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Altered breathing mechanics and ventilatory response during exercise in children born extremely preterm

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ABSTRACT

Background Extreme preterm birth confers risk of long-term impairments in lung function and exercise capacity. There are limited data on the factors contributing to exercise limitation following extreme preterm birth. This study examined respiratory mechanics and ventilatory response during exercise in a large cohort of children born extremely preterm (EP).

Methods This cohort study included children 8–12 years of age who were born EP (≤28 weeks gestation) between 1997 and 2004 and treated in a large regionalised neonatal intensive care unit in western Canada. EP children were divided into no/mild bronchopulmonary dysplasia (BPD) (ie, supplementary oxygen or ventilation ceased before 36 weeks gestational age; n=53) and moderate/severe BPD (ie, continued supplementary oxygen or ventilation at 36 weeks gestational age; n=50). Age-matched control children (n=65) were born at full term. All children attempted lung function and cardiopulmonary exercise testing measurements.

Results Compared with control children, EP children had lower airway flows and diffusion capacity but preserved total lung capacity. Children with moderate/severe BPD had evidence of gas trapping relative to other groups. The mean difference in exercise capacity (as measured by oxygen uptake (VO_2)% predicted) in children with moderate/severe BPD was −18±5% and −14±5.0% below children with no/mild BPD and control children, respectively. Children with moderate/severe BPD demonstrated a potentiated ventilatory response and greater prevalence of expiratory flow limitation during exercise compared with other groups. Resting lung function did not correlate with exercise capacity.

Conclusions Expiratory flow limitation and an exaggerated ventilatory response contribute to respiratory limitation to exercise in children born EP with moderate/severe BPD.

Key messages

What is the key question?
► What is the relationship between lung function and limitation to exercise in children born extremely preterm (EP)?

What is the bottom line?
► Expiratory flow limitation and an exaggerated ventilatory response contribute to respiratory limitation to exercise in subgroups of children born EP.

Why read on?
► Despite lung function impairments in children born EP with no/mild and moderate/severe bronchopulmonary dysplasia, only those with moderate/severe bronchopulmonary dysplasia demonstrate impaired exercise capacity, altered breathing mechanics and heightened ventilatory response during exercise compared with control children.

during the late canalicular stage of lung development when airways and lung vasculature come together.[1] The impact of EP birth on lung development is fewer and larger alveoli, loss of small pulmonary arteries, lower capillary density and altered airway mechanics.[1] Follow-up studies of children born preterm in the surfactant era and studied in middle childhood or adolescence document reduced airway flows, lung diffusion impairment and increased gas trapping compared with control children.[2–6] While some studies document greater levels of lung function impairment in children with a history of BPD,[2 4 5] compared with preterm birth alone, others show limited or no differences between preterm children with and without a history of BPD.[3 6] Exercise capacity, measured by peak oxygen uptake (VO_{2peak}), may be impaired in children born preterm.[7–9] Limited data are available on how impaired lung function in children born preterm alters exercise capacity and breathing mechanics during exercise.[7]

Exercise impairments in children born preterm, with and without a history of BPD, are attributed

INTRODUCTION

Children born preterm have a significant risk for long-term impairment of respiratory and cardiovascular function. Infants at imminent risk for early respiratory impairment, including bronchopulmonary dysplasia (BPD), are those born extremely preterm (EP; ≤28 weeks gestational age, GA)

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to ventilatory limitation despite few studies reporting ventilatory data during exercise. These studies report higher oxygen uptake for the same power output in children with BPD,[10] impaired[11] and enhanced[12] soluble gas transfer in response to exercise in children with BPD and young adults born preterm, respectively, and altered breathing mechanics during exercise in children born preterm[7] and children with BPD[10] compared with control children with little information on the mechanisms behind these changes. Expiratory flow limitation (EFL) may develop during exercise in children with a history of preterm birth;[7] however, EFL and operating lung volumes during exercise have not previously been examined.

The aim of this study was to investigate respiratory mechanics and ventilatory response during exercise in a large cohort of children born EP in the era of routine antenatal steroids and surfactant use. We hypothesised that children born EP will show impairments in VO_{2peak} proportionate to reduction in lung function and reduced airway flows during exercise relative to control children. Understanding the determinants of reduced exercise capacity is an important step towards reducing the risk of long-term cardiorespiratory complications of EP birth.

METHODS
Subjects
This single-centre cohort study included children born EP ($\leq$28 weeks GA) who were alive at 18 months of age; children diagnosed with non-ambulatory cerebral palsy or legal blindness at the 18 month assessment were excluded because of potential physical limitations to completing exercise testing. This definition of EP is the current minimal standard for follow-up in Canada, varies from that of WHO (<28 weeks GA; http://www.who.int/mediacentre/factsheets/fs363/en/) but is consistent with the GA recommendation of the National Institute of Child Health and Human Development (NICHD).[13] EP children were cared for at a large regionalised tertiary care centre in western Canada between 1997 and 2004. Children born EP were categorised as no/mild BPD or moderate/severe (mod/sev) BPD using the definitions of the NICHD/National Heart, Lung, Blood Institute (NHLBI)/Office of Rare Diseases (ORD) workshop.[14] This corresponded to the definition of BPD used in the neonatal intensive care unit (NICU) at the time of these admissions of supplementary oxygen use at 36 weeks GA such that infants off supplementary oxygen at 36 weeks would have no/mild BPD and those using supplementary oxygen or ventilation, mod/sev BPD. There was insufficient information available for further retrospective subclassification. Controls were born at term ($\geq$37 weeks GA) and had no significant history of cardiorespiratory disease based on parental report. Controls could have a history of mild asthma if this was well controlled[15] at the time of the study. Controls were recruited as friends of EP children, and through posters as well as word of mouth within the university/hospital community. The Health Research Ethics Board approved this study. Additional details of the protocol are included in the online supplement.

Study protocol
Families who agreed to participate were mailed a package of questionnaires and scheduled for an activity day. On the activity day, informed consent and assent were obtained from the parent/guardian and child, respectively. The activity day included lung function testing and cardiopulmonary exercise testing (CPET). A subset of children completed echocardiography at rest. Medical chart review was completed for children

born EP to collect the NICU data. GA and birth weight for controls were obtained by parent report.

Ethnicity, anthropometry, cardiorespiratory health and activity
Ethnicity was identified for each parent. Children with parents of different ethnicities were coded as mixed ethnicity. Height, weight and body mass index (BMI) were converted to z-scores using available normative data (http://www.cdc.gov/growthcharts/cdc_charts.htm). Children were deemed to have a history of asthma if parents reported a history of asthma at enrolment or on questionnaires. Illness history, respiratory symptoms and medication use for the last 12 months were collected by parent report. Activity was assessed using questions from the Child Behaviour Checklist; parents were asked to rate how much time their child spent in each sport/physical activity compared with other children (less than average, average, more than average, don't know). All children rated as spending 'more than average' time in any sport/physical activity were considered to be active more than average.

Lung function testing
Lung function testing was performed according to published criteria.[16–18] Testing was completed using a mass flow sensor and plethysmography (Vmax series; SensorMedics Corporation, Yorba Linda, California, USA). Measured spirometry values were converted to z-scores using Global Lung Initiative equations.[19] Published reference equations for Caucasian children were used for lung volumes and diffusion capacity (transfer factor) with equations for residual volume (RV)/total lung capacity (TLC) obtained through personal communication with the author.[20]

Cardiopulmonary exercise testing
An incremental exercise test was performed on a cycle ergometer. A ramped exercise protocol was used with the workload increments selected (5–20 W/min) based on the child's predicted peak power output such that peak oxygen consumption would be obtained in 10–12 min of exercise. Breath-by-breath measurements were collected by a metabolic cart (Vmax Spectra V29 system; SensorMedics, Yorba Linda, California, USA). Satisfactory participant effort was confirmed based on one or more of the following criteria: (1) plateau in oxygen consumption; (2) respiratory quotient (RQ) >1.15; (3) patient exhaustion; or (4) evidence of a ventilatory limitation to exercise.[21] Results were expressed as VO_{2peak} (L/min) and VO_{2peak} relative to body weight (L/min/kg). VO_{2peak} % predicted was calculated using published reference equations for children.[22] Inspiratory capacity (IC) manoeuvres were conducted at rest, every 2 min and at peak exercise. EFL was present when the intersection of the exercising tidal volume (V_T) loop and the maximal flow volume loop was greater than 5%.[23] This was determined by a single blinded reviewer. Rating of perceived exertion (RPE) and dyspnoea were assessed using standard numerical scales.[24] Maximal voluntary ventilation (MVV) was measured following published criteria;[16] 40 children were unable to successfully complete MVV measurement (26%; 15 BPD, 5 EP, 20 control) and were excluded from analysis involving MVV. Breathing reserve (BR) was calculated as BR=(MVV−V_{Epeak})/MVV.

Data management and analysis
The study data were managed using REDCap electronic data capture tools. Statistical analyses were performed using IBM SPSS Statistic V.21 (IBM and others, 1989, 2013). χ^2 and

Goodman and Kruskal's γ were used to test associations between groups and categorical or ordinal data, respectively. Student's t-tests and one-way analysis of variance (ANOVA) were used to compare continuous normally distributed outcome variables between groups. Multivariable linear regression models were developed for VO_{2peak} with variables for inclusion selected based on univariable analysis where $p<0.10$; perinatal variables were entered into the model only for EP children. A $p<0.05$ indicated statistically significant effects with Bonferroni correction applied for post hoc comparisons.

RESULTS
Study population
A total of 357 children born EP met eligibility criteria for inclusion in the study and had GA, birth weight and BPD status available. Of these, 103 (29%) consented to participate in this follow-up study. There were no differences with respect to GA (26.4±1.3 weeks vs 26.4±1.3 weeks, p=not significant (ns)), birth weight (896±200 g vs 920±1.79 g, p=ns) and the

prevalence of mod/sev BPD (45% vs 49%, Pearson's χ^2 3.4, p=ns) between participants and non-participants. Figure 1 shows the distribution of mod/sev BPD, no/mild BPD and control children successfully completing lung function and CPET measurements. Children noted by parents to have physical or cognitive limitations were less likely to complete testing (see online supplement).

Perinatal data show that children with mod/sev BPD were born earlier, and had lower birth weight than children with no/mild BPD (table 1). Premature rupture of membranes, antenatal corticosteroids, clinical chorioamnionitis and respiratory distress syndrome did not differ between groups. Doses of surfactant, days of ventilation and NICU length of stay (LOS) were higher for mod/sev BPD. Children with mod/sev BPD were more likely to be born by caesarean section, and to receive postnatal corticosteroids as well as surgical management for patent ductus arteriosus than children with no/mild BPD.

There were no differences in sex and ethnicity frequencies between mod/sev BPD, no/mild BPD and control children

Figure 1 Distribution of extremely preterm eligible and enrolled children as well as control children. The number of children successfully completing each activity day measure is shown. More children with mod/sev BPD were unable to complete lung volume (20% vs 5.7% vs 1.5%, p<0.01), diffusion capacity (26% vs 3.8% vs 4.6.%, p<0.001) and CPET (14% vs 1.9% vs 4.6% p<0.05). BPD, bronchopulmonary dysplasia; CPET, cardiopulmonary exercise testing; mod/sev, moderate/severe.
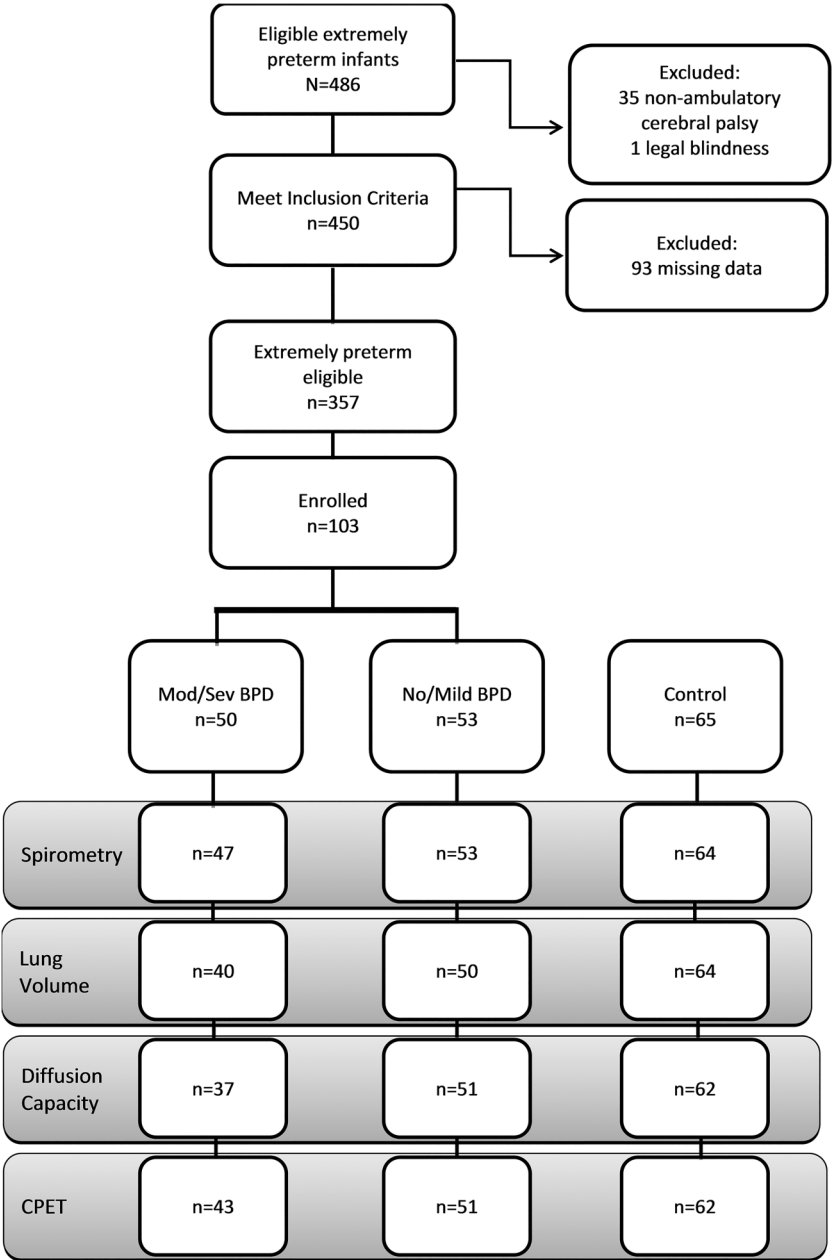
Table 1 Perinatal data for children born extremely preterm

	Moderate/severe BPD (mean±SD; n(%))	No/mild BPD (mean±SD; n(%))
n	47	53
Gestational age (weeks)*	26.0±1.9	26.7±1.1
Birth weight (g)‡	813±191	982±163
Maternal age (years)	29.6±5.8	30.3±6.3
Doses of surfactant†	2.3±2.1	1.1±1.8
Days of initial ventilation‡	29±22	6±11
NICU LOS (days)‡	104±32	65±28
PROM	10 (21%)	7 (13%)
Antenatal corticosteroids	33 (70%)	43 (83%)
Clinical chorioamnionitis	3 (6%)	4 (8%)
Caesarean section*	34 (72%)	27 (52%)
RDS	45 (98%)	51 (98%)
PDA requiring surgery*	12 (27%)	5 (10%)
Postnatal corticosteroids*	13 (28%)	3 (6%)

*$p<0.05$; †$p<0.01$; ‡$p<0.001$.
BPD, bronchopulmonary dysplasia; NICU LOS, neonatal intensive care unit length of stay; PDA, patent ductus arteriosus; PROM, premature rupture of membranes >24 h prior to delivery; RDS, respiratory distress syndrome.

Table 2 Demographics at follow-up for extremely preterm and control children

	Mod/sev BPD (mean±SD, n (%))	No/mild BPD (mean±SD, n (%))	Control (mean±SD, n (%))
n	47	53	64
Age (years)	11.9±1.6	12.3±1.5	11.6±1.9
Height z-score‡	−0.27±0.98	−0.07±1.05	0.45±0.88
Weight z-score‡	−0.074±1.28	−0.39±0.99	0.45±0.85
BMI z-score†	0.074±1.24	−0.42±1.01	0.33±1.04
% Male	27 (57%)	34 (64%)	37 (58%)
% Caucasian	34 (79%)	40 (82%)	45 (82%)
Maternal smoking in pregnancy	11 (24%)	10 (19%)	7 (12%)
Household cigarette smoke exposure	15 (32%)	16 (31%)	12 (20%)
Asthma*	18 (38%)	16 (30%)	11 (17%)
Wheeze in last 12 months*	19 (40%)	13 (24%)	9 (15%)
Asthma medications in last 12 months	10 (21%)	7 (13%)	4 (6%)
Activity more than average†	15 (32%)	27 (51%)	37 (63%)
SOB with activity†	18 (38%)	8 (15%)	9 (15%)

Post hoc ANOVA one-way comparisons (mean±SE):
Height z-score: mod/sev BPD 0.72±0.19<control‡; no/mild BPD 0.53±0.18<control*.
Weight z-score: mod/sev BPD 0.52±0.20<control*; no/mild BPD 0.83±0.19<control‡.
BMI z-score: no/mild BPD 0.75±0.20<control†.
*$p<0.05$; †$p<0.01$; ‡$p<0.001$.
ANOVA, analysis of variance; BMI, body mass index; BPD, bronchopulmonary dysplasia; mod/sev, moderate/severe; SOB, shortness of breath.

(table 2). Children with mod/sev BPD and no/mild BPD had lower height, weight and BMI z-scores than control children. Rates of asthma and wheeze in the last 12 months, but not asthma medication use, differed by group with the highest rates in children with mod/sev BPD. A greater proportion of control children were reported to be more active than average and shortness of breath (SOB) with activity was more common in children with mod/sev BPD.

Lung function and echocardiography
Lung function results differed between groups (table 3). FEV_1, FEV_1/FVC, FEF_{25-75} were lower in mod/sev BPD and no/mild BPD compared with control children with no statistically significant differences between EP groups. The proportion of children with spirometric measures below the lower limit of normal differed by group with a higher proportion of children with mod/sev BPD and no/mild BPD with abnormal results compared with control children (see online supplementary table E1). Lung volume measurements showed higher RV and RV/TLC in

children with mod/sev BPD compared with control children. zTLCO/alveolar volume was lower in both EP groups compared with control children. MVV did not differ between groups. No group differences were seen in routine clinical echocardiography results (see online supplementary table E2).

Cardiopulmonary exercise testing
Peak RQ and heart rate were similar between the three groups, indicating that all three groups achieved similar relative peak intensity during CPET (table 4). VO_{2peak} relative, $VO_2\%$ predicted and peak carbon dioxide uptake VCO_{2peak} were lower in children with mod/sev BPD compared with no/mild BPD and control children with no significant differences between children with no/mild BPD and control children (table 4). In the mod/sev

Table 3 Lung function tests comparing extremely preterm and control children

	Mod/sev BPD (mean±SD)	No/mild BPD (mean±SD)	Control (mean±SD)	Differences from control Mod/sev BPD (mean (95% CI))	No/mild BPD (mean (95% CI))
$zFEV_1$‡	−0.92±1.36	−0.50±1.10	0.09±1.01	−1.00 (−1.54 to −0.47)†	−0.58 (−1.10 to −0.068)*
zFVC	−0.85±1.67	0.35±1.25	0.47±0.90		
$zFEV_1/FVC$†	−1.14±1.5	−1.3±0.80	−0.57±1.14	−0.56 (−1.11 to −0.015)†	−0.71 (−1.25 to −0.19)†
$zFEF_{25-75}$‡	−1.6±1.22	−1.3±0.87	−0.48±1.12	−1.09 (−1.59 to −0.58)‡	−0.84 (−1.33 to −0.35)‡
zTLC	0.63±1.08	0.66±1.10	0.38±1.02		
zRV*	0.092±1.12	−0.16±0.95	−0.47±0.97	0.56 (0.70 to 1.06)*	
zRV/TLC†	−0.19±1.33	−0.55±1.04	−0.91±1.00	0.72 (0.18 to 1.27)†	
zFRC	0.22±1.12	0.072±0.92	−0.29±1.11		
zTLCO	−0.49±0.76	−0.52±0.82	−0.32±0.69		
zTLCO/VA†	−1.64±0.89	−1.57±0.76	−1.06±0.95	−0.58 (−1.02 to −0.13)†	−0.50 (−0.91 to −0.10)†
MVV (L)	79.5±27.5	83.3±27.9	93.1±30.7		

*$p<0.05$; †$p<0.01$; ‡$p<0.001$.
BPD, bronchopulmonary dysplasia; FEF_{25-75}, forced expiratory flow between 25–75% of FVC; FRC, functional residual capacity; mod/sev, moderate/severe; MVV, maximum voluntary ventilation; RV, residual volume; TLC, total lung capacity; TLCO, transfer factor for carbon monoxide; VA, alveolar volume; z, z-score.

Table 4 Cardiopulmonary exercise test (CPET) cardiovascular responses at peak exercise comparing extremely preterm and control children

	Mod/sev BPD (mean±SD)	No/mild BPD (mean±SD)	Control (mean±SD)
Exercise time (min:sec)	6:52±2:01	8:33±2:12	7:45±1:39
RQ	1.07±0.086	1.07±0.84	1.07±0.081
Heart rate (beats/min)	175.8±14.9	178.1±19.1	182.5±15.5
Work (W)	89.2±32.4	104.5±33.2	109.6±35.8
VO_{2peak} (L/min)	1.65±0.65	1.83±0.55	1.87±0.43
VO_{2peak} % predicted (%)†	89.3±23.0	107.4±22.7	103.4±26.5
VO_{2peak} relative (mL/kg/min)†	36.9±10.7	44.6±9.2	42.6±9.6
VCO_{2peak} (L/min)*	1.71±0.62	1.98±0.65	2.03±0.49

Post hoc ANOVA one-way comparisons (mean±SE).
VO_{2peak} relative: mod/sev BPD 5.73±1.94 L/min<control*; mod/sev BPD 7.72 ±2.02 L/min<no/mild BPD†.
VO_{2peak} % predicted: mod/sev BPD 14±5%<control*; mod/sev BPD 18±5%<no/mild BPD†.
VCO_2 peak: No statistically significant one-way differences.
*p<0.05; †p<0.01.
ANOVA, analysis of variance; BPD, bronchopulmonary dysplasia; mod/sev, moderate/severe; RQ, respiratory quotient; VCO_{2peak}, peak carbon dioxide uptake; VO_2, oxygen uptake.

BPD group, VO_2% predicted was 18.2±5.0% (mean±SE) lower than children with no/mild BPD and 14.2±4.9% (mean±SE) lower than control children.

Breathing mechanics during exercise

Minute ventilation (V_E)/kg at peak exercise was lower in children with mod/sev BPD compared with no/mild BPD (table 5),

with the difference attributable to lower V_T/kg in children with mod/sev BPD. Oxygen saturation pulse (SpO_2) was maintained through exercise in all groups, and there was no between-group difference in SpO_2 at baseline or peak exercise. All three groups demonstrated a comparable hyperventilatory response at peak exercise with similar end tidal carbon dioxide tension ($P_{ET}CO_2$) between groups. V_E/VCO_2 slope was greater in the mod/sev BPD group as compared with controls but similar in children with no/mild BPD and controls. The greater V_E/VCO_2 slope in mod/sev BPD despite similar $P_{ET}CO_2$ supports greater dead space ventilation in mod/sev BPD.

BR was lower in children with no/mild BPD compared with controls though similar in children with mod/sev BPD compared with controls (table 5). EFL at peak exercise was more common in children with mod/sev BPD as compared with no/mild BPD and controls. No group showed evidence of dynamic hyperinflation as IC was not reduced at peak exercise compared with baseline in any group. RPE and dyspnoea at peak exercise did not differ between groups.

Multivariable model for VO_{2peak}

Perinatal, demographic and lung function variables were tested to identify univariable predictors of VO_{2peak} % predicted. BPD group (mod/sev BPD, no/mild BPD, control), age and sex were included a priori. An additional 10 variables were identified on univariable analysis and entered into the initial model: 5 perinatal variables (antenatal corticosteroids, doses of surfactant, days of initial ventilation, postnatal steroids, NICU LOS), household cigarette smoke exposure, zWeight, zBMI, 'SOB with activity' and 'active more than average'. All of the identified perinatal variables correlated with BPD group and each other and, therefore, were removed from the model. zWeight and

Table 5 Cardiopulmonary exercise test (CPET) peak respiratory responses comparing extremely preterm (EP) children and control children

	Mod/sev BPD (mean±SD)	No/mild BPD (mean±SD)	Control (mean±SD)
RR baseline (breaths/min)*	23.0±4.6	20.2±4.7	20.6±5.2
RR peak (breaths/min)	48.0±12.8	46.9±10.9	47.5±12.4
V_T/kg baseline (mL/kg)*	12.2±4.0	14.9±6.3	13.4±5.1
V_T/kg peak (mL/kg)†	25.7±7.5	31.9±5.8	29.5±6.5
V_E/kg baseline (mL/kg/min)	266±101	275±91	250±90
V_E/kg peak (mL/kg/min)*	1393±428	1631±431	1433±378
Inspiratory capacity baseline (L)	1.75±0.56	1.74±0.74	1.67±0.58
Inspiratory capacity peak (L)	1.84±0.47	1.85±0.68	1.94±0.68
SpO_2 baseline (%)	97.5±2.9	97.7±2.7	98.3±1.2
SpO_2 peak (%)	94.3±4.9	95.2±4.7	95.3±4.9
$P_{ET}O_2$ peak (mm Hg)	103.0±4.8	103.8±4.9	102.1±10.1
$P_{ET}CO_2$ peak (mm Hg)	35.6±4.1	35.6±3.9	36.1±3.8
V_E/VO_2 slope	27.9±3.3	27.4±2.7	26.4±2.8
V_E/VCO_2 slope*	30.5±3.8	28.9±2.9	28.6±3.2
BR (%)*	18.5±23.6	15.5±20.9	24.6±16.9
Expiratory flow limitation (n, %)*	16/34 (47%)	16/49 (33%)	14/59 (24%)
End exercise—dyspnoea	4.0±2.8	4.4±2.2	3.8±2.4
End exercise—RPE	6.0±2.5	5.6±2.4	5.0±2.7

*p<0.05.
†p<0.001.
Post hoc ANOVA one-way comparisons (mean±SE).
RR baseline: mod/sev BPD 2.8±1.0 breaths/min>no/mild BPD*.
V_T/kg baseline: mod/sev BPD 2.7±1.1mL/kg<no/mild BPD*.
V_T/kg peak: mod/sev BPD 6.2±1.4 mL/kg<no/mild BPD†; mod/sev BPD 3.8±1.3 mL/kg<control*; no/mild EP 3.8±1.3 mL/kg>control*.
V_E/kg peak: mod/sev BPD 233±88 mL/kg/min<no/mild BPD*.
V_E/VCO_2 peak: mod/sev BPD 1.94±0.69<Control*.
BR: no/mild BPD 9.0±3.8% <control*.
ANOVA, analysis of variance; BPD, bronchopulmonary dysplasia; BR, breathing reserve; mod/sev, moderate/severe, $P_{ET}CO_2$, end tidal carbon dioxide tension; $P_{ET}O_2$, end tidal oxygen tension; RPE, rating of perceived exertion; RR, respiratory rate; SpO_2, oxygen saturation pulse; VCO_2, carbon dioxide uptake; V_E, minute ventilation; VO_2, oxygen uptake; V_T, tidal volume.

Table 6 Predictors of exercise capacity as measured by $VO_2\%$ predicted

Variables	B±SE	Standardised coefficient	p Value
Group*	−17.21±6.02	−0.56	0.005
Male sex	−24.42±9.03	−0.48	0.008
Shortness of breath with activity	−9.63±4.01	−0.16	0.018
More active than average	10.69±3.41	0.21	0.003
Age	−3.19±0.95	−0.22	0.001
zBMI	−10.06±1.43	−0.47	<0.001
Interaction: group×sex	15.17±4.04	0.95	<0.001

The R^2 for the model is 0.43, p<0.001.
*Group: 1=mod/sev BPD, 2=no/mild BPD, 3=control.
BMI, body mass index; BPD, bronchopulmonary dysplasia; VO_2, oxygen uptake; z, z-score.

household cigarette smoke exposure were not significant predictors and were removed. Finally, group was tested for significant interactions with other predictor variables and these interactions were added to the model. The final model used the 'enter' method for covariate inclusion, six main effects and one interaction term (table 6; adjusted R^2 0.43, p<0.001). BPD group, male sex, 'SOB with activity', higher age and higher BMI predicted lower VO_{2peak} % predicted. 'Active more than average' predicted higher VO_{2peak} % predicted. Post hoc analysis demonstrated that, after controlling for other variables, VO_{2peak} % predicted was lower in girls with mod/sev BPD compared with boys and higher in no/mild BPD and control girls compared with boys.

DISCUSSION
The results from the present study confirm impaired lung function and exercise capacity in preadolescents after EP birth in an era of routine antenatal steroids and postnatal surfactant, and highlight breathing mechanics and ventilatory response contributions to exercise limitation. Compared with control children, FEV_1 was approximately 1.0 z-score lower in children with mod/sev BPD and 0.5 z-score lower in children with no/mild BPD. TLC was preserved with impairments in diffusion capacity in both EP groups compared with controls. VO_{2peak} was 18% and 14% lower, respectively, in children with mod/sev BPD compared with children with no/mild BPD and control children. Our results provide the first data documenting the factors contributing to respiratory limitation to exercise in preadolescent children with a history of mod/sev BPD. This includes greater prevalence of EFL that cannot be explained by airflow obstruction alone and a heightened ventilatory response to exercise.

Expiratory flow limitation
In highly trained athletes and adults with respiratory disease, EFL promotes dynamic hyperinflation and intrinsic positive end-expiratory pressure leading to functional impairment of inspiratory muscle strength, increased work of breathing and increased sensations of dyspnoea.[25] With ongoing EFL, end-expiratory lung volumes are increased with a corresponding reduction in IC and inspiratory reserve volumes; this decrease in IC during exercise would limit the ability to increase V_T and may increase dyspnoea. In the present study, we demonstrate a greater prevalence of EFL in children with a history of BPD without group differences in IC suggesting that dynamic hyperinflation was not present. While there was reduction in peak V_T

response to exercise in the children with BPD compared with control and EP children, there was no evidence of hypercapnia or hypoxaemia at peak exercise. A blunted V_T at peak exercise has previously been reported in children with a history of EP birth,[7] and may be a compensatory mechanism to reduce work of breathing in the presence of EFL. Despite evidence of altered respiratory mechanics, dyspnoea at peak exercise was not more prevalent in children with mod/sev BPD suggesting either dyspnoea was not sensed or that the standard Borg scale may not be appropriate for assessing dyspnoea in this group. There were, however, group differences with respect to reported activity patterns such that children with a history of mod/sev BPD were less active than children with no/mild BPD and control children. EFL leading to respiratory limitation during exercise could contribute to a chronic reduction in physical activity which, over time, would lead to a reduction in aerobic fitness and, hence, a lower VO_{2peak}. Further work is needed to explore the role of EFL in exercise limitation after EP birth.

Potentiated ventilatory response
Ventilatory inefficiency during exercise, as measured by an increase in the V_E/VCO_2 slope, is an important predictor of health outcomes in adult patients with a range of cardiorespiratory diseases. A potentiated ventilatory response to exercise has been reported in patients with mild COPD[26] and pulmonary arterial hypertension (PAH), and is predictive of mortality in PAH.[27] The potentiated ventilatory response in these conditions may be linked to cardiac or pulmonary vascular abnormalities leading to stimulation of receptors in the lung and high vascular pressures.[28] In the present study, children with a history of mod/sev BPD showed a greater V_E/VCO_2 slope response to exercise with similar $P_{ET}CO_2$ values throughout exercise compared with children with no/mild BPD and control children. Echocardiographic measures at rest did not differ between groups suggesting this difference is unlikely due to cardiac or pulmonary vascular effects. However, exercise induced pulmonary vascular responses cannot be excluded. This pattern of response is consistent with the exercise response described in preadolescents with cystic fibrosis, another form of obstructive lung disease, who had mild to moderate airway obstruction where the ratio of dead space ventilation to V_T was higher than controls throughout exercise.[29] It is important to note that exercise training and breathing training have been shown to lower the slope of V_E/VCO_2 response to exercise[30] and reduce EFL[31] and, therefore, may be appropriate therapeutic strategies in children and adults with a history of BPD.

Relationship between lung function and exercise capacity
The relationship between lung function and exercise capacity differs by the type of lung disease with limited data in children. For example, lung function (ie, FEV_1) and VO_{2peak} are positively, though weakly, correlated in some adult obstructive lung disease[32 33] and cardiac conditions[34] though poorly correlated in restrictive lung disease.[32] In adolescents with asthma FEV_1 has been shown to be unrelated to VO_{2peak}[35] suggesting that factors other than FEV_1 explain the reduced VO_{2peak} in asthma. Consistent with prior studies of preterm birth,[8 9 36] the present study of children born EP showed no significant relationships between lung function and VO_{2peak}. Exploration of the contribution of deconditioning and exercise training to reductions in exercise capacity in children following EP birth is needed.

Potential impact on adult lung function and exercise

Airway flows and vital capacity of the lung as well as VO_{2max} begin to decrease in early adulthood.[37 38] For young adults with a history of EP birth, the normal decline in lung function and maximal oxygen uptake beginning in their mid-20's may have greater and earlier consequences. In addition to decline from a lower peak, factors associated with EP and impaired lung function may predispose to accelerated decline in lung function: inflammation, infection and hyperoxia are thought to contribute to the pathogenesis of BPD and are also linked to exaggerated age-related decline in lung function.[39] Studies of young adults with a history of BPD, born at the beginning of the surfactant era, have documented abnormalities in lung function, exercise impairments and early emphysema.[36 40] Together, these studies suggest the development of a chronic obstructive lung disease in early adulthood. In the present study, children born EP have impaired FEV_1 relative to controls with a doubling of this impairment in children with a history of mod/sev BPD. Even if differences from controls remain stable during ageing, EP birth will confer a high risk of earlier respiratory and exercise limitations in adulthood.

Limitations

Our study measurements precluded inclusion of children unable to pedal a bike, and, therefore, cannot be generalised to children with major disability. In addition, children with mod/sev BPD were more likely to be unable to complete components of testing excluding their results from these analyses. Our results are likely biased towards children with better exercise capacity and, therefore, will underestimate overall impairments following EP birth. Of note, lung measurements in controls differed from the anticipated z-score of 0 suggesting that the reference equations used may not be completely appropriate for this population. Measurements of activity were collected by parents' report rather than by objective measurement; future studies including objective activity data will be important to determine whether activity patterns are a factor in exercise limitation in mod/sev BPD and whether prescribed activity is a meaningful therapy. The prevalence of EFL was determined by plotting the tidal flow-volume loops within the maximum flow-volume curve at baseline. As such, we did not account for any exercise-induced bronchodilation, nor did we correct for thoracic gas compression. Lastly, we did not assess changes in lung diffusion, perfusion or ventilation/perfusion matching during exercise. These factors should be considered in future studies given at least one report of impairments in gas transfer during exercise and recovery, despite comparable resting measurements, in children born preterm with BPD compared with preterm and term control children.[11]

Summary

In summary, preadolescents with a history of EP birth with no/mild BPD and mod/sev BPD have lower lung function relative to controls. Mod/sev BPD is associated with a greater reduction in lung function and impairments in exercise capacity. A heightened ventilatory response to exercise and EFL impact exercise capacity in those children with a history of mod/sev BPD. Both lung function and exercise testing are needed to fully characterise respiratory function and limitations in children born EP. Future research efforts should focus on defining the mechanisms for exercise limitation with the goal of identifying therapeutic targets to improve long-term cardiorespiratory outcomes following EP birth.

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