ON-LINE SUPPLEMENT

Altered breathing mechanics during exercise in children born extremely preterm

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The overall aim of the New Breath study was to describe the long-term cardio-respiratory health of a large cohort of children born extremely preterm (EP) in the era of routine antenatal steroids and surfactant use. In this manuscript, we present the results of lung function and cardio-respiratory exercise testing (CPET) in children born EP, with No/Mild bronchopulmonary dysplasia (BPD) or Moderate/Severe (Mod/Sev) BPD, and Control children. We hypothesized that children born EP will show a reduction in airway function relative to control children and that Mod/Sev BPD will further impair lung function. In addition, children born EP will demonstrate impairment in exercise capacity attributable to altered airway mechanics with a greater impairment in children with a history of BPD. This on-line data supplement provides additional details with respect to methods and results.

Methods

Time period

This time period 1997 to 2004 was chosen as an electronic database was available in the NICU starting in 1997. Reviewing practices in this NICU shows that at this time and moving forward antenatal corticosteroids and surfactant were used routinely and post-natal corticosteroids were used with careful consideration. This period also precedes significant changes in ventilation and oxygen strategies.

EP Clinical Follow-up

All EP infants were followed in the Neonatal and Infant follow-up clinic at the Glenrose Rehabilitation Hospital as a standard of care. This is a participating site in the Canadian Neonatal Follow-up Network where the minimal criterion for inclusion in follow-up is ≤28 weeks GA for all sites. Children were excluded prior to contacting the family if they were identified as having a

disability that would preclude pedaling a stationary bike based on the assessment at the final follow-up visit at 18 months (e.g. non-ambulatory cerebral palsy). This was done out of respect for families to limit, if not eliminate, contacting families whose children would not be able to participate in the study.

Study protocol

Initial contact with families of EP born children was by letter with follow-up phone calls. After agreement to participate, families were asked if they could identify a friend of their child who was born at term, healthy and interested in participating. Friends were scheduled on the same activity day. Additional community controls were recruited through key contacts and poster advertisements. All families with a participating child were mailed a package of questionnaires prior to the activity day. These included a general and cardio-respiratory health questionnaire, the Child Sleep Habits Questionnaire (CSHQ), the Child Health Questionnaire (CHQ) – Parent Report, the Child Behaviour Check List (CBCL), and the Pediatric Quality of Life Survey (PedsQL). For families who reported a history of asthma for their child, the PedsQL Asthma Survey was also included in the package. For children $\geq$ 13 years of age, both the parent and teen versions of the PedsQL and the PedsQL Asthma Survey were sent.

On the activity day children completed lung function testing, including spirometry, lung volumes and diffusion capacity, and cardio-pulmonary exercise testing (CPET) using a cycle ergometer. A sub-set of children completed additional testing including oxygen (O_2) and carbon dioxide (CO_2) response testing, echocardiography, and quality of life interviews. If additional testing could not be completed in a single day, families were asked if they were willing to return on a separated day for echocardiography. Some quality of life interviews were completed by phone.

Medical chart review was completed for children born EP. This was restricted to the child's NICU chart which included a copy of the delivery record and included both free text and tabulated data. The data extraction was carried out by experienced neonatal research nurses.

Height was recorded, without shoes, using a fixed stadiometer. Weight was measured with exercise clothing, without shoes, using a digital scale. Height, weight and body mass index (BMI) were converted to z-scores using normative data from the Centre for Disease Control.[14]

Lung function testing

Lung function testing was performed and best maximal effort selected according to published criteria.[1;2] Measured spirometry values were converted to percent predicted (%pred) and z-scores using the equations of the Global Lung Initiative (GLI)[3] with 2 decimal points used for age. These equations account for ethnicity, height and sex. As GLI equations are not yet available, previously published reference equations for %pred and z-scores in children were used for lung volumes and transfer factor (ie diffusion capacity)[4] with equations for RV/TLC obtained through personal communication with the author. These equations were developed for Caucasian children and thus may not be representative of lung volume and diffusion predicted values for other ethnicity groups. These equations, however, were used as race corrected equations for Canadian or other children are not available, and these equations have been used in other studies of children with a history of preterm birth.[5;6]

Cardio-pulmonary exercise testing

The incremental exercise test was performed on an electromagnetically-braked cycle ergometer (Ergoslect 200P; Ergoline GmbH, Blitz, Germany) calibrated for accurate power output prior to the study. A ramped exercise protocol was used, with the workload increments selected (5-20W min^{-1}) based on the child's predicted peak power output such that peak oxygen consumption

would be obtained in 10-12 minutes of exercise. Breath-by-breath measurements of minute ventilation (V_E), tidal volume (V_T), respiratory rate (RR), oxygen uptake (VO_2), carbon dioxide production (VCO_2), end-tidal oxygen ($P_{ET}O_2$) and end-tidal carbon dioxide ($P_{ET}CO_2$) were collected. Subjects were monitored with a 12-lead electrocardiogram (ECG, Cardiosoft; SensorMedics, Yorba Linda, CA) and pulse oximetry (N-595; Nellcor Oximax, Boulder, CO). Only tests terminated because of participant inability to continue exhaustion (i.e. inability to maintain cadence despite encouragement) were included in the analysis. VO_{2peak} percent predicted (%pred) was calculated using published reference equations for children with different equations for males and females.[7]

At rest, and every two minutes until peak exercise an inspiratory capacity (IC) manoeuvre was conducted. Assuming that total lung capacity (TLC) did not change with exercise, the changes in IC reflected changes in end-expiratory lung volume (EELV = TLC – IC). Consistent with previous work,[8-10] expiratory flow limitation was defined as being present when the intersection of the exercising VT loop and the maximal flow volume loop was greater than 5%. Blood pressure (BP) was measured by manual blood pressure cuff and barometer at baseline, every 4 minutes, and at peak exercise. Post-exercise spirometry was conducted as per guidelines and a 10% reduction in FEV1 was defined as exercise-induced bronchoconstriction.[11] Breathing reserve was calculated using (Maximal voluntary ventilation (MVV) – VE_{peak})/MVV. MVV was measured following ATS/ERS criteria.[1] Dyspnea and perceived exertion were assessed using standard numeric scales using a 10-point system.[12] The scales were anchored such that 0 represents “no breathing discomfort or leg fatigue” and 10 represents “the most severe breathing discomfort or leg fatigue ever experienced or could imagine experiencing”.

Echocardiograms

Complete M mode and 2 dimensional cross sectional echocardiograms were performed together with pulsed, continuous wave and color Doppler interrogations using standard views. Testing was performed at rest either prior to CPET or on a different day. Results were reviewed by two reviewers trained in the interpretation of paediatric echocardiography.

Results

Ability to complete testing

Children noted by parents to have an illness or disability (excluding asthma) were less likely to complete testing (91% vs 99%, Pearson's Chi-square 6.5, $p<0.05$; Table E1). Illness or disability was noted in 40% of Mod/Sev BPD, 20% of No/Mild/BPD and 10% of control children (Pearson's Chi-square 13.7, $p<0.01$).

Proportion of spirometry results below the lower limit of normal

A greater proportion of Mod/Sev BPD and No/Mild BPD children had at least one spirometry value below the lower limit of normal (LLN; BPD 62%, 49% vs 20%, $p<0.001$). Table E2 shows the proportion of individual spirometric measures that were below the LLN for Mod/Sev BPD, No/Mild BPD and Control children.

Echocardiography

Routine clinical echocardiography results did not show group differences with respect to structural measurements, ventricular size or systolic functional measurements (Table E3).

Summary

Children born EP have a higher prevalence of impaired lung function compared to Control children with a higher prevalence of impaired lung function in Mod/Sev BPD compared to

No/Mild BPD. A higher proportion of children born EP have FVC below the LLN suggesting differences in lung volumes as well as airway flows. Echocardiography results do not differ between groups suggesting that baseline cardiac structure and function is not responsible for exercise limitations in children with Mod/Sev BPD.

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Table E1: Association between successful completion of spirometry and the presence of illness or disability noted by parent.

		Successful completion of spirometry	
		No	Yes
Presence of illness or disability noted by parent*	No	1	122
	Yes	3	32

*Illness or disability (excluding asthma) as listed by parents included: Wolfe-Parkinson-White syndrome, Tourette syndrome, cerebral palsy, epilepsy, fetal alcohol syndrome disorder, autism spectrum disorder, obsessive compulsive disorder, general anxiety disorder, attention deficit disorder, attention deficit hyperactivity disorder, oppositional defiant disorder, physical delay, learning disability, developmental delay, brain damage, mental delay, language delay, auditory processing issue, cognitive processing delay, congenital brain anomaly, visual impairment, hearing impairment.

Table E2: Proportion of children with spirometry results below the Global Lung Index lower limit of normal (LLN) by group.

	Mod/Sev BPD *[mean ±(SD)]*	*No/Mild BPD* *[mean ±(SD)]*	*Control* *[mean ±(SD)]*
n	47	53	64
FEV_1[†]	34%	13%	6%
FVC[†]	15%	4%	0%
FEV_1/FVC[†]	38%	36%	17%
FEF_{25-75}[†]	47%	36%	11%

[*]$p<0.05$; [**]$p<0.01$; [†]$p<0.001$.

Table E3: Echocardiography results comparing bronchopulmonary dysplasia, extreme preterm, and control children.

	Mod/Sev BPD [mean ±(SD)]	*No/Mild BPD [mean ±(SD)]*	*Control [mean ±(SD)]*
n	32	34	34
LVPWd (cm)	0.59 ± 0.13	0.69 ± 0.35	0.64 ± 0.10
IVSd (cm)	0.60 ± 0.13	0.63 ± 0.11	0.71 ± 0.27
FS (%)	37.0 ± 6.5	38.9 ± 7.3	38.6 ± 7.1
RVIDd (cm)	2.0 ± 0.5	2.0 ± 0.6	2.4 ± 1.2
Pulmonary valve annulus (cm)	2.3 ± 0.3	2.3 ± 0.3	2.5 ± 0.3
MPAs (cm)	2.1 ± 0.4	2.1 ± 0.4	2.2 ± 0.3
MPAd (cm)	1.7 ± 0.4	1.6 ± 0.3	1.6 ± 0.3
Aortic valve annulus (cm)	1.8 ± 0.2	1.8 ± 0.2	1.9 ± 0.2
RAFAC (%)	38.3 ± 6.4	36.4 ± 8.4	39.2 ± 7.8
RVFAC (%)	34.8 ±9.7	33.6 ± 10.8	36.7 ± 10.4
RVSP (TR jet; mmHg)[¥]	21.1 ± 1.4	20.7 ± 1.9	20.9 ± 3.0
Mean PA pressure (peak PR jet; mmHg)[‡]	10.4 ± 3.7	10.4 ± 4.0	8.6 ± 2.3
Tei myocardial performance index (Septal)	0.56 ± 0.53	0.42 ± 0.07	0.45 ± 0.08
Tei myocardial performance index (Lateral)	4.5 ± 14.6	0.45 ± 0.15	0.46 ±0.14
Tei myocardial performance indext (RV)	0.31 ±0.20	0.30 ± 0.21	0.42 ± 0.08

[¥]RVSP (TR jet) was present and measured in 12 BPD, 6 EP, and 12 Control children.

[‡]Mean PA pressure (peak PR jet) was presented and measured in 18 BPD, 16 EP and 21 Control children.