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Effect of *in utero* growth retardation on lung function at follow-up of prematurely born infants

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Effect of in utero *growth retardation on lung function at follow-up of prematurely born infants. A. Greenough, B. Yuksel, P. Cheeseman. ©ERS Journals Ltd 2004.*
ABSTRACT: The aim of the study was to determine if prematurely born children who had suffered intra-uterine growth retardation (IUGR) had more severe lung function abnormalities than those born an appropriate weight for gestational age (AGA).

Analysis of the lung function results of 119 infants (median (range) gestational age of 30 (23–35) weeks) was undertaken. In total, 31 of the infants had suffered IUGR and were born small for gestational age (SGA). Functional residual capacity and airways resistance (R_{aw}) were measured at a median post-natal age of 10 (6–24) months. Specific airway conductance (sG_{aw}) was calculated from thoracic gas volume and R_{aw}.

The SGA children were born at a greater gestational age and had a lower body weight at testing than the AGA children. R_{aw} and sG_{aw} differed between the SGA and AGA children. Regression analysis demonstrated that lung volumes were significantly related to body weight at testing, R_{aw} was related to IUGR, maternal smoking and bronchopulmonary dysplasia, and sG_{aw} to maternal smoking.

In conclusion, these results suggest that prematurely born infants who have suffered intra-uterine growth retardation may be at increased risk of impaired lung function at follow-up.
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Children born prematurely may suffer respiratory morbidity at follow-up [1] and, as a consequence, have a high healthcare utilisation [2]. *In utero* growth retardation (IUGR) may also be a risk factor for respiratory morbidity in childhood. Both wheezing and respiratory infections [3, 4] appear more common in children who suffered IUGR and, as a consequence, were small for gestational age (SGA) at birth. In addition, a significant association between birth weight (adjusted for gestational age) and lung function (forced vital capacity and forced expiratory volume in one second (FEV1)) has been reported in children aged 5–11 [5] and 7–15 yrs who were born SGA, and had lower maximum mid-expiratory flows, but not lung volumes [6]. Diminished airway function has even been reported in adults who were born of low birth weight [7], leading to the speculation that the association is mediated by foetal programming. Therefore, it seems likely that, amongst children born prematurely, those who were SGA, compared with those who were born at an appropriate weight for gestation (AGA), would have worse lung function abnormalities. The aim of this study was to test that hypothesis by comparing the lung function test results of SGA with AGA children born prematurely and examined during prospective follow-up.

Materials and methods

Study subjects

A total of 119 children with a median (range) gestational age of 30 (23–35) weeks were studied. Thirty-one of the children had suffered IUGR and been born SGA, with a birth weight of <10th percentile for gestational age. Parents gave informed consent for their child to take part and the study was approved by the King's College Hospital Ethics Committee.

For editorial comments see page 722.

Study design

Infants were eligible for entry into the cohort if they had a birth weight of <1,500 g, or their birth weight was 1,500–2,000 g and they had required mechanical ventilation in the neonatal period. Infants with chromosomal or congenital anomalies were excluded. Lung function had been measured during the first 2 yrs in a cohort of prematurely born children, who were prospectively followed. Lung function results from the cohort have been previously reported [8]. Lung function measurements were performed in the Paediatric Respiratory Laboratory, King's College Hospital. Children were not tested for $\geqslant$48 h after having respiratory symptoms (wheeze and/or cough) or an upper respiratory tract infection. Measurements were made while the child was in quiet sleep following administration of 80–100 mg·kg^{-1} of chloral hydrate.

Methods

Functional residual capacity (FRC$_{PLETH}$) and airway resistance (Raw) were measured using a whole body plethysmograph (Hammersmith Hospital, London, UK). From FRC$_{PLETH}$ and Raw, specific airway conductance (sGaw) was calculated. The techniques used to measure lung function have been described in detail previously [8]. The child breathed through a face mask, which was connected to a

rebreathing bag *via* a heated pneumotachograph and was sealed around the child's nose and mouth using silicone putty to ensure an airtight seal. The child breathed through a heated, humidified rebreathing system to avoid box pressure changes due to heating and cooling of respired gas. FRCPLETH was measured at the end of a normal inspiration, and *R*aw was measured at two-thirds of maximum respiratory flow using the techniques of DUBOIS and colleagues [9, 10], suitably modified for use in young children. FRCPLETH was calculated from five breaths during an occlusion, and the reported value was adjusted to end-expiratory lung volume. At least five separate occlusions were made. *R*aw was calculated from $\geqslant 10$ breaths. All measurements were corrected for the apparatus dead space, including the face mask (15 mL) and resistance (8 cm $H_2O \cdot L^{-1} \cdot s^{-1}$). The coefficients of variation of FRCPLETH and *R*aw were 6% and 9%, respectively. The plethysmograph was calibrated before and after each measurement. *In vitro* calibration of the plethysmograph demonstrated a 3% difference in the volume measurement.

After completion of the measurements of FRCPLETH and *R*aw, FRC was measured using a helium gas dilution technique (FRCHE). The child's face mask was connected to a water-sealed spirometer (Gould pulmonet III; Gould, Cleveland, OH, USA). The spirometer had an internal carbon dioxide absorber, an adjustable oxygen supply and a total volume of 6 L. It incorporated a digital display of FRC that was recorded at 15-s intervals. Equilibration was assumed to have occurred when there had been no change in the FRC readout over 30 s. All the FRC traces were coded and analysed without knowledge of the clinical details. From the trace, the equilibration point and end-expiratory level were determined, and FRC was calculated. The results were then converted to body temperature, pressure and saturation conditions. The accuracy of the spirometer was checked daily using a calibrated syringe (Vitalograph, Buckingham, UK).

Analysis

Differences between the groups were assessed for statistical significance using ANOVA Kruskal-Wallis, Fisher's exact test or Chi-squared test, as appropriate. AGA children had a birth weight 10–90th percentile for gestational age. Mothers were described as smoking if they smoked during pregnancy, and bronchopulmonary dysplasia (BPD) was diagnosed if the children had been oxygen dependent beyond 36 weeks post-menstrual age. Any multivariate association with lung function results were obtained by using multiple linear regression analysis; dependent variables were FRCPLETH, FRCHE, *R*aw and s*G*aw. Numeric independent variables tested were IUGR, maternal smoking and BPD. In the multivariate analysis of *R*aw and s*G*aw, weight at follow-up was excluded as there is not a direct relationship between *R*aw and weight.

Results

The SGA children were born at a greater gestational age ($p<0.0001$), but were of similar birth weight to the AGA children. The SGA children were lighter at the time of measurement ($p=0.0036$; table 1). The median FRCPLETH and FRCHE did not differ significantly between the SGA and AGA children, but the SGA compared with the AGA children had a higher median *R*aw ($p=0.004$) and a lower median s*G*aw ($p=0.036$; table 1).

Multiple regression analysis demonstrated that FRCPLETH and FRCHE at the time of measurement were significantly related to weight at testing (both $p<0.0001$), independently of all other factors (see Analysis). *R*aw was significantly related to IUGR ($p=0.0227$), maternal smoking ($p=0.0008$) and BPD ($p=0.0308$), independently of other factors, and s*G*aw was significantly related to maternal smoking ($p=0.0194$) independently of other factors (see Analysis).

Discussion

The current study has demonstrated that amongst prematurely born children, those born SGA had significantly different lung function at follow-up compared with those born AGA. The same techniques of measurement were used in both groups, thus the comparison between them is robust. A birth weight of <10th percentile for gestational age was used to diagnose SGA. It is possible that, if a birth weight of <3rd percentile for gestational age was used, differences between the two groups might have been more marked. The children born SGA had significantly higher *R*aw and lower s*G*aw than those born AGA (table 1). Regression analysis demonstrated that, when other factors were taken into account, a raised *R*aw was significantly associated with IUGR. Diminished airway function has been demonstrated in SGA infants aged 6 weeks when examined using partial and raised volume expiratory manoeuvres [11]. However, the differences between AGA and SGA infants disappeared when body size and sex were taken into account, causing the

Table 1. – Comparison of the demographics and lung function test results of the small for gestational age (SGA) and appropriate weight for gestation (AGA) children

	SGA	AGA	p-value
Subjects n	31	88	
Gestational age weeks	31 (23–35)	28 (23–33)	<0.0001
Birth weight kg	1092 (506–1950)	1203 (540–1866)	0.329
Maternal smoking	10	24	0.597
BPD	5	30	0.059
Duration of ventilation days	1 (0–34)	3 (0–75)	0.151
Supplementary oxygen days	4 (0–340)	8.5 (0–385)	0.049
Post-natal age months#	9 (6–23)	10 (6–24)	0.477
Body weight# kg	6.6 (3.8–10.5)	7.8 (4.1–11.8)	0.0036
FRCPLETH# mL	248 (144–324)	256 (147–414)	0.1482
FRCHE# mL	214 (127–292)	213 (120–380)	0.5171
*R*aw# $cmH_2O \cdot L^{-1} \cdot s^{-1}$	38 (25–100)	34 (19–56)	0.0044
s*G*aw# $s^{-1} \cdot cmH_20^{-1}$	0.11 (0.04–0.20)	0.12 (0.06–0.24)	0.0359

Data are presented as n or median (range). BPD: bronchopulmonary dysplasia; FRCPLETH: functional residual capacity measured by plethysmography; FRCHE: functional residual capacity measure by the He dilution technique; *R*aw: airways resistance; s*G*aw: specific airway conductance. #: at the time of measurement.

authors to suggest that diminished airway function in SGA infants was primarily due to impaired somatic growth [11]. More recent analysis of the whole cohort, including infants born to smoking mothers, as well as those born to nonsmoking mothers previously reported [11], demonstrated that low birth weight for gestation did account for a proportion of the reduction in airway function in infants born after 35 weeks of gestation [12]. The findings of the current study are in keeping with those results [13], as the regression analysis demonstrated *R*aw to be significantly related to IUGR, as well as smoking. However, s*G*aw, which takes into account lung volume and is primarily influenced by bodyweight as demonstrated by the regression analysis, was only significantly related to maternal smoking.

Examination at 15 yrs of age demonstrated children born with a very low birth weight to have medium and small airway obstruction when compared with controls matched for age, sex and school [14]. In contrast to the findings of the present study, the abnormalities were demonstrated to relate to prematurity, rather than IUGR or the receiving of respiratory support during the neonatal period. However, the cohort in ANAND *et al.* [14] was born in 1980–1981 and, thus, before the routine use of antenatal steroids and post-natal surfactant. The results from the current study support earlier findings demonstrating a significant association between birth weight and FEV1 in children aged 5–11 yrs [5] and the diminished airway function noted in adults of low birth weight [7].

Lung function had originally been measured in this cohort to further understand the effect of premature birth on respiratory morbidity at follow-up and the current study has subsequently examined the influence of IUGR. Nevertheless, the results are comparable with findings reported from children born at or near term [5, 7, 13]. In addition, regression analysis demonstrated significant associations of a raised *R*aw and lower s*G*aw at follow-up with maternal smoking, which is consistent with previous findings [15]. Maternal smoking during pregnancy has been shown to be associated with a reduction in flow at FRC [15].

The SGA children were born at a significantly greater gestational age than the AGA children. Immaturity at birth is a major risk factor for the development of respiratory distress syndrome (RDS) and BPD. It had been assumed that growth-retarded infants, as a result of stress *in utero*, would have improved respiratory outcome. However, there are reports of SGA infants being more likely to develop RDS [16] and BPD [12, 13] and require more ventilatory support [17]. In this study, the SGA infants, compared with the rest of the cohort, tended to require a shorter duration of respiratory support (table 1), and a smaller proportion developed BPD, although this did not reach statistical significance. The regression analysis demonstrated both IUGR and BPD influenced *R*aw at follow-up.

As has been noted before, the SGA compared with the AGA children had significantly lower body weights at follow-up [18]. As a consequence, the influence of weight at follow-up on lung volumes was examined in the regression analysis. This highlighted that weight at testing was significantly related to lung volume independently of all other factors, emphasising the importance of taking body weight into account when analysing lung function at follow-up in similar populations in future studies. Length at follow-up was not measured, so the current authors cannot comment on whether lung volumes were similarly significantly related to length.

In conclusion, children born very prematurely who have suffered intra-uterine growth retardation had significantly different lung function at follow-up compared with appropriate weight for gestation children. The cause and prevention of this problem merits investigation.

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