6%) experienced at least one wheezing episode in their lifetime; 61 (31.4%) had at least one, and 12 (6.2%) more than three wheezing episodes in the previous 12 months. A positive association was found between at least one wheezing episode in the previous 12 months and Rrs8 ($P = 0.04$) and AX ($P = 0.08$) Z-scores and an inverse correlation with Xrs8 Z-score ($P = 0.04$), while there was no association with Rint ($P = 0.14$). Forty children (20.7%) had been hospitalized at least once for an acute lower respiratory infection, including bronchiolitis, asthmatic bronchitis, bronchitis, or pneumonia.

4 | DISCUSSION

This is the largest study on respiratory function of unselected pre-school children born very preterm in a defined geographic area.

As expected, we found that these children had impaired lung function with higher resistance and lower reactance (ie, poor lung compliance or distensibility), although only a small proportion had Z-score values above the 95th or below the 5th centile. Children with

TABLE 3 Univariable linear regression models using lung function indices Z-scores as the dependent variable and perinatal factors and age at test as independent predictors. Data are presented as coefficients (95%CI)

	Rint	Rrs8	Xrs8	AX
GA	3.29 (1.50;5.08)[c]	2.21 (0.44;3.97)[b]	−2.98 (−5.14;−0.81)[b]	2.89 (0.61;5.17)[b]
GA squared	−0.06 (−0.09;−0.03)[c]	−0.04 (−0.07;−0.01)[b]	0.05 (0.02; 0.09)[b]	−0.05 (−0.09;−0.01)[b]
BW <1500 g	0.31 (−0.07;0.70)	0.37 (0.01;0.74)[a]	−0.68 (−1.13;−0.22)[b]	0.93 (0.47;1.40)
BW-Z-score	−0.05 (−0.22;0.11)	−0.03 (−0.19;0.13)	0.05 (−0.15; 0.25)	−0.18 (−0.39;0.03)
Male sex	−0.05 (−0.37;0.27)	−0.15 (−0.46;0.17)	0.30 (−0.09; 0.69)	−0.46 (−0.87;−0.05)[b]
Mechanical ventilation	0.08 (−0.24;0.40)	−0.06 (−0.38;0.25)	−0.38 (−0.76; 0.01)[b]	0.34 (−0.07; 0.74)
Preeclampsia or IUGR	0.41 (−0.02;0.81)	0.19 (−0.19;0.57)	−0.28 (−076; 1.19)	0.40 (−0.09;0.90)

Rint: interrupter resistance; Rrs8: resistance at 8 Hz; Xrs8: reactance at 8 Hz; AX: area under the reactance curve; GA: gestational age; BW: birth weight; IUGR: intrauterine growth restriction.

[a]$P = <0.10$.

[b]$P < 0.05$.

[c]$P < 0.01$.

TABLE 4 Multivariable linear regression models using lung function indices Z-scores as the dependent variable and perinatal factors and age at test as independent predictors. Data are presented as coefficients (95%CI)

	Rint	Rrs8	Xrs8	AX
GA	3.25 (1.44;5.06)[c]	2.17 (0.38;3.96)[b]	−2.78 (−4.96;−0.60)[b]	2.45 (0.18;4.71)[a]
GAsquared	−0.06 (−0.09;−0.02)[c]	−0.04 (−0.07;−0.01)[b]	0.05 (0.01;0.09)[b]	−0.05 (−0.09;−0.01)[b]
BW-Zscore	0.01 (−0.16;0.17)	−0.02 (−0.18;0.15)	0.02 (−0.19;0.22)	−0.18 (−0.39;0.03)
Male sex	−0.01 (−0.33;0.30)	−0.12 (−0.43;0.20)	0.31 (−0.07;0.69)	−0.49 (−0.89;−0.09)[b]
Mechanical ventilation	0.16 (−0.19;0.51)	−0.08 (−0.43;0.26)	−0.25 (−0.67; 0.17)	0.09 (−0.35;0.53)

Rint: interrupter resistance; Rrs8: resistance at 8 Hz; Xrs8: reactance at 8 Hz; AX: area under the reactance curve; GA: gestational age; BW: birth weight.
[a]P = <0.10.
[b]$P < 0.05$.
[c]$P < 0.01$.

BPD had lung function values slightly, albeit not significantly, more impaired than non-BPD peers. Lower GA was associated with impairment of all the lung function indices. From a clinical perspective, children overall had a burden of respiratory symptoms and diseases, both ever and in the previous 12 months.

Data on respiratory function in preschool children born very preterm are still scarce.[5–8] Previous reports using Rint or FOT to measure lung function in this population had sample sizes between 64 and 118,[5–8] while our cohort included 194 participants. Furthermore, our study was representative of the general population of very preterm infants discharged home in a defined geographical area and was not restricted to cases discharged from selected NICUs.

In agreement with previous studies[7,8,23] we found an impaired airway resistance and reactance in our population. Interrupter resistance values were higher than reference, while we found a normal resistance with FOT at 8 Hz. This discrepancy could be at least partially due to the small component of lung tissue and chest wall resistance included in Rint measures that thus provide information on the overall viscoelastic properties of the respiratory system.[16]

Lung function indices were only slightly worse in the subgroup of children with BPD in comparison with peers without BPD. The two previous studies using Rint in preterm preschool children[6,7] found that a diagnosis of BPD was associated with higher airway resistance. Similar results were reported with FOT[5,7,23,24] with children with BPD showing also lower reactance. As underlined also in a recent review,[25] however, BPD is variably defined in the literature and studies investigating correlations with long term pulmonary outcomes reported a range of predictive values from low to moderate. In our study, only less than 50% of our children were treated with mechanical ventilation in NICU for an average duration of 7.4 days, and only 1% was still oxygen dependent at 40 weeks of postmenstrual age, suggesting a mild form of the disease. We therefore agree with the conclusion of a recent study on lung function and structure of school-aged children born very preterm that "differences between studies may also reflect heterogeneity of lung disease in preterm children and the cohorts associated with each of these studies."[26]

Almost a fifth of the participating children (18.4%) showed a positive bronchodilator response in Rint. This is in agreement with other studies which found an airway obstruction reversibility in 23% of school aged children born <1500 g.[27]

Overall, our cohort of children born very preterm showed some degree of respiratory impairment, suggesting that preterm birth alone can negatively affect the development of the lung even without significant postnatal exposure to long-term mechanical ventilation and oxygen therapies. Interestingly, recent studies found signs of peripheral airway obstruction also in children born late preterm[28] and in absence of respiratory complications.[29] On the other hand, in area-based prospective cohorts where a number of maternal and perinatal variables[9] or GA[10] were studied in relation to lung function indices at school age no relationship was found. We found a prevalence of wheeze in the 12 months before assessment of 31.4%, which is much higher than the 15% recently reported in the general population of Italian preschool children.[30] This finding confirms previous reports of a two- to three-fold higher prevalence of respiratory symptoms in very preterm children compared with term-born controls independently of BPD.[7,9] The observation that in our children at preschool age symptoms correlate with high resistance and low compliance is of concern.

The strengths of this study include the area-based design and the lung function assessment in more than 95% of participants. We extended the recruitment period of children with GA <28 weeks to have a balanced sample, with similar numbers in all GA groups, hence an increased power without loss of representativeness.

Compared with spirometry, Rint and FOT are more feasible in preschool children because they just require passive cooperation and can be performed also by children with physical and cognitive problems.

There are also some limitations. Five children with severe neurological impairment did not participate in the follow-up. Thus, our results might slightly underestimate the true degree of respiratory dysfunction in the very preterm population. This limitation however is common to all lung function studies performed in children born very preterm, where neuromotor and cognitive disabilities are a possible outcome. The low frequency of BPD found

in our cohort may have reduced the study power to detect differences between BPD and non-BPD participants. However, this BPD frequency is concordant with the data reported in 2003 for another Italian region, confirming the lower incidence of the disease compared to other European countries.[31] Whether this can be attributed to different clinical practices, such as less invasive ventilation, or to specific genetic risk factors, needs to be further evaluated. Finally, from a clinical perspective the assessment of respiratory symptoms using a parental questionnaire, although common to most studies, may overestimate the real prevalence of wheezing, since parents might label a single episode of noisy breathing as wheezing, while reports of recurrent wheezing are less affected.[32]

In conclusion, our cohort of children born very preterm showed high respiratory resistance and low reactance, likely due to an impairment of the peripheral lung, suggesting that very preterm birth alone can negatively affect the development of the lung even in the absence of BPD. Rint and FOT, being feasible and non-invasive methods, can provide useful information about the respiratory function also in preschoolers and offer the opportunity to further follow-up and monitor these children in the long-term. This is particularly important since lung function tracks throughout life,[33] putting children born preterm, even without BPD, at risk of developing chronic obstructive pulmonary disease in adulthood.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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