Increased incidence of expiratory flow limitation during exercise in children with bronchopulmonary dysplasia

Christopher A O'Dea[1, 2,3], Karla Logie [3],[4,5], Andrew Maiorana[2,6], Andrew C Wilson[1,2,3,4], J Jane Pillow[7,8], Georgia L Banton[3], Shannon J Simpson[#2,3,4] and Graham L Hall[#2,3,4]

1. Respiratory Medicine, Princess Margaret Hospital, Perth, Western Australia.
2. School of Physiotherapy and Exercise Science, Curtin University, Perth, Western Australia
3. Telethon Kids Institute, Perth, Western Australia.
4. Centre for Child Health Research, University of Western Australia
5. Division of Paediatrics and Child Health, Medical School, University of Western Australia, Perth, Western Australia
6. Allied Health Department and Advanced Heart Failure and Cardiac Transplant Service, Fiona Stanley Hospital, Western Australia.
7. Centre for Neonatal Research and Education, Division of Paediatrics and Child Health, Medical School, University of Western Australia, Perth, Western Australia, Australia.
8. School of Human Sciences, University of Western Australia, Perth, Western Australia, Australia

Online data supplement

Methods

Participants

Children aged 9-12 years, born preterm (≤32 w completed gestational age (GA)) between 1996 and 2001 were identified from the neonatal database of King Edward Memorial Hospital, Perth, Western Australia. Preterm children were classified as having BPD if they had required at least 28 days supplemental oxygen at 36 weeks postmenstrual age, consistent with the NHLBI guidelines[1]. Age-matched healthy full-term controls (>37 w GA) were recruited from the general population. Term born children with a parentally reported history of wheeze, chronic cough, asthma or other cardiopulmonary disease were excluded. Written informed consent from parents and assent from the child were obtained. Ethics approval was obtained from the Princess Margaret Hospital for Children human ethics committee (approval 1760EP).

Pulmonary function testing

Spirometry and lung volume measurements by multiple breath nitrogen washout were performed according to international standards [2, 3] using Sensormedics Vmax 229 (Sensormedics Encore 21-1A, Yorba Linda, CA). Spirometry results are reported as z-scores using the GLI reference values [4]. Lung volume results are reported as z-scores using the Cook and Harman reference values[5].

Peak Exercise test

All peak exercise tests occurred within the exercise laboratory at atmospheric temperatures and pressure, all results reported are corrected for body temperature, pressure and saturated with water vapor (BTPS). Participants performed an incremental exercise test on a treadmill (Marquette, Sensormedics, Yorba Linda, CA) employing a modified Balke protocol [6]. Baseline observations were obtained over 5 minutes. Subsequently, participants commenced jogging at comfortable pace on a gradient of 0 %. After two minutes of jogging, the gradient was increased to 4 % for two minutes, followed by 2 % increments every two minutes until volitional exhaustion, a peak exercise test was defined as peak heart rate >90% predicted and physical signs of peak performance (sweating, flushed face and inability to maintain running speed). Metabolic ($\dot{V}O_2$, $\dot{V}CO_2$) and ventilatory data (tidal volume and breathing frequency) were recorded continuously by breath-by-breath analysis (SensorMedics 229 Metabolic Cart, SensorMedics, Yorba Linda, CA).

Tidal flow volume loops

Tidal flow volume loops were assessed based on the technique described by Nourry et al [7] and adapted by our group [8]. Briefly, placement of the tidal flow volume loop relative to total lung capacity (TLC) was determined from tidal breathing followed by a maximal inspiratory capacity (IC) maneuver to TLC at the end of each exercise stage. Tidal flow volume loops were set within the maximal flow volume loop obtained during baseline spirometry based on IC. TLC was assumed to remain constant throughout the exercise. Dynamic flow limitation was diagnosed if 5 % or more of the tidal flow volume loop tracked the maximum flow volume loop.

Breathing strategy during exercise

End expiratory lung volume (EELV) was assessed at each stage as a measure of dynamic FRC [8, 9]. The EELV was calculated from the difference between the TLC measured at baseline and the IC obtained from the tidal flow volume loops during exercise. The EELV was expressed as a change from baseline (ΔEELV) and as a percentage of TLC (EELV%TLC). End inspiratory lung volume (EILV) was calculated as TLC – inspiratory reserve volume (IRV). The IRV was calculated as IC – tidal volume. EILV was expressed as a change from baseline (ΔEILV) and EILV as a percentage of TLC (EILV%TLC).

Neonatal data and exercise symptoms

Neonatal information including gestational age, and duration of supplemental oxygen use and ventilatory support (including continuous positive airway pressure (CPAP), and mechanical ventilation (MV)) were extracted from the Hospital’s neonatal clinical database.

Parentally reported exercise symptoms within the preceding three months were recorded using a respiratory symptom questionnaire [10]. Children were classified as having current exercise-induced symptoms if parents reported cough, wheeze or shortness of breath on exertion, or symptoms that limited their child’s physical activity within the preceding three months.

Results

Table E1. Demographic, neonatal and exercise outcomes for subjects who performed successful exercise flow volume loops and those who did not.

	Successful tidal FVL (n =149)	Unsuccessful tidal FVL (n =73)
Pre-term, n (%)	106 (71%)	57 (79%)
Male sex, n (%)	88 (59%)	38 (52)
Gestational age (PMA)	28.0 (25.0, 30.0)	27.0 (25.0, 29.1)
Birth weight (g)	1010 (788, 1356)	890 (740, 1205)
Birth weight Z-Score	-0.46 (-0.66, 0.42)	-0.33 (-0.80, 0.45)
Mechanical ventilation (days)	40 (0, 24.7)	5.0 (0.1, 40.7)
CPAP (days)	6.4 (1.0, 19.3)	4.0 (0.5, 18.0)
Supplemental O_2 (days)	48.0 (2.0, 93.0)	46.0 (1.8, 89.0)
Recent exercise symptoms, n (%)	44 (39%)	32 (65%)*
Age at test (y)	10.8 (10.3, 11.3)	10.9 (10.2, 11.4)
Height at test (cm)	142 (137, 148)	144 (137, 151)
Weight at test (kg)	33.4 (29.5, 39.8)	32.2 (29.6, 42.3)
FEV_1 z-score	-0.30 (-1.04, 0.31	-0.78 (-1.47, -0.11) *
FVC z-Score	0.11 (-0.54, 0.86)	-0.05 (-0.79, 0.76)
FEV_1/FVC z Score	-0.98 (-1.67, -0.30)	-1.23 (-0.186, -0.50)
TLC z score	-0.13 (-0.64, 0.55)	-0.26 (0.69, 0.31)
FRC z score	0.3 (-0.41, 0.90)	-0.09 (-0.70, 0.87)

RV z score	-0.21 (-1.01, 0.4)	-0.35 (-1.05, 0.33)
Inspiratory Capacity (L)	1.49 (1.26, 1.80)	1.41 (0.91, 1.76)
$\dot{V}O_2$ peak (L/min)	1.62 (1.42, 1.84)	1.76 (1.57, 1.96)
$\dot{V}O_2$ peak (ml/kg/min)	47.6 (43.1 52.3)	47.2 (37.7, 51.4)
Peak V_T (L)	0.88 (0.71, 1.04)	1.05 (0.90, 1.18) *
Peak f_R (breaths/min)	60 (53, 69)	56 (48, 61)
Peak V_E (L/min)	52.8 (44.8, 60.8)	55.6 (49.5, 63.0)

All data are presented as median (IQR) unless otherwise stated. *p<0.05. PMA, postmenstrual age; CPAP, continuous positive airway pressure; f_R, respiratory frequency; V_E, minute ventilation.

Table E2. Univariate regression analysis for neonatal and lung function variables and the incidence of dynamic flow limitation in preterm children.

	OR	95% CI	P
Gestation (PMA)	0.872	0.748- 1.015	0.078
Supplemental Oxygen (d)	1.011	1.002 - 1.020	0.019*
Mechanical Ventilation (d)	1.014	0.993 - 1.037	0.199
Birth Weight z-score	0.827	0.525 - 1.303	0.412
CPAP (d)	1.031	0.998 - 1.065	0.063
Age at test (y)	0.703	0.376 - 1.314	0.269
Height at test (cm)	0.981	0.933 - 1.031	0.451
Weight at test (cm)	0.952	0.902 - 1.005	0.073
Sex (Female)	1.45	0.41 - 3.280	0.372
FEV_1 z-score	0.244	0.128 - 0.463	<0.001*

FVC z-score	0.758	0.481 - 1.193	0.231
FEV_1/FVC z-score	0.179	0.081 - 0.394	<0.001*
FRC z-score	1.007	0.753 - 1.346	0.962
TLC z-score	0.696	0.660 - 1.424	0.874
RV z-score	1.24	0.893 - 1.722	0.198

PMA, postmenstrual age; CPAP, continuous positive airway pressure

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