ABNORMAL RESTRICTIVE CONTRAINTS ON VENTILATION AND BREATHLESSNESS DO NOT CONTRIBUTE TO EXERCISE INTOLERANCE IN ADULT SURVIVORS OF PRETERM BIRTH WITH BRONCHOPULMONARY DYSPLASIA

by

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B.Sc., McGill University, 2015

A THESIS SUBMITTED TO McGILL UNIVERSITY IN PARTIAL FULFILLMENT OF THE REQUIREMENTS OF THE DEGREE OF

MASTER OF SCIENCE

in

THE FACULTY OF EDUCATION
(Department of Kinesiology and Physical Education)

McGILL UNIVERSITY
MONTREAL, QUEBEC, CANADA

August 2017

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ACKNOWLEDGEMENTS

Firstly, and most importantly, I want to thank my thesis supervisor, Dr. Dennis Jensen, for everything that he has been to me over these past two years. Dennis is one of the most selfless people that I have ever had the privilege of working with, and I am truly grateful to be among the students to have graduated from his lab. Not only was he supportive as a supervisor in my academic and extracurricular endeavours, but he is a person that has become a cornerstone in my life.

Secondly, I want to thank the other members of the CERPL, both past and present: Sara Abdallah, Marcus-Waskiw Ford, Courtney Wilkinson-Maitland, Jared Ferguson, Lauren Tracey, Michelle Moore, Irina Uscatescu, and Tara Greiss. Every one of you made it fun to be in the lab/hospital each day, and I appreciate all of your support, guidance and good times along the way.

Thirdly, I want to thank the other members of my thesis committee: Dr. Benjamin Smith and Dr. Jean Bourbeau. Your wisdom and guidance throughout this process was crucial to my success, and I appreciate you taking the time out of your own busy careers to help further mine.

Lastly, I want to thank my family: Wayne, Sue, Jordan, and Kaileigh for letting me fly the coup and spend 6 years in Montreal going on this journey. Your support over the years has not gone unappreciated, and this certainly would never have been possible without the thought that no matter what, you all had my back.

Special thanks goes out to the members of the McGill Track Team that always let the fieldhouse be my home away from home. Ryan McClelland, Ethan Wilkinson, Patrick Farias,

Jeffrey Vautour and Ellen Parker, you guys made each and every day at school a blast, and it is something that I will never forget.

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ABSTRACT

Background and rationale. Bronchopulmonary dysplasia (BPD) is characterized as a respiratory consequence of preterm birth resulting from exposure to mechanical ventilation and/or supplemental oxygen therapy. Over the last 30 years, improvements in neonatal care practices have increased survival of babies born premature and who develop BPD. Consequently, an increasing number of infants with BPD are now reaching adulthood. Thus, understanding the long-term consequences of BPD is critically important to optimizing clinical care and health outcomes of this patient population.

In addition to the established (adverse) effects of BPD on baseline pulmonary function, a growing body of evidence suggests that the exercise tolerance of adult survivors of preterm birth complicated by BPD is abnormally low. The physiological mechanisms of impaired exercise tolerance among adults with BPD are poorly understood, although abnormal restrictive constraints on tidal volume (V_T) expansion and breathlessness may be contributory.

Aim and objective. The general aim of this single-center, cross-sectional, observational cohort study was to better under the physiological mechanism(s) of impaired exercise tolerance in adult survivors of preterm birth complicated by BPD. To this end, the specific objective of this study was to compare (i) baseline pulmonary function test parameters, (ii) dual energy x-ray absorptiometry (DXA)-derived body composition parameters, (iii) daytime physical (in)activity levels and (iv) detailed assessments of the ventilatory, breathing pattern, dynamic operating lung volume, cardiac, metabolic, gas exchange and perceptual responses to symptom-limited incremental cycle exercise testing in young adult (18-26 years) survivors of preterm birth with

BPD (*n*=31), adult survivors of preterm birth with no neonatal respiratory complications (PRE, *n*=26) and healthy young adults born at full-term with no neonatal respiratory complications (TERM, *n*=35).

Summary of main results. Spirometric pulmonary function test parameters (i.e., forced expiratory volume in 1-sec [FEV_1], FEV_1-to-forced vital capacity ratio [FEV_1/FVC] and forced expiratory flows between 25% and 75% of FVC [$FEF_{25-75\%}$]) and pulmonary diffusion capacity for carbon monoxide (D_LCO) were significantly lower, while residual volume was significantly higher in BPD vs. both PRE and TERM. DXA-derived estimates of lean body mass (LBM) and fat mass were not significantly different between groups. Activity monitor-derived estimates of average daily activity-related energy expenditure, step count and time spent in vigorous activity were significantly lower in BPD vs. TERM. The power output (PPO, expressed in W and W/kg LBM) and rate of O_2 consumption ($\dot{V}O_{2peak}$, expressed in L/min, ml/kg/min and ml/kg LBM/min) achieved at the symptom-limited peak of incremental cycle exercise testing was significantly lower (by ~17% and ~15%, respectively) in BPD compared with TERM. With few isolated exceptions, cardiac, metabolic and gas exchange responses during submaximal exercise were not significantly different between-groups. Peak absolute ventilation ($\dot{V}_E$, expressed in L/min) was significantly lower in BPD vs. TERM. Otherwise, $\dot{V}_E$ (expressed in L/min) responses during submaximal exercise were not significantly different between-groups. By contrast, the ratio of $\dot{V}_E$-to-maximal voluntary ventilation ($\dot{V}_E$/MVV) was significantly higher during exercise at power outputs ≥1.0 W/kg LBM in BPD vs. TERM. Respiratory frequency (f_R) was consistently higher, while V_T was no different during submaximal exercise in BPD vs. TERM. Mean values of

inspiratory capacity (IC) and inspiratory reserve volume (IRV) – expressed in L and as a percentage of FVC – were similar between groups throughout exercise when examined in relation to both power output (expressed W/kg LBM) and $\dot{V}_E$ (expressed in L/min). However, the change in IC from rest to peak exercise was significantly different in BPD vs. TERM, with IC decreasing by 0.11 (0.61) L in BPD and increasing by 0.05 (0.71) L in TERM. The reasons for stopping exercise were not significantly different between groups, with the majority of participants in each group stopping because of intolerable leg discomfort. Intensity ratings of leg discomfort were consistently higher during exercise at power outputs ≥1.0 W/kg LBM in BPD vs. TERM, although the differences were not statistically significant. The relationship between exercise-induced changes in ratings of perceived breathlessness and each of power output (expressed in W/kg LBM), $\dot{V}_E$ (expressed in L/min and as a percentage of MVV) and IRV (expressed as a percentage of FVC) were similar between groups.

Conclusions. On the basis of the results of this study, we concluded that the abnormally low exercise tolerance of adult survivors of preterm birth with BPD cannot be easily explained by abnormal restrictive constraints on V_T expansion and breathlessness, but that it likely reflects an exaggerated leg discomfort response to exercise, presumably due to the long-term consequences of abnormally low levels of daytime physical activity (e.g., locomotor muscle deconditioning and weakness). Fortunately, daytime physical activity levels (and presumably therefore exercise tolerance) can be improved by tailored exercise/physical activity interventions in adult survivors of preterm birth complicated by BPD.

RÉSUMÉ

Contexte et raisonnement. La dysplasie broncho-pulmonaire (DBP) est une conséquence respiratoire de la naissance prématurée. Elle résulte d'une exposition à la ventilation mécanique et/ou à l'oxygénothérapie. Au cours des 30 dernières années, l'amélioration des pratiques des soins néonataux a fait augmenter le taux de survie des bébés prématurés qui développent la DBP. Par conséquent, il y a de plus en plus de bébés atteints de la DBP qui se rendent à l'âge adulte. Ainsi, la compréhension des conséquences à long terme de la DBP a une haute importance afin d'optimiser les soins cliniques et les paramètres de la santé de cette population.

En plus des effets (négatifs) connus de la DBP sur la fonction pulmonaire de base, il y a de plus en plus de preuves qui suggèrent que la tolérance à l'exercice des survivants adultes d'une naissance prématurée compliquée par la DBP est très bas. Les mécanismes physiologiques d'une tolérance à l'exercice réduite chez les adultes atteints de DBP ne sont pas très bien connus, mais des restrictions anormales sur l'expansion du volume courant et la dyspnée pourraient y contribuer.

But et objectifs. Cette étude de cohorte transversale et observationnelle vise à mieux comprendre le(s) mécanisme(s) physiologique(s) de la tolérance réduite à l'exercice des survivants adultes d'une naissance prématurée compliquée par la DBP. Dans ce but, cette étude a comme objectifs spécifiques de comparer i) les paramètres de fonction pulmonaire de base, ii) les paramètres de la composition du corps dérivés par l'absorpsiométrie de photons x à deux longueurs d'onde (DXA), iii) les niveaux d'activité physique quotidiens, et iv) les évaluations

détaillées du profil respiratoire, des volumes pulmonaires dynamiques, de l'échange gazeux, des réponses ventilatoires, cardiaques, métaboliques et perceptuelles lors d'un test d'exercice incrémental limité par les symptômes chez de jeunes adultes (18 à 26 ans) survivants d'une naissance prématurée compliquée par la DBP (DBP, *n*=31), des adultes nés prématurés sans complications respiratoires néonatales (PRE, *n*=26), et de jeunes adultes en bonne santé nés à terme sans complications respiratoires (TERM, *n*=35).

Résumé des résultats. Les paramètres de spirométrie (volume expiratoire maximal en 1 seconde [VEMS], VEMS/CV [capacité vitale], débit expiratoire médian mesuré entre 25% et 75% [DEM2575]) et la diffusion libre du monoxyde de carbone (DLCO) étaient significativement plus bas, mais le volume pulmonaire en fin d'expiration était significativement plus haut dans le groupe DBP comparé à PRE et TERM. Les estimés de masse mince et de masse grasse n'ont pas démontré de différences significatives entre les groupes. La dépense énergétique moyenne quotidienne liée à l'activité, le nombre de pas et le temps consacré à faire des activités vigoureuses tels qu'estimé par le moniteur d'activité ont été significativement plus bas dans le groupe de DBP comparé à TERM. La puissance de sortie (exprimé en W et W/kg de masse mince) et le taux d'absorption de l'oxygène (VO2peak, exprimé en L/min, ml/kg/min et ml/kg masse mince/min) atteint à la limite symptomatique d'un test d'exercice incrémental étaient significativement plus bas (~17% et 15%, respectivement) dans le groupe DBP comparé à TERM. Avec seulement quelques exceptions, les réponses cardiaque, métabolique et de l'échange gazeux pendant l'exercice sous-maximale n'ont pas démontré de différences significatives entre groupes. La ventilation maximale absolue (VMA, exprimée en L/min) était significativement plus

bas dans le groupe de DBP comparé à TERM. Autrement, pendant l'exercice sous-maximale, VE (exprimée en L/min) n'a pas démontré de différences significatives entre groupes. Par contre, le ratio VMA/VVM (ventilation volontaire maximale) était significativement plus haut pendant l'exercice aux puissances de sortie ≥1W/kg de masse mince dans le groupe de DBP compare à TERM. Les valeurs moyennes de capacité inspiratoire (CI) et de volume de réserve respiratoire (VRI) - exprimés en L et comme pourcentage de capacité vitale forcée (CVF) – étaient semblables entre groupes pendant l'exercice lorsqu'ils étaient évalués par rapport à la puissance de sortie (W/kg de masse mince) et VMA (L/min). Par contre, le changement de capacité inspiratoire de repos à l'exercice maximale était significativement différent dans le groupe de DBP comparé à TERM. La capacité a diminuer de 0.11 (0.61) L dans le groupe de DBP et a augmenter de 0.05 (0.71) L dans le groupe de TERM. Les raisons pour lesquelles les sujets ont cessé de continuer le test d'exercice n'ont pas démontré de différences significatives entre groupes; la majorité de sujets dans chaque groupe ont arrêté à cause de la fatigue intolérable des jambes. Les notations de l'intensité de la fatigue des jambes étaient toujours plus hautes pendant l'exercice aux puissances de sortie ≥1 W/kg de mass mince dans le groupe de DBP compare à TERM, mais les différences n'ont pas démontré de signification statistique. Le lien entre les changements en intensité perçue de l'essoufflement causés par l'exercice et la puissance de sortie (W/kg de mass mince), la VMA (L/min %VVM) et le volume inspiratoire en réserve (%CVF) étaient tous semblables entre groupes.

Conclusions. La tolérance à l'exercice réduite aux adultes survivants d'une naissance prématurée compliquée par la DBP ne peut pas être expliquée simplement par des restrictions

anormales sur l'expansion du volume courant et la dyspnée, mais possiblement par une réponse exagérée de fatigue des jambes lors de l'exercice. Ceci peut être expliqué par les conséquences à long terme des bas niveaux d'activité physique quotidiens (déconditionnement et faiblesse des muscles locomoteurs). Heureusement, les niveaux d'activité physique quotidiens (et vraisemblablement la tolérance à l'exercice) peuvent être améliorés par des interventions d'exercice/d'activité physique chez les adultes survivants d'une naissance prématurée compliquée par la DBP.

PREFACE AND CONTRIBUTION OF AUTHORS

Steven Murray was the principal contributor to the analysis, and interpretation of data; and was primarily responsible for thesis/manuscript preparation.

Genevieve Tremblay contributed to the collection and analysis of data.

Ryan Reid contributed to the analysis of data.

Courtney Wilkinson-Maitland contributed to the collection and analysis of data.

Dr. Benjamin Smith contributed to data analysis and interpretation.

Dr. Jennifer Landry secured financial support of the experiments, contributed to the review of the protocol, and contributed to all aspects of the study.

As principal investigator, **Dr. Dennis Jensen**, helped with the analysis and interpretation of data as well as to prepare the final draft of the thesis/manuscript. He is the guarantor of the thesis/manuscript and takes responsibility for the integrity of the data and accuracy of the data analysis.

CHAPTER ONE: REVIEW OF LITERATURE

1.0 BRONCHOPULMONARY DYSPLASIA

With the ever growing and advancing perinatal medical practices, the survival rate of preterm births occurring <37 weeks gestation has significantly risen in the last 30 years.[1] Consequently, the number of viable preterm births worldwide has also risen steadily over that time period, with preterm births currently accounting for 11% of births worldwide.[2] While that is a very welcoming statistic for preterm children and their families, surviving a preterm birth is associated with increased risk for several impairments to health later in life, including chronic lung abnormalities,[3] arterial hypertension,[4] type II diabetes,[5] cardiovascular abnormalities,[6] educational disadvantage[7] and earlier death.[8] One of the most common complications of pre-term birth is bronchopulmonary dysplasia (BPD), which was first described by Northway et al.[9] as a typical consequence of using mechanical ventilation and supplemental oxygen therapy in the treatment of premature neonates. Pathophysiologically, BPD is characterized by (i) abnormally low alveolarization and capillarization of the bronchial tree and (ii) abnormally high airway smooth muscle cross sectional area and bronchial hyperresponsiveness.[10] The molecular mechanisms, and clinical and physiological consequences of these manifestations are discussed in depth later in this chapter, while current National Institutes of Health diagnostic criteria for BPD are summarized in **Table 1.1**.[11]

By definition, a preterm infant is one that is born before 37 weeks of gestational age. Most preterm infants are born between 32-26 weeks of gestation, and account of 6.5% of all babies born worldwide.[12] While these babies are considered preterm, they are at a lower risk of developing respiratory diseases such as BPD compared with infants born before 32 weeks because their respiratory systems are almost fully developed. In contrast, babies that are born before 32 weeks (28-31 weeks gestation are considered very preterm; 24-27 weeks are

extremely preterm) have a higher risk of developing BPD, because their lungs are not yet fully developed.[12]

Table 1.1 National Institutes of Health diagnostic criteria for Bronchopulmonary Dysplasia

	Gestational Age	
	<32 weeks	**>32 weeks**
Time point of assessment	36 weeks post-menstrual age or discharge*	>28 days but <56 days postnatal age or discharge*
Treatment with Oxygen	>21% for at least 28 days	>21% for at least 28 days
Bronchopulmonary Dysplasia		
Mild	Breathing room air at 36 weeks post-menstrual age, or discharge*	Breathing room air at 56 days post-natal age, or discharge*
Moderate	Need for <30% O_2 at 36 weeks post- menstrual age, or discharge*	Need for <30% O_2 at 56 days post-natal age, or discharge*
Severe	Need for >30% O_2, with or without positive pressure ventilation or continuous positive pressure at 36 weeks post- menstrual age, or discharge*	Need for >30% O_2, with or without positive pressure ventilation or continuous positive pressure at 56 days post- natal age, or discharge*

** Whichever comes first*

Currently, BPD is second to asthma as the most common chronic lung disease in children.[13] Of surviving preterm infants, 40% born before 28 weeks of gestational age develop BPD,[14] with those numbers increasing up to 70% among infants born between 22-25 weeks gestational age.[15] If an infant is born at <32 weeks gestational age, the incidence of BPD is reportedly 12-32% depending on the demographics of the population studied.[16] Risk factors for the development of BPD are discussed later in this chapter. Beyond gestational age, low birth weight greatly impacts the risk of developing BPD in preterm babies. The rate of BPD climbs to almost 50% in infants who are born with a gestational weight <1,000 g.[17] In fact, 97% of all infants that develop BPD are born with a gestational weight of <1,250 g, highlighting

the devastating impact of small, premature lungs on the development of BPD.[18] As a result, extremely preterm babies stay in the hospital an average of 6 times longer than babies born after 32 weeks gestational age to ensure the survival of the infant.[19] According to the results of an Australian cohort study, it is estimated that very preterm and extremely preterm babies represent 0.8% and 0.9% of all babies born, respectively.[3]

During the last 40 years, the development and use of prenatal steroids, surfactant treatment, new ventilator strategies, improved nutrition and other treatments have improved the outcomes of infants that develop acute respiratory distress syndrome (ARDS), although these improved pre-, peri- and postnatal practices have not changed the overall incidence of BPD.[20, 21] ARDS is a breathing disorder characterized by a decrease in blood oxygenation that develops within the first 24 hours of a preterm infant's life due to the lack of endogenous surfactant.[22] One of the consequences of the unchanging incidence of BPD, and the increased survival of infants who develop BPD, is that more and more adults who survived BPD as children are seeking treatment by pulmonologists later in life (i.e., as adults) for relief of breathlessness and management of wheeze and complications due to asthma, thereby increasing burden on the healthcare system.[23] Re-hospitalization of infants in the first 2 years of life is significantly higher for infants with BPD compared to both full-term infants and infants with very low birth weight (VLBW) without neonatal respiratory complications, with complications due to BPD being one of the most common causes of re-hospitalization.[24] Through childhood, children with BPD have a significantly greater prevalence of respiratory symptoms such as breathlessness and wheeze (and use of respiratory medications including bronchodilators and inhaled corticosteroids) than their full-term and preterm non-BPD classmates.[25] However,

the rate of respiratory symptoms, medication use and re-hospitalization decreases over time from 0-6 years of age, suggesting that children with BPD do have some "catch up" effect and that the severity of their chronic lung condition improves over time. Regardless, adults aged 18 years and older who survived preterm birth complicated by BPD are more likely than their non-BPD counterparts to have persistent spirometric lung function abnormalities, clinically diagnosed asthma, wheeze, cough and breathlessness, with the accumulation of these traits leading to a lower perceived quality of life compared to their term-born peers.[23, 26, 27] It was confirmed that adult survivors of BPD report more respiratory symptoms than term-born controls and continue to have progressive decreases in lung function into their adult lives.[26] In addition to worse respiratory health and symptomatology, some studies have shown that both children and adults with BPD are more intolerant to exercise (i.e., lower cardiorespiratory fitness) and also less physically active than term born controls[28-30] With BPD having such a significant impact on the well-being of a relatively large percentage of the adult population, understanding the course of the disease beyond childhood is needed to help guide clinical care of this aging patient population. Currently, most of the research in BPD has focused on its functional and respiratory consequences during childhood (5-18 years), as that is when the disease first presents itself. However, as BPD is now more common among young adults than ever, with infants who have BPD living longer than ever, the current focus of research needs to also include understanding the functional and respiratory consequences of BPD in the adult population.

1.1. ETIOLOGY/ PATHOGENESIS OF BRONCHOPULMONARY DYSPLASIA

As previously mentioned, it is currently accepted that the main causes of BPD in infants born preterm are the use of mechanical ventilation and supplemental oxygen therapy post-birth. Although mechanical ventilation and supplemental oxygen therapy improve survival of preterm infants, they can adversely affect lung development post-birth, resulting in BPD. The specific pathophysiologic consequences of BPD are very heterogeneous and depend largely on the extent on pulmonary inflammation that the newborn is subjected to after birth, consequent to the use of mechanical ventilation and the administration of supplemental oxygen. However, there are also additional factors that can influence the severity of BPD that develops, including: severity of prematurity; sex; maternal smoking history; genetic susceptibility to BPD; antenatal corticosteroid exposure; oxidative stress; pre- or post-natal infection and inflammation; oligohydramnios; intrauterine growth restriction; and post-natal nutrition (**Fig 1.1**).[26, 31]

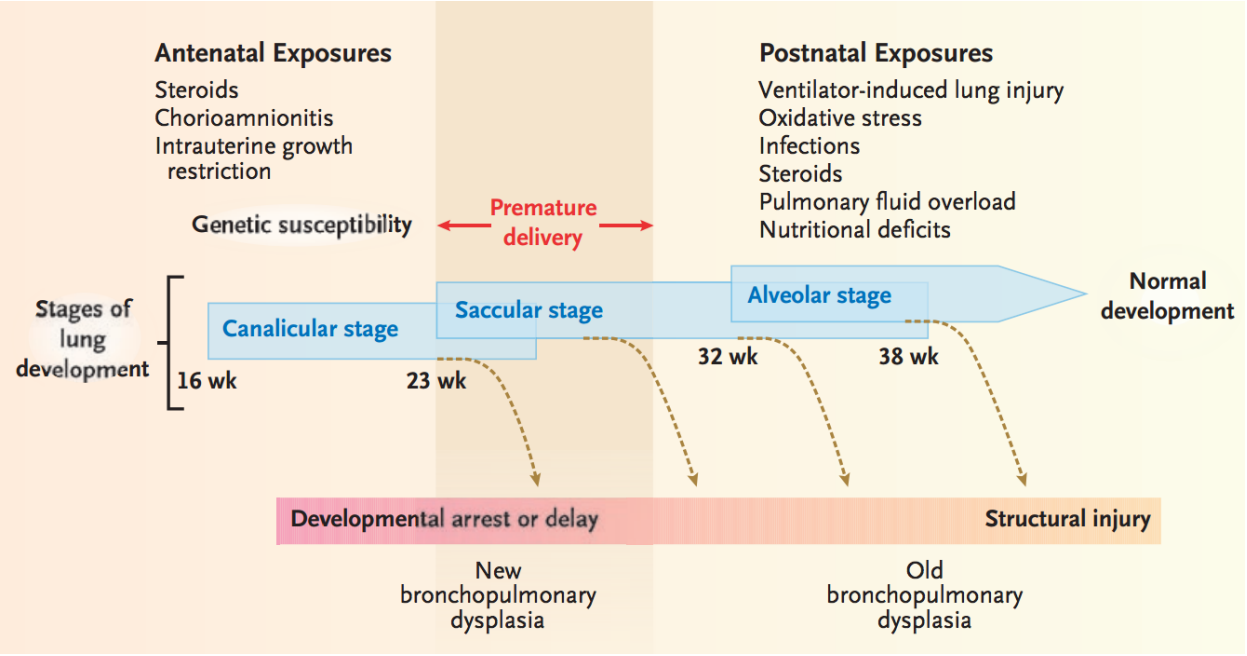

Figure 1.1 Development of the fetal lung with various antenatal and postnatal factors that can influence the development of BPD. Reprinted from Baraldi and Filippone [32].

The development of the lung is among the last processes to occur during gestation; thus, infants delivered preterm can have underdeveloped lungs at birth and require the use of external treatments to help oxygenate their cells and vital organs. Babies born extremely preterm (24-27 weeks) are still in the canalicular phase of lung development (**Fig 1.1**) and are therefore born without any definitive saccules (precedes alveoli formation) and have not yet developed surfactant, a substance composed of lipoprotein that is secreted by the alveolar cells of the lung and that serves to maintain the stability of pulmonary tissue(s) and help prevent alveolar collapse by reducing the surface-tension of the air-liquid interface of alveoli.[33] Additionally, the lung interstitium has not yet adequately thinned to allow for the formation of the air-blood barrier used for gas exchange. Babies born very preterm (28-31 weeks) are in the saccular phase of lung development (**Fig 1.1**) and are therefore born with thin-walled saccules and have developed surfactant, but have not yet developed definitive alveoli.[34] As a result, the distal lung is not yet optimized for pulmonary gas-exchange; however, because of the presence surfactant, these babies do have some "alveolar" stability during expiration.

In the case of both very and extremely preterm infants, underdeveloped alveolar and pulmonary surfactant systems are major causes of respiratory distress syndrome (RDS), a condition that requires the use of prolonged respiratory support after birth to ensure survival of the infant.[34] Paradoxically, the use of respiratory support in the context of an underdeveloped lung is the major cause of lung injury and the development of BPD in this population of infants.[34]

1.1.i. Inflammation

Regardless of its origin, inflammation in the lung of a premature infant can cause serious damage to lung tissue and is a leading risk factor for the development of BPD. Some of the most common causes of increased bronchial-alveolar inflammation in premature infants is supplemental oxygen therapy, mechanical ventilation, and prenatal/early childhood infections such as chorioamnionitis.[35]

Chorioamnionitis is an intra-uterine bacterial infection that occurs during gestation. Babies that are born with chorioamnionitis have increased levels of tumor necrosis factor alpha (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6) interleukin-8 (IL-8), cytokine modifiers (p55, p75, IL-1R antagonist) and C-reactive protein in the umbilical serum.[36] Premature children with chorioamnionitis are subsequently at an greater risk of developing BPD compared with children born at full-term, suggesting that an increased inflammatory state during the later stages of lung development *in utero* may have a negative effect on alveolarization and vascularization of the lung tissue.[37] Recently, these findings have been extended into a possible mechanism for inflammation-mediated disruption of lung branching. Fibroblast growth factor-10 (FGF-10) is among the key mesenchymal growth factors that mediates lung branching and development in humans.[38] It has been found that pro-inflammatory mediators (e.g., IL-1β, TNF-α) produced during oxidative and mechanical stress, infection, etc., can interact with nuclear factor kappa B (NF-κB) to disrupt the normal expression of FGF-10 in the fetal lung, with attendant disruption of normal lung morphogenesis (**Fig. 1.2**).[39] Transforming growth factor beta (TGF-β) has also been implicated as a contributing factor to the development of BPD as (i) increased concentrations of TGF-β in the bronchoalveolar lavage fluid of newborn infants

predictis the development of BPD [40] and (ii) a relationship between TGF-β, chorioamnionitis, and fetal lung injury has also been found, further linking prenatal inflammation as a risk factor for the development of BPD.[41]

1.1.ii. Supplemental Oxygen Therapy

The use of supplemental oxygen therapy in infants suffering from RDS is considered standard of care and is of the upmost importance to promoting survival of these children, with upwards of 50% of infants receiving supplemental oxygen (fraction of inspired O_2 [FiO_2] ranging from 21% to 40%) after birth.[3] *In utero*, the arterial partial pressure of oxygen (P_aO_2) within a healthy fetus is 25 mmHg with a blood oxygen saturation of 70-80%.[42] Upon delivery, the alveolar partial pressure of oxygen (P_AO_2) of a healthy fetus will increase to 150 mmHg on room air and will increase to even higher levels if a newborn is subjected to supplemental oxygen (hyperoxia). While this postnatal increase in P_AO_2 is imperative to survival, it can cause severe lung tissue damage in preterm infants. More specifically, preterm infants have underdeveloped anti-oxidant enzyme systems, specifically in the lung, and have an overall decreased level of anti-oxidant vitamins such as vitamin C and E.[43, 44] Consequently, exposure of the underdeveloped lung architecture to hyperoxia can cause damage to the lung through the generation of reactive oxygen species (ROS) that are not adequately dealt with by underdeveloped anti-oxidant mechanisms. ROS are generated from an elevated FiO_2 *via* increased generation of free radicals during cellular respiration. Generation of free radicals is a normal process in the electron transport chain (ETC) during cellular respiration.[45] However, the high levels of intracellular oxygen during supplemental oxygen therapy leads to increased mitochondrial ROS production, overwhelming the antioxidant defense system, and allowing

free radicals to (i) directly damage DNA, protein and lipid structures and (ii) contribute to inflammation within the lung.[44, 46] The generation of pro-inflammatory cytokines, specifically TGF-β, through ROS-induced cell damage can act of the airway epithelium to disrupt cell-cell signaling,[47, 48] leading to a decrease in the alveolarization and vascularization of the developing lung tissue (**Fig. 1.2**).[49]

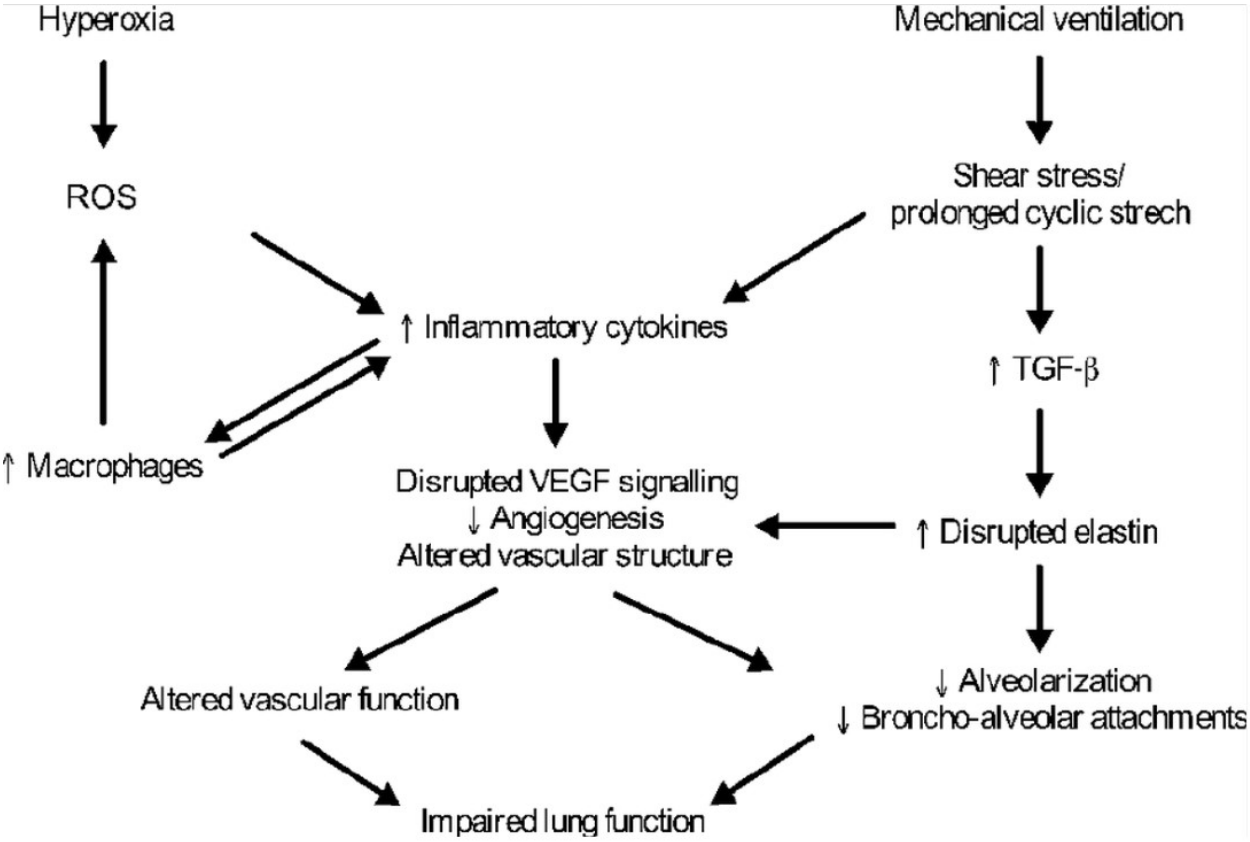

Figure 1.2 Pathways in which supplemental oxygen therapy and mechanical ventilation can lead to a decrease in alveolarization, altered vascular function and impaired lung function in BPD. ROS, reactive oxygen species; TGF-β, transformative growth factor beta; VEGF, vascular endothelial growth factor. Reprinted from O'Reilly, Sozo [3].

One of the suggested mechanisms for hyperoxia-induced lung damage that is still currently under investigation is the role of altered vascular endothelial growth factor (VEGF)

expression in the lungs of premature infants that develop BPD. In human studies of BPD, it has been found that VEGF levels are decreased in the tracheal fluid samples from infants. It was also found that lung VEGF and VEGF-receptor expression levels were further decreased in infants that died from BPD.[50, 51] Two pieces of evidence from animal models that support an integral role of VEGF in oxygen-mediated lung damage include: (i) hyperoxia exposure decreases alveolar VEGF expression;[52] and (ii) selective inhibition of VEGF-receptor expression in day-old rats reduces lung vascular growth and alveolarization.[53] Taken together, these results suggest that (i) VEGF signaling is imperative for the development of the lung and (ii) hyperoxia may inhibit the cross-talk between epithelial cells in the lung, reducing VEGF signaling, and inhibiting the VEGF-induced alveolarization and vascular growth within the developing lung (**Fig. 1.2**). It has been suggested that the decrease in alveolarization (possibly through the inhibition of VEGF) is responsible for the abnormal lung function seen in BPD patients, namely the increased ventilation-perfusion mismatching and increased physiologic dead space with impaired exercise ventilatory efficiency, each of which may contribute to the manifestation of exercise intolerance.[54] Each of the aforementioned consequences of impaired lung development will be discussed in more detail in the following sections.

Most recently, hyperoxia-induced alterations to the progenitor cell pool have been implicated in the pathogenesis of BPD and it has been suggested that these cells play an important (and possibly reduced) role in mediating lung repair after hyperoxia-induced lung damage.[55] In neonatal mice, circulating and lung epithelial progenitor cells (EPCs) are significantly reduced after exposure to hyperoxia.[55] In humans, it has been shown that the abnormally low number of cord blood EPCs following premature birth may be associated with

higher risk of portraying the underdeveloped pulmonary vascular system that is a hallmark characteristic of BPD.[56] This suggests a possible therapeutic role for stem cells in this patient population and potentially also other lung diseases characterized by pulmonary vascular dysfunction.

In summary, supplemental oxygen therapy is a necessary and beneficial treatment to help ensure survival of infants born premature. However, it does not come without consequences. As a result of the underdeveloped antioxidant system of the premature lung, exposure to hyperoxia can cause increased ROS production, increased inflammation and a disruption of the VEGF signaling pathway, all of which can compromise development of pulmonary vasculature and alveolarization with attendant long-term pulmonary dysfunction in BPD patients.

1.1.iii Mechanical Ventilation

Once an infant is born and leaves the womb, their lungs must cope with increased physical strain on pulmonary tissues that accompanies the mechanics of breathing. However, if an infant is born premature, there may not be the adequate lung structure (saccules, defined alveoli, surfactant) to allow for normal pulmonary ventilation without the use of external mechanical ventilation. While mechanical ventilation critically supports pulmonary ventilation and increases the likelihood of survival of a premature newborn, it can also cause a variety of injuries to the underdeveloped lung that is not structurally sounds enough to handle the relatively large changes in intrapulmonary pressure and alveolar volume associated with mechanical ventilation. Some of the ventilator-induced lung injuries that increase the risk of an infant developing BPD, include: volutrauma, caused by overexpansion of the lung due to high

tidal volumes; atelectrauma, caused by the continuous opening and collapsing of alveoli; and biotrauma, caused by the production of inflammatory mediators in response to mechanical ventilation (**Fig. 1.2**).[57] In humans, evidence for the effects of volutrauma comes from the inverse relationship between $PaCO_2$ levels during mechanical ventilation and the risk of developing BPD;[58] that is, artificially increasing tidal volume (V_T) expansion above and beyond the prevailing rate of CO_2 production ($\dot{V}CO_2$) *via* mechanical ventilation decreases $PaCO_2$ levels, and may also lead to volutrauma of a premature lung. This has been shown to be true in animal studies where lung damage was seen in lambs with increases in V_T by as little as 8 mL/kg of body mass.[59] It has also been shown in animal models that the use of mechanical ventilation in a premature lung can lead to a decrease in the number of bronchiolar-alveolar attachments and disrupt elastin production, which leads to a decrease in the alveolarization and vascularization of the developing lung.[60] Although phasing out of common practice, the use of an endotracheal tube during mechanical ventilation can cause irritation and damage to the airways, with attendant infection and airway inflammation.[61]

Each one of the aforementioned lung injuries can cause lung infection and an associated airway inflammatory response, or can directly lead to inflammation through damage to lung tissue. An exaggerated or prolonged inflammatory response in the underdeveloped infant lung can cause permanent alteration in lung architecture by disrupting any one or combination of the aforementioned pathways involving TGF-β, VEGF, etc. (**Fig. 1.2**).

Disrupting the lung architecture in the developing lung of BPD patients also has long lasting functional consequences such as impaired pulmonary function and respiratory health, greater respiratory symptoms, ventilatory abnormalities, and has been suggested to be the root

cause of exercise intolerance and physical activity avoidance.[27, 30, 62-66] Taken together, early changes in the lung architecture due to neonatal care during prematurity has lifelong effects on the quality of life that a BPD patient has, and will each be a topic of discussion in upcoming sections of this chapter.

1.2 PATHOPHYSIOLOGY OF BRONCHOPULMONARY DYSPLASIA

1.2.i Anthropometric Characteristics

Children suffering from BPD show the same physical characteristics as children that are born preterm without BPD. That is, they are typically shorter, lighter, and have a lower fat free mass (FFM) than their age-matched term-born peers.[67] However, other studies have shown that once FFM is adjusted for differences in height, it is not significantly lower in preterm children as compared to term-born controls but fat-mass is significantly lower.[68]

1.2.ii Lung function

1.2.ii.a Children

As previously discussed, children that are born premature and exposed to mechanical ventilation and/or supplemental oxygen may develop lung damage that can permanently alter lung structure and function (**Fig. 1.2**). The most immediate effect of the lung damage caused in early infancy is obstructive lung disease characteristics that are already present in early childhood (as early as 5 years old).[69] Many studies have consistently reported that children (5-12 years of age) with BPD present with expiratory flow limitation (EFL) and pulmonary gas trapping, as evidenced by: (i) an abnormally low forced expiratory volume in 1-sec (FEV_1), forced vital capacity (FVC), FEV_1/FVC and forced expiratory flows between 25% and 75% of vital capacity (FEF_{25-75}); and (ii) an abnormally high residual volume (RV), expressed in liters and as a

percentage of total lung capacity (RV/TLC).[13, 69-71] Landry et al.[62] also showed that the early diagnosis of BPD in infants correlated with a lower FEV_1 and $FEF_{25-75\%}$ later in childhood, suggesting that infants with the most severe BPD will likely present with the most severe EFL and pulmonary gas trapping later in life. In addition to EFL and pulmonary gas trapping, children with BPD often present with abnormally low pulmonary diffusion capacity for carbon monoxide (D_LCO), presumably due to the aforementioned damage of the alveoli and abnormal development of the of pulmonary vasculature.[72]

Furthermore, many premature children, both with and without BPD, are more likely to have bronchial hyperresponsiveness to methacholine challenge testing compared with children born at term.[30, 73] While there are differing opinions about the causal role of a familial history of asthma in the development and severity of BPD, it has been suggested that a familial history of asthma may worsen BPD symptoms and/or increase the chances that a premature infant develops BPD.[69]

The association between a low birth weight and impaired lung function continues beyond childhood and into the teenage years.[26] Longitudinal studies done in premature children with and without BPD have shown that, while there is an improvement in lung function over time, spirometric, plethysmographic and D_LCO based measurements of pulmonary function do not reach normal predicted levels by 14 years of age.[70, 71] Teenagers with BPD show a "catch-up" effect, whereby FEV_1 improves progressively throughout adolescence and into the teenage years; for example, percent predicted FEV_1 (FEV_1%predicted) values have been shown in separate studies to increase from 65% to 72% from age 7-10 years,[70] and from 89% to 95% from age 8-14 years,[71] with those who had the lowest starting FEV_1%predicted

showing the greatest "catch-up" effect. However, even with progressive age-related improvements in spirometric pulmonary function test parameters, RV and RV/TLC (i.e., pulmonary gas trapping) remained abnormally high during this time.[70] Furthermore, the majority of children in these studies still showed a chronically elevated level of bronchial hyperresponsiveness, despite age-related improvements in FEV_1.[70]

1.2.ii.b Adults

Once into adulthood (greater than 18 years of age), the "catch-up" effect of continued lung growth can fully be seen, as lung function abnormalities in adults with BPD, although present, are not as extreme as they are in early childhood. Adults who had BPD as children show the same obstructive lung disease characteristics, as evidenced by abnormally low FEV_1, FEV_1/FVC and $FEF_{25-75\%}$ values (**Fig 1.3**).[27, 30, 74] However, there is still debate around the extent of pulmonary gas trapping in these adult patients with BPD, with some [30] but not all studies [27, 74] reporting an abnormally high RV and RV/TLC. It is possible that the severity of BPD during childhood plays a role in the severity of EFL in adulthood, and that pulmonary gas trapping only occurs in those with the most severe EFL. Adults with BPD also present with abnormal small airway function compared with preterm and term born controls without BPD, as evidenced by higher airway resistance [30] and higher lung clearance index scores.[27]

In addition to the aforementioned lung function abnormalities, ex-preterm adults, with and without BPD, have D_LCO values that are significantly lower than term-born controls, but may still be within the normal predicted range (**Fig 1.3**).[26, 27, 30, 74, 75]

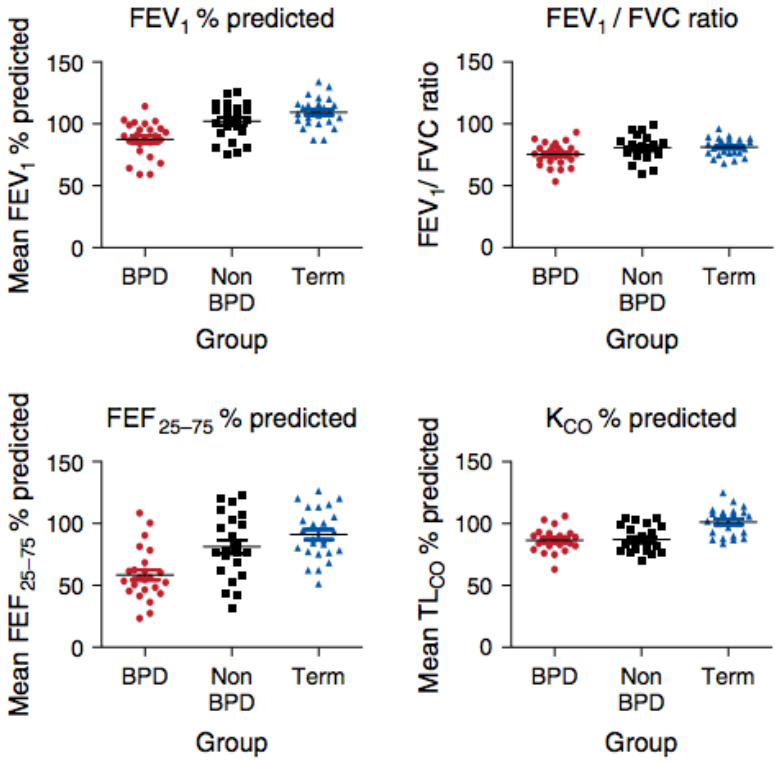

Figure 1.3 Spirometric values for adults with and without BPD. BPD, bronchopulmonary dysplasia; Non-BPD, preterm born without respiratory complications; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; FEF_{25-75}, forced expiratory flows between 25% and 75% of vital capacity; K_{CO}, diffusion capacity for carbon monoxide; TL_{CO}, transfer capacity of the lung for carbon monoxide. Reprinted from Caskey et al.[27].

While adults with BPD do show some age-related improvements in lung function compared with childhood, it is thought that the structural abnormalities that are caused in early infancy do not fully redevelop and repair, leaving adult survivors of preterm birth complicated by BPD with a persistent obstructive pulmonary disorder that may predispose them to the development of other obstructive lung diseases of late adulthood, most notably COPD.[32] In theory, because adult survivors of BPD do not reach peak predicted values of lung function (FEV_1, FVC, FEV_1/FVC, FEF_{25-75}), the natural age-related decline in pulmonary function test parameters would occur from a lower peak value.[26] While controlled longitudinal studies in this area are necessary, it is reasonable to assume that lower peak lung function values in BPD

surviving adults, with or without the combination of an accelerated age-related rate of decline in pulmonary function test parameters due to increased inflammation, infection and hyperoxia exposure, would increase the risk of developing a chronic lung disease such as COPD later in life [76].

One method of examining the physical abnormalities in the lung caused by BPD is high-resolution computed-tomography (HRCT) scanning of the chest. While most of the studies that used HRCT to determine the extent of lung abnormalities used a relatively low sample size with specific inclusion criteria, evidence suggestions that BPD is associated with structural changes in lung morphology that persist into adulthood. For instance, Northway et al.[7] reported that young adult survivors of preterm birth with BPD have more radiographic abnormalities in their lungs than both birth-weight matched and term-matched controls, including interstitial and pleural thickening and hyper-expansion. However, it should be noted that these patients were from a pre-surfactant era and likely had a much more severe form of BPD compared to children living with BPD today. Still, recent studies have found that subjects with BPD had significantly more parenchymal abnormalities, such as linear and triangular opacities, than term-born controls, but that these abnormalities are considered to be relatively minor.[27, 77] Importantly, there is still a significant positive association between lung function abnormalities on HRCT and spirometric pulmonary function test parameters, further supporting the structure-function relationship of the lung and the long-term pulmonary consequences of mechanical ventilation and/or exposure to hyperoxia.[27] In addition, researchers have found HRCT-derived evidence of emphysema and regional gas trapping in the lungs of young adult BPD

survivors, further adding to the idea that BPD during infancy may increase the risk of developing COPD later in life.[27, 78]

1.2.iii. Ventilatory responses

1.2.iii.a Children

It is becoming increasingly clear that prolonged exposure to hyperoxia and/or mechanical ventilation in the postnatal period of premature babies has the potential to adversely affect the action(s) of extra-pulmonary centers involved in respiratory control, especially the carotid (peripheral) chemoreceptors.[79-81] It is thought that perinatal hyperoxia disrupts the development of the carotid chemoreceptors and changes their responses to hypoxia/hyperoxia. Because premature infants do not yet have fully developed carotid chemoreceptors they are physiologically unable to undergo the necessary changes required after birth as *in utero and ex utero* environments have very different oxygen levels.[80] During normal term pregnancies lasting ≥37 weeks, the carotid chemoreceptors need to develop by increasing their activation threshold to a level consistent with post-natal PaO_2 levels, develop the modular activity to changes in CO_2, and increase in volume with matured receptor and neurotransmitter expression.[82] However, this process may be altered and/or interrupted in infants with BPD as both mechanical ventilation and supplemental oxygen therapy alter the blood gas milieu in which the carotid chemoreceptors develop.

Calder et al.[79] were among the first to demonstrate that infants with BPD have an abnormal (blunted) minute ventilation ($\dot{V}_E$) response to a hypoxic challenge, which is in contrast to premature infants who did not need supplemental oxygen therapy had the appropriate hypoxic $\dot{V}_E$ response. Katz-Salamon et al.[81] subsequently showed that infants with BPD do not

show the normal decrease in $\dot{V}_E$ in response to hyperoxia (i.e., Dejours test). Taken together, these results suggest that infants with BPD have altered (blunted) carotid chemoreceptor function and may be unable to appropriately sense blood gas levels and correctly alter ventilation in order to maintain homeostasis. It was also found in the same study that the severity of BPD negatively correlated with the magnitude of the $\dot{V}_E$ response to hypoxia, suggesting that the infants who were the most-severe, and required supplemental oxygen and mechanical ventilation the longest, had the greatest dysfunction in carotid chemoreceptor function.[81] In rodent models, extended hyperoxia exposure at birth causes carotid chemoreceptor dysfunction through a combination of decreased sensitivity to oxygen, carotid body hypoplasia and decreased neuronal density of the carotid body.[80] This supports the theory that the carotid chemoreceptors do not correctly develop in response to extended hyperoxia exposure, and this alters their ability to correctly respond to changes in blood gas levels. Clinically, carotid body dysfunction can have deleterious effects on an infant's ability to breast feed due to inappropriate response to apnea, increased central and obstructive apnea during sleep, which may lead to an increase in the risk of sudden infant death syndrome due to inappropriate $\dot{V}_E$ response during sleep.[80]

1.2.iii.b Adults

In adults born premature, residual abnormalities in the $\dot{V}_E$ response to hyperoxia and hypoxia persist (**Fig. 1.4**). Bates et al.[83] showed that adults who survived premature births have a blunted $\dot{V}_E$ response to hypoxia as compared to term born controls. In addition, only 8 of 13 preterm adults showed depression of $\dot{V}_E$ in response to hyperoxia where all term born control subjects had an appropriate response characterized by depression of $\dot{V}_E$ (**Fig. 1.4**).

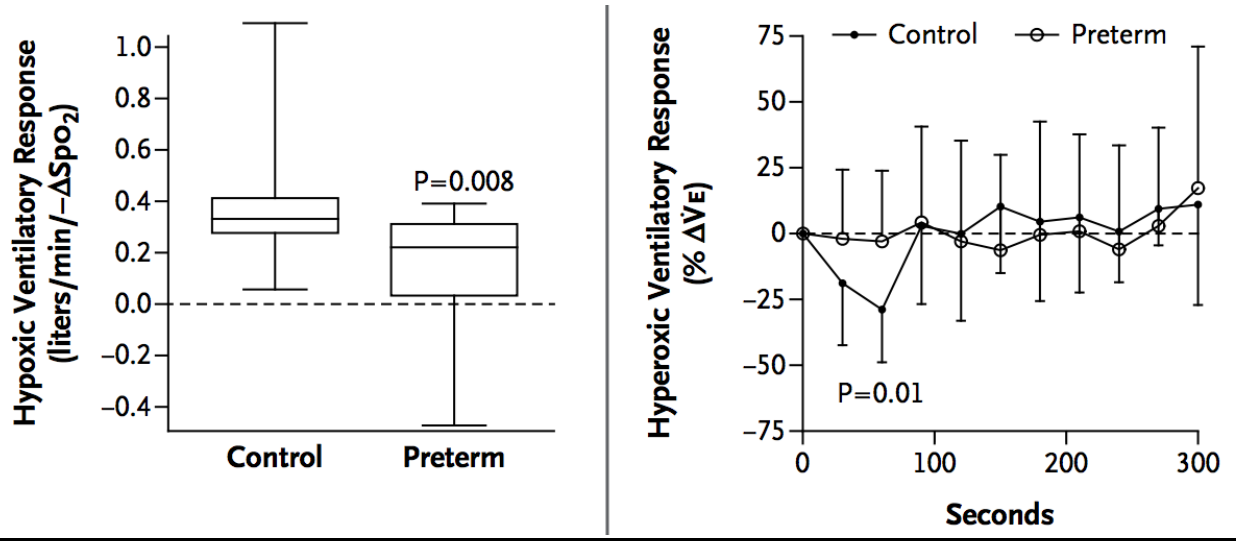

Figure 1.4 Ventilatory response to hypoxia (left) and hyperoxia (right) in adults born preterm as compared with at adults born at full term. Reprinted from Bates et al.[83]

1.2.iv. Physical activity in BPD

In children born preterm, with or without BPD, it has been speculated that a lower exercise capacity in early childhood may cause avoidance of physical activity, as they may not be able to keep up with their peers due to physical differences such as a smaller stature and/or respiratory limitations (and associated symptomatology) resulting from preterm birth. This is turn may lead to a negative feedback loop whereby avoidance of physical activity would further compromise their already impaired exercise capacity, and may have long lasting effects into adulthood.[84] However, it appears that this may not be the case, at least not in the very early stages of childhood (ages 5-7). For instance, a cohort study of young children with BPD did not show any significant differences in parent-reported physical activity levels compared with unaffected preterm and term-birth peers, despite children with BPD having impaired lung function and higher levels of exercise-induced bronchoconstriction.[69] This result was later confirmed by Lowe et al.[85] who reported that the time spent participating in moderate-to-

vigorous physical activities (quantified by tri-axial accelerometry) was just 9 min/day less in preterm compared with term-birth children; however, children with BPD were not specifically studied.

One possible explanation for the relatively lower daytime physical activity levels in BPD children is that they suffer from impaired postural control compared to term-born controls.[67] Specifically, BPD children have higher rates of kyphosis compared with term-born children, suggesting dysfunction of the postural control muscles. On the basis of these observations, it has been hypothesized that dysfunction of the postural control muscles (and attendant abnormalities in coordination and physical capabilities) may contribute, at least in part, to BPD children's lower physical activity levels by facilitating an overall aversion to participation in physical activity. Additional research is needed to substantiate this hypothesis.

Another possible explanation for the abnormally low physical activity levels of children with BPD is the effect of muscle size on sport participation. To this end, children with BPD have abnormally low muscle strength; however, it remains unclear whether this is an intrinsic characteristic of the muscle fibers (due to deconditioning from lack of physical activity) or is reflection of lower muscle mass because of a smaller body size. Vardar-Yagli et al.[67] found a significantly lower quadriceps force production in children with BPD compared to term born controls, but the lower muscle strength was correlated to a lower body mass index (BMI), implicating muscle size and not muscle dysfunction as the major cause of impaired muscle strength in BPD. Similar findings were reported in ex-extremely low birth weight (ELBW) teenagers who showed lower muscular strength and coordination compared with term-born controls, but the authors attributed this to the former group's lower physical activity levels and

smaller stature.[29] Conversely, Svien [86] found that children 7-10 years of age who were born preterm (with no history of BPD) had lower muscle strength, endurance and coordination compared with term-born controls, but that there were no differences in cardiorespiratory fitness or parent (for child)-reported physical activity levels between groups. Continuing work must be done in this area to resolve whether impaired muscle function in BPD is due to a decrease in body size from premature birth, sedentary lifestyle and/or dysfunction of the muscle fibers themselves. It is also possible that BPD children have more severe physical limitation(s) than those who are just born preterm and are thus more likely to avoid participating in physical activity starting at a young age.

Once children start to age and become teenagers, the amount of physical activity performed each week declines, a trend that is evident in all children, regardless of health status.[87] This decline in physical activity may be exacerbated in children with BPD because, as mentioned previously, it is possible that ventilatory limitations and accompanying symptoms during exercise deter children with BPD from wanting to participate in physical activity. This result was found in a study conducted using 10 year old BPD children, who had lower self-reported physical activity levels compared with both preterm and term-born control subjects.[28] This group of BPD subjects also showed a greater exercise-induced fall in FEV_1 compared with the other two groups (i.e., greater exercise-induced bronchoconstriction), suggesting that exercise may cause acute impairment of lung function (above and beyond that present at rest) with attendant avoidance of physical activity in this population. This hypothesis is further supported by the greater respiratory symptoms seen in this population, where exercise-induced wheeze was found in 17% of BPD patients but only 6% of preterm and 0% of

term-born controls.[28] Parents of children with BPD also report that their children have comparatively more exercise-induced wheeze, cough and breathlessness than the parents reporting on behalf of their preterm and term-born control children.[72] In addition, children born full-term were found to be more likely to be participate in organized sports than children born premature with and without BPD.[72]

Once adulthood is reached, physical activity becomes more of a lifestyle (behavior) choice since organized physical activity during school and parental-guided extracurricular physical activity is reduced. Rogers et al.[29] reported that physical activity, sport participation and exercise capacity were abnormally low in ELBW teenagers, a population that has a high incidence of BPD, although the exact number of participants with BPD was not published. This was also found in a Scandinavian cohort where VLBW adults participated in less "conditioning" physical activity compared with term-birth controls, where "conditioning" was defined as "training to maintain physical condition or competitive training."[84] Interestingly, there may be a large psychological component to physical activity avoidance in ex-preterm adults, as ELBW adults have been shown to have significantly lower scores in measurements of physical efficacy and perceived physical ability, and concurrently reported less participation in sports and other strenuous physical activities as compared to term born controls.[88] This conclusion was further supported by Landry et al.[30] who found that, despite similar scores in terms of patient-reported quality of life and activity-related breathlessness, activity-monitor derived estimates of daytime physical activity levels (e.g., physical activity duration, active energy expenditure, and number of steps) were significantly lower, while sedentary time was

significantly higher in young adult survivors of preterm birth complicated by BPD compared with term-born controls.

1.2.v. Exercise performance

1.2.v.a. Children

It has been shown that maximal exercise capacity as measured by peak power output (PPO) correlates with gestational age in newborns, with the children born most premature having the lowest exercise capacity during young adulthood.[84] This has implications for individuals living with BPD since the prevalence of BPD is highest in infants that are born the most preterm; that is, on average, infants who develop BPD will have the most impaired exercise capacity. Indeed, PPO has been found to correlate positively with both FEV_1 (expressed as a percentage of the predicted normal value) and body mass percentile (%), indicating that the children most severely affected by BPD (i.e., highest degree of EFL and smallest body size) had the lowest maximal exercise capacity.[89, 90] However, these results have not been universally reproduced with studies finding non-significant correlations between measures of maximal exercise capacity and baseline pulmonary function.[13, 64] The lower FFM seen in children born premature (with and without BPD) has been shown to correlate with a lower exercise capacity as measured by the 6-minute walk test (6MWT).[67] Additionally, the correlation between FEV_1 and exercise capacity during cycle ergometry has also been seen to be independent of BMI during adulthood, suggesting that the deleterious effects of preterm birth may continue into adulthood, even after the person has regained a normal body mass [89].

1.2.v.a.i. Cardiovascular and metabolic responses. Starting at an early age, children who survive preterm birth complicated by BPD have abnormally low maximal exercise capacity.[13,

64, 69, 89, 90] While there is still some debate surrounding the extent of exercise intolerance, most studies have reported that the PPO achieved during cycle ergometer exercise testing is significantly lower (by 5-20 W) in children with BPD compared with preterm children without BPD and term-born controls.[64, 69, 89, 90] The rate of O_2 consumption at the symptom-limited peak of exercise ($\dot{V}O_{2peak}$) is seen to be normal or near normal in some exercise studies in BPD,[69, 89, 90] while it is abnormally low in others.[13, 64] Santuz et al.[13] found that $\dot{V}O_{2peak}$ was significantly lower in children with vs. without BPD matched for self-reported physical activity levels, an observation that was subsequently confirmed by Welsh et al.[65] in premature children with and without BPD. In keeping with the results of Tsopanoglou et al.,[91], Vardar-Yagli et al.[67] recently reported that children with BPD walked an average of 103 m less during the 6MWT than term-born, aged-matched control subjects at age 8.

Another possible abnormality it BPD is shown in a small subset of studies that the slope of the linear relationship between increasing $\dot{V}O_2$ and increasing power output during incremental cycling exercise testing is higher in children with BPD compared to both preterm non-BPD and term born controls, suggesting that there may be some mechanical inefficiency in children with BPD.[69] This has implications on the rate of muscle fatigue development during prolonged aerobic exercise, as it may increase ratings of perceived leg discomfort and accelerate the onset of intolerable leg discomfort at a lower PPO.

While cardiac function is largely considered to be normal during exercise in children with BPD, there is some evidence that it may be abnormal in at least a subset of BPD children. Right ventricular dysfunction has been seen as effective right ventricular stroke volume (pulmonary blood flow/heart rate) was significantly lower in BPD children as compared to

preterm and term born controls during exercise.[72] This is thought to stem from pulmonary hypertension that limits pulmonary blood flow and may contribute to the development of right ventricular hypertrophy.[92]

1.2.v.a.ii. Ventilatory responses. Regardless of what earlier studies have observed in terms of peak aerobic capacity, almost all studies have reported that children with BPD adopt an altered breathing pattern during exercise compared with preterm without BPD and term born children.[64] For any given $\dot{V}_E$ during exercise, BPD children breathe with a lower tidal volume (V_T) and higher respiratory frequency (f_R).[64] It has been suggested that the preference for increasing f_R over V_T to support a given $\dot{V}_E$ during exercise may be a result of the low inspiratory muscle strength of very low birth weight (VLBW) children.[93]

Furthermore, children with BPD use a greater percentage of their ventilatory reserve during exercise, as measured by the ratio of peak $\dot{V}_E$ to maximal voluntary ventilation ($\dot{V}_E$/MVV).[28, 64, 69, 89, 90] In addition to using a greater fraction of their ventilatory reserve, children with BPD show a significant exercise-induced decline in FEV_1 (reflecting exercise-induced bronchoconstriction) as compared to both preterm and term-born controls.[28]

Interestingly, even though BPD children have (i) abnormal pulmonary function at rest (i.e., abnormally low FEV_1, FEV_1/FVC, $FEF_{25-75\%}$ and D_LCO; an abnormally high RV, RV/TLC and airway resistance), (ii) a higher $\dot{V}_E$/MVV at end-exercise compared with preterm and term-born children and (iii) greater EFL during exercise, there is little to no evidence of dynamic lung hyperinflation and abnormal restrictive constraints on V_T expansion. To this end, MacLean et al.[64] recently reported that the behavior of dynamic end-expiratory lung volume during

exercise (as assessed by serial changes in inspiratory capacity [IC] from rest to peak exercise) was not significantly different between BPD, preterm and term-born control groups.[64]

1.2.v.a.iii. Ventilatory efficiency and gas exchange. During exercise, the ventilatory equivalent for carbon dioxide ($\dot{V}_E/\dot{V}CO_2$) – an index of exercise ventilatory efficiency – is significantly higher in children with BPD compared to both term-born and premature controls, despite similar end-tidal CO_2 tensions ($P_{ET}CO_2$), suggesting that there is a greater level of dead space ventilation throughout exercise in BPD.[54, 64, 93] Some studies have also found that the degree of exercise-induced oxyhemoglobin desaturation is greater in children with BPD compared to premature non-BPD children and term-born controls.[13, 89] It is hypothesized that the greater exercise ventilatory inefficiency and exercise-induced oxyhemoglobin desaturation may stem from an impaired gas transfer ability of the pulmonary system at rest and in response to exercise in BPD vs. health.[72] Impaired pulmonary gas transfer (and elevated physiologic dead space) in BPD likely reflects abnormally low number of alveoli [94], abnormally low pulmonary capillary density[95] and an underdeveloped pulmonary vascular tree.[96]

If impaired pulmonary gas transfer was a major determinant of BPD patients' greater exercise-induced oxyhemoglobin desaturation and abnormally low exercise capacity, then it is reasonable to assume that resting measures of D_LCO should correlate positively with the magnitude of the exercise-induced fall SpO_2 and/or PPO. However, this does not appear to be the case, at least not based on the results of a recent and important study by MacLean et al.[64]

1.2.v.a.iv. Symptom responses. Even though children with BPD have greater levels of EFL at rest and during exercise, more pulmonary gas trapping, greater exercise ventilatory inefficiency, greater oxyhemoglobin desaturation, lower skeletal muscle weakness and use a greater percentage of their MVV, MacLean et al.[64] recently reported that intensity ratings of breathlessness and of perceived exertion are not significantly different during exercise in children with BPD compared with both preterm and term-born control subjects.

1.2.v.b. Adults

Over the last 30 years, improvements in neonatal care have increased post-partum survival of preterm births complicated by BPD. Consequently, an increasing number of infants affected by BPD are now reaching adulthood. While the effects of preterm birth, and specifically the development of BPD, have been extensively studied in children, much less is currently known about peak exercise capacity (and its physiological determinants) among adult survivors of preterm birth complicated by BPD. In keeping with observations made in children and adolescent survivors of preterm birth with BPD, the collective results of studies in young adult subpopulations with a history of BPD suggest that peak exercise tolerance is lower in these individuals compared with healthy term-born controls.[27, 74, 97] The pathophysiological mechanism(s) of impaired exercise tolerance in young adult survivors of preterm birth complicated by BPD remain unclear and are the primary focus of the research presented in Chapter 2 of this thesis.

1.2.v.b.i. Cardiovascular and metabolic responses. The most comprehensive study to date concerning the impact of childhood BPD on the exercise capacity of adults was done by

Lovering et al.[74] who compared the lung function and exercise capacity of adult survivors of preterm birth with BPD (*n*=20), adult survivors of preterm birth without BPD (PRE, *n*=15) and healthy term-born control subjects (TERM, *n*=20). The investigators found that, although $\dot{V}O_{2peak}$ was not significantly different between the 3 groups, PPO was significantly lower in both BPD and PRE compared with TERM. However, a follow up study by the same group of investigators[63] found that, in addition to having a significantly lower PPO, adults with BPD also had a lower $\dot{V}O_{2peak}$ when compared to term born subjects. Vrijlandt et al.[97] similarly reported that PPO was 15% lower in BPD compared with TERM. More recently, Caskey et al.[27] conducted a study in young adults wherein $\dot{V}O_{2peak}$ recorded during a symptom-limited treadmill exercise test was compared between BPD (*n*=25), PRE (*n*=24) and TERM (*n*=25). In that study, $\dot{V}O_{2peak}$ and the total distanced travelled on the treadmill were significantly lower in both BPD and PRE compared with TERM. The relatively impaired exercise capacity of the participants within the BPD and PRE groups remained significant even after accounting for differences in self-reported physical activity levels,[27] suggesting that the relatively impaired exercise tolerance of adult survivors of preterm birth (with and without BPD) cannot be easily explained by deconditioning due to adoption of a more sedentary lifestyle.

1.2.v.b.ii. Ventilatory and perceptual responses. The extent to which abnormal restrictive mechanics on ventilation contribute to exercise intolerance in BPD compared with TERM still remains unclear. Lovering et al.[63] recently examined the impact of altered breathing pattern and dynamic respiratory mechanics on exercise tolerance in adult survivors of preterm birth with BPD. In this study of young adults aged 18-31 years, detailed assessments of resting

pulmonary function and of the physiological and perceptual response to incremental cycle exercise testing were compared between BPD, PRE and TERM. The main conclusions of the study were that, compared to healthy term born control subjects, young adults with BPD (i) had lower PPO and $\dot{V}O_{2peak}$; (ii) adopted a more rapid and shallow breathing pattern during exercise (**Fig 1.5**); (iii) had more severe EFL at any given $\dot{V}_E$ and relative $\dot{V}O_2$ throughout exercise (**Fig 1.6**); (iv) utilized a greater percentage of their MVV at end-exercise; (v) did not display a greater degree of dynamic lung hyperinflation during exercise; (vi) reached a critical minimal inspiratory reserve volume (IRV) at a lower $\dot{V}_E$ and power output during exercise (**Fig 1.7**); (vii) had higher intensity ratings of leg discomfort throughout exercise (**Fig 1.8**); and (viii) were not more breathlessness (dyspneic) at any given $\dot{V}_E$ (**Fig. 1.8**), relative $\dot{V}O_2$ and IRV during exercise (**Fig 1.9**). On the basis of these observations, Lovering et al.[63] concluded that severe breathlessness (dyspnea) associated with abnormal restrictive constraints on V_T expansion are mechanistically linked to impaired exercise tolerance in young adult survivors of preterm birth with and without BPD.

However, if severe breathlessness due to abnormal restrictive constraints on V_T expansion was, in fact, responsible for the impaired exercise tolerance of young adult survivors of preterm birth (whether complicated by BPD or not), then it is reasonable to assume, based on the collective results of (i) external thoracic restriction studies in health[98-101] and (ii) observational studies in chronic obstructive and restrictive pulmonary disease populations,[102, 103] that the slope of the relationship between increasing breathlessness intensity ratings and increasing $\dot{V}_E$ during exercise was significantly higher in BPD and PRE vs.

TERM. However, it is clear from **Fig. 1.8A** that breathlessness-$\dot{V}_E$ relationships were remarkably similar throughout exercise in both BPD and PRE vs. TERM in the study of Lovering et al.[63]

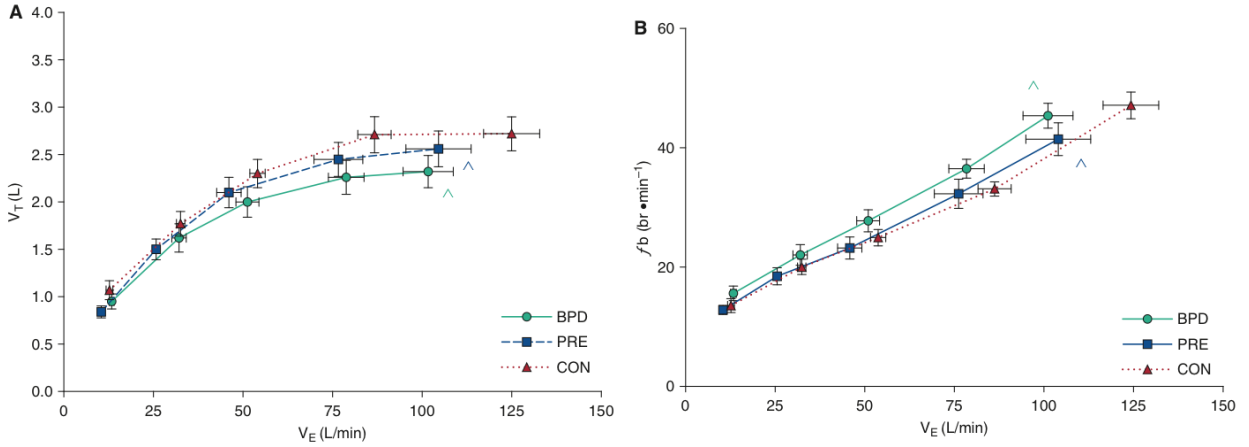

Figure 1.5 Ventilatory strategies in ex-preterm subjects <32 weeks gestational age with bronchopulmonary dysplasia (BPD, green), ex-preterm subjects <32 weeks gestational age without bronchopulmonary dysplasia (PRE, blue), and full-term control subjects (CON, red). Data are presented as mean (SD), with tidal volume (V_T) (**A**) and frequency of breathing (f_b) (**B**) plotted as a function of ventilation (V_E) at rest prior to exercise and during exercise standardized submaximal exercise intensities of 25, 50, 75, and 90% of the symptom-limited peak rate of O_2 consumption (VO_{2peak}). ^Significantly different V_E than CON. Adapted and modified from Lovering et al.[63]

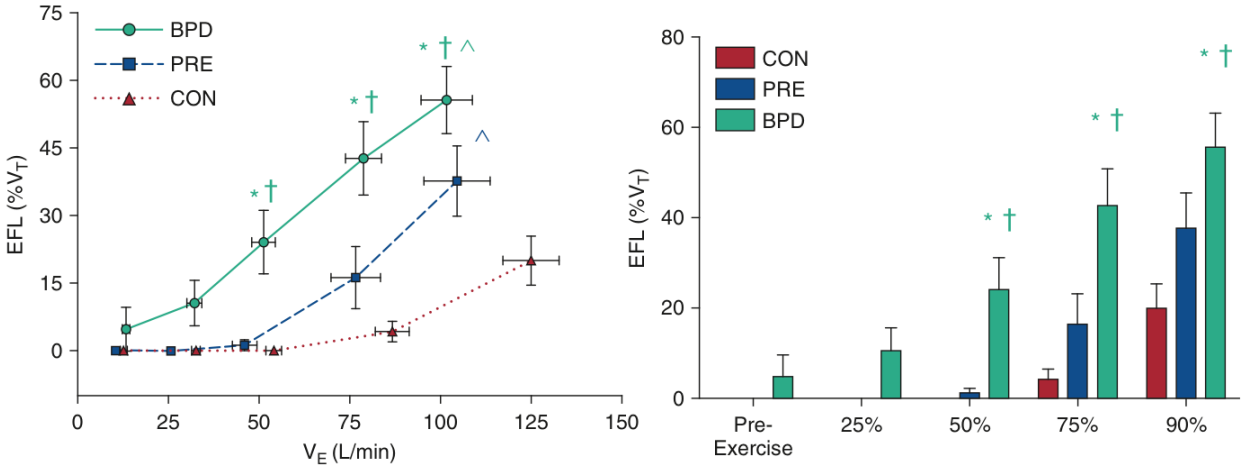

Figure 1.6 Expiratory flow limitation (expressed as a percentage of overlap with tidal volume [EFL (%V_T)]) versus ventilation (V_E) (**left**) and exercise intensity (expressed as a percentage of symptom-limited peak rate of O_2 consumption [VO_{2peak}]) (**right**) during incremental cycle exercise testing in ex-preterm subjects <32 weeks gestational age with bronchopulmonary dysplasia (BPD, green), ex-preterm subjects <32 weeks gestational age without bronchopulmonary dysplasia (PRE, blue), and full-term control subjects (CON, red). Data are presented as mean (SD) at rest prior to exercise and during exercise at standardized submaximal exercise intensities of 25, 50, 75, and 90% of VO_{2peak}. *Significantly different EFL from CON. †Significantly different EFL from PRE. ^Significantly different V_E from CON. Adapted and modified from Lovering et al.[63]

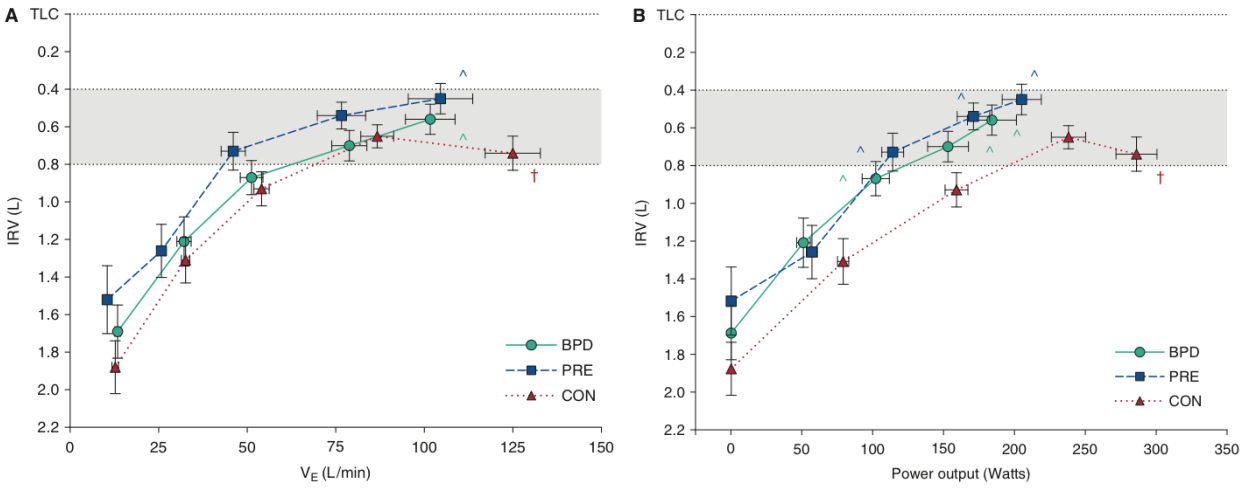

Figure 1.7 Behavior of inspiratory reserve volume (IRV) during incremental cycle exercise testing in ex-preterm subjects <32 weeks gestational age with bronchopulmonary dysplasia (BPD, green), ex-preterm subjects <32 weeks gestational age without bronchopulmonary dysplasia (PRE, blue), and full-term control subjects (CON, red). Data are presented as mean (SD), with IRV plotted as a function of ventilation (V_E) (**A**) and power output (**B**) at rest prior to exercise and during exercise at standardized submaximal exercise intensities of 25, 50, 75, and 90% of the symptom-limited peak rate of O_2 consumption (VO_{2peak}). †Significantly different IRV from PRE. ^Significantly different V_E or power output from CON. Adapted and modified from Lovering et al.[63].

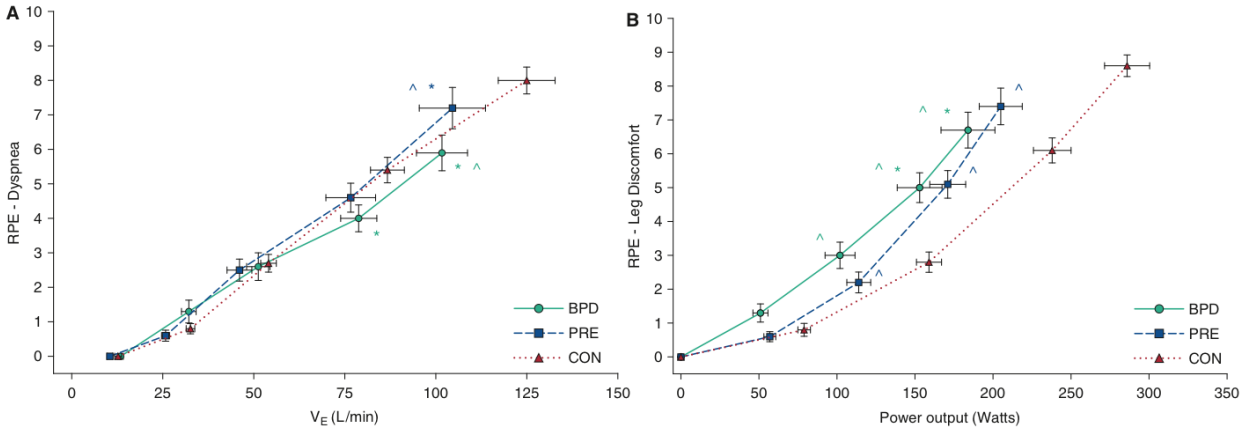

Figure 1.8 Ratings of perceived dyspnea (**A**) and leg discomfort (**B**) during incremental cycle exercise testing in ex-preterm subjects <32 weeks gestational age with bronchopulmonary dysplasia (BPD, green), ex-preterm subjects <32 weeks gestational age without bronchopulmonary dysplasia (PRE, blue), and full-term control subjects (CON, red). Data are presented as mean (SD), with ratings of dyspnea and leg discomfort plotted as a function of ventilation (V_E) and power output, respectively, at rest prior to exercise and during exercise at standardized submaximal exercise intensities of 25, 50, 75, and 90% of the symptom-limited peak rate of O_2 uptake (VO_{2peak}). *Significantly different RPE than CON at iso-% VO_{2peak}. ^Significantly different V_E or power output compared with CON. Adapted and modified from Lovering et al.[63].

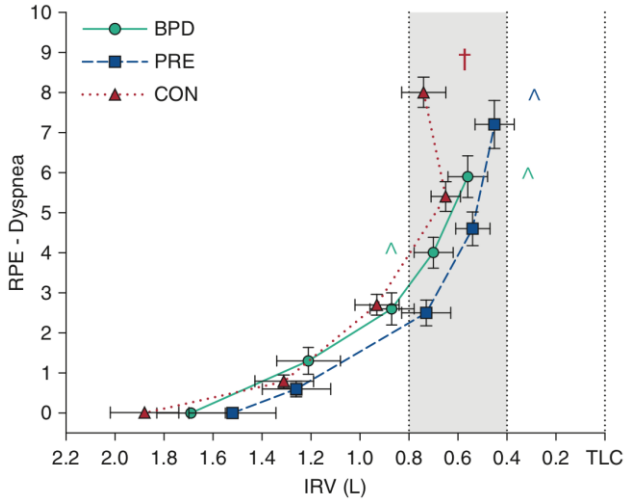

Figure 1.9 Relationship between increasing dyspnea intensity ratings and decreasing inspiratory reserve volume (IRV) during incremental cycle exercise testing in ex-preterm subjects <32 weeks gestational age with bronchopulmonary dysplasia (BPD, green), ex-preterm subjects <32 weeks gestational age without bronchopulmonary dysplasia (PRE, blue), and full-term control subjects (CON, red). Data are presented as mean (SD) at rest prior to exercise and during exercise at standardized submaximal exercise intensities of 25, 50, 75, and 90% of the symptom-limited peak rate of O_2 uptake (VO_{2peak}). †Significantly different IRV from PRE. ^Significantly different dyspnea rating than CON. Adapted and modified from Lovering et al.[63].

On the basis of these observations, it is reasonable to draw an alternative conclusion from the aforementioned results of the study by Lovering et al.[63] That is, by adopting an abnormally rapid and shallow breathing pattern during exercise (**Fig. 1.5**) in the setting of greater EFL (**Fig. 1.6**), adult survivors of preterm birth with and without BPD effectively prevent excessive reductions in IRV for any given $\dot{V}_E$ during exercise (**Fig. 1.7A**). Under these circumstances, V_T expansion at any given $\dot{V}_E$ during exercise in BPD, PRE and TERM most likely occurs on a similar portion of the respiratory system's sigmoid-pressure volume relation, where similar levels of elastic loading and functional weakening (i.e., shortening) of the inspiratory pump muscles would be expected to produce similar intensity ratings of breathlessness. Thus, the alternative interpretation of Lovering and colleagues'[63] study results is that the impaired exercise tolerance of adult survivors of preterm birth (whether complicated by BPD or not) cannot be

easily explained by abnormal restrictive constraints on V_T expansion and breathlessness, but that it likely reflects an exaggerated leg discomfort response to exercise (**Fig. 1.8**). The mechanisms underlying the exaggerated leg discomfort response to exercise in BPD and PRE vs. TERM remain unclear, although lower limb muscle weakness (dysfunction) due to abnormally low levels of daytime physical activity (i.e., deconditioning) is a definite possibility that warrants further investigation.

1.2.v.b.iii. Ventilatory efficiency and gas exchange. It is well documented that adults with BPD have abnormally low D_LCO.[26, 27, 30, 74, 75] Unlike term-born control subjects, adult survivors of preterm birth do not increase D_LCO in response to exercise, suggesting impaired alveolar recruitment during exercise,[97] which may account for the observance of greater exercise ventilatory inefficiency and possibly also abnormally low exercise tolerance in survivors of preterm birth with and without BPD.[27, 49, 54] However, despite differences in D_LCO at rest and during exercise, Lovering et al.[74] showed that there was no difference in pulmonary gas exchange efficiency (measured by the alveolar-to-arterial O_2 difference) and no evidence of arterial hypoxemia during exercise in BPD compared with both PRE and TERM.

1.3 AIM & OBJECTIVE

The general aim of this thesis was to better under the physiological mechanism(s) of impaired exercise tolerance in adult survivors of preterm birth complicated by BPD. To this end, our specific objective was to compare (i) baseline pulmonary function test parameters, (ii) dual energy x-ray absorptiometry-derived body composition parameters, (iii) daytime physical (in)activity levels and (iv) detailed assessments of the ventilatory, breathing pattern, dynamic

operating lung volume, cardiac, metabolic, gas exchange and perceptual responses to symptom-limited incremental cycle exercise testing in adult survivors of preterm birth with BPD (*n*=31), adult survivors of preterm birth with no neonatal respiratory complications (*n*=26) and healthy young adults born at full-term with no neonatal respiratory complications (*n*=35).

CHAPTER TWO: ABNORMAL RESTRICTIVE CONTRAINTS ON VENTILATION AND BREATHLESSNESS DO NOT CONTRIBUTE TO EXERCISE INTOLERANCE IN ADULT SURVIVORS OF PRETERM BIRTH WITH BRONCHOPULMONARY DYSPLASIA

2.1. ABSTRACT

The mechanisms of impaired exercise tolerance among adult survivors of preterm birth with bronchopulmonary dysplasia (BPD) are poorly understood, although abnormal restrictive constraints on tidal volume (V_T) expansion have been implicated. The objective of this study was to elucidate the physiological mechanisms of exercise intolerance in adults with BPD by comparing (i) baseline pulmonary function test parameters, (ii) dual energy x-ray absorptiometry-derived body composition parameters, (iii) daytime physical activity levels and (iv) detailed physiological and perceptual responses to symptom-limited incremental cardiopulmonary cycle exercise testing between adult survivors of preterm birth with BPD (*n*=31), adult survivors of preterm birth without BPD (PRE, *n*=26) and adults born at full-term with no neonatal respiratory complications (TERM, *n*=35). Spirometric pulmonary function test parameters and pulmonary diffusion capacity were significantly lower, while residual volume was significantly higher in BPD vs. PRE and TERM. Total lean body mass and fat mass were similar between-groups. Average daily activity-related energy expenditure, step count and time spent in vigorous activity were significantly lower in BPD vs. TERM. The power output and rate of O_2 consumption achieved at peak exercise was significantly lower by ~15-17% in BPD vs. TERM. Respiratory frequency was higher, while ventilation ($\dot{V}_E$) and V_T were not different during exercise in BPD vs. TERM. Inspiratory capacity, inspiratory reserve volume and ratings of perceived breathlessness were comparable at any given power output and $\dot{V}_E$ during exercise across groups. In conclusion, the impaired exercise tolerance of adults with BPD cannot be easily explained by breathlessness due to abnormal restrictive constraints on V_T expansion, but likely reflects deconditioning due to abnormally low daytime physical activity levels.

2.2. INTRODUCTION

Bronchopulmonary dysplasia (BPD) was first described by Northway et al.[9] as a respiratory consequence of infants born premature and exposed to insistent treatments of mechanical ventilation and/or supplemental oxygen. Over the past 30-40 years, improvements in neonatal care practices have increased survival rates of babies born premature and who develop BPD. Consequently, an increasing number of infants born with BPD are now reaching adulthood.[26] Understanding the consequences of BPD among adult survivors of preterm birth is important to optimizing clinical care and health outcomes of this patient population.

In addition to the established adverse effects of BPD on baseline pulmonary function (i.e., spirometry, plethysmography, pulmonary diffusion capacity for carbon monoxide [D_LCO] and bronchial hyperresponsiveness).[13, 27, 30, 62, 69, 70] a growing body of evidence suggests that the exercise tolerance of children, adolescent and adult survivors of preterm birth complicated by BPD is abnormally low.[13, 63, 64, 67, 69, 84, 89] The physiological mechanisms of impaired exercise tolerance in these populations remain poorly understood and largely understudied, although recent reports by Lovering et al.[63] and MacLean et al.[64] suggest that abnormal restrictive constraints on tidal volume (V_T) expansion during exercise may be contributory. It has also been suggested that there is a decrease in physical activity (PA) levels in young adults living with bronchopulmonary dysplasia compared to healthy adults, and this may, in part, contribute to the lower exercise tolerance in adults living with BPD. However, this data was collected in preterm subjects without a specific analysis of BPD subjects, and this data was collected through patient-based questionnaires and not objectively measured through accelerometry [29, 84].

If abnormal restrictive constraints on V_T expansion during exercise contribute meaningfully to the impaired exercise tolerance of individuals with BPD, then it is reasonable to assume, according to the collective results of (i) external thoracic restriction studies in health[98-101] and (ii) observational studies in chronic obstructive and restrictive pulmonary disease populations,[102, 103] that breathlessness intensity ratings would be consistently higher at any given ventilation ($\dot{V}_E$) during exercise (particularly near the limits of tolerance when ventilatory requirements are high) in individuals with BPD compared with healthy term-born control subjects (TERM) and perhaps also survivors of preterm birth without BPD (PRE). However, Lovering et al.[63] recently found that breathlessness-$\dot{V}_E$ relationships were remarkably similar throughout incremental cycle exercise testing in young adults with BPD compared with both PRE and TERM. Thus, it remains unclear the extent to which abnormal restrictive constraints on V_T expansion are mechanistically linked to impaired exercise tolerance in adults born premature with BPD.

The purpose of this study was to better understand the physiological and perceptual determinants of impaired exercise tolerance in young adult survivors of preterm birth complicated by BPD. To this end, we compared (i) baseline pulmonary function test parameters, (ii) dual energy x-ray absorptiometry (DXA)-derived body composition parameters, (iii) activity-monitor derived estimates of daytime physical activity levels and (iv) detailed physiological and perceptual responses to symptom-limited incremental cardiopulmonary cycle exercise testing between adult survivors of preterm birth with BPD, adult survivors of preterm birth without BPD (PRE) and adults born at full-term with no neonatal respiratory complications (TERM). If abnormal restrictive constraints on V_T expansion are mechanistically linked to

impaired exercise tolerance in adults born premature with BPD, then we hypothesized that (i) inspiratory reserve volume (IRV) would be lower and breathlessness intensity ratings would be higher at any given $\dot{V}_E$ during exercise in BPD vs. PRE and TERM and (ii) a greater percentage of adults with BPD would report intolerable breathlessness as their main exercise-limiting symptom compared with PRE and TERM.

2.3. METHODS

2.3.i. Participants. As described in detail by Landry et al., [30] participants included young adults born in Canada between 1987 and 1993 and living in the province of Quebec at the time of the study. Participants were categorized into one of three groups based on (i) hospital discharge diagnosis at birth or (ii) birth information obtained from a copy of the birth medical chart or the Canadian health and vaccination booklet for participants born inside Canada but outside Quebec, or for those born inside Quebec whose birth information was not previously known: (1) survivors of preterm birth (born at <37 weeks gestation) complicated by BPD (BPD; *n*=31); (2) survivors of preterm birth with no neonatal respiratory complications (PRE; *n*=26); and (3) individuals born at term with no neonatal respiratory complications (TERM; *n*=35). The hospital discharge diagnosis data at birth was obtained for the majority of participants (BPD, *n*=30; PRE, *n*=17; TERM, *n*=10) from the Régie de l'Assurance Maladie du Québec (RAMQ), using the *International Classification of Diseases*, 9th revision (ICD-9) diagnostic codes for BPD (770.7) and PRE (765.**)[30, 104]. Additional recruitment of patients was completed through local advertisements. This was the method of recruitment for the minority of patients.

2.3.ii. Study design. Conducted between 2011 and 2014, this single-center, cross-sectional, observational cohort study (the companion to Landry et al.[30]) consisted of 2 experimental visits separated by ≥24 hrs. The study protocol and consent form were approved by the Centre for Applied Ethics at the Research Institute of the McGill University Health Centre (10-149-BMB). Written and informed consent was obtained from each participant prior to study initiation.

2.3.iii. Physical activity monitoring. Physical activity levels were measured in a subset of participants from each group (BPD, *n*=19; PRE, *n*=19; TERM, *n*=24) using a SenseWear Pro3 armband activity monitor (BodyMedia, Inc., Pittsburgh, PA, USA). With the exception of time spent on personal hygiene, participants were instructed to wear the activity monitor 24-hr per day for 7 consecutive days. Days were considered valid for the physical activity dataset if ≥10 hrs of wearing time was recorded each day and while asleep on ≥4 days within 1 week (not necessarily consecutive), including at least 1 weekend day and ≥3 weekdays. The following physical activity parameters were obtained by generating a report using the SenseWear 7.0 Pro software: average number of steps per day; time spent in sedentary (≤3 metabolic equivalents [METs]), moderate (3 to ≤6 METs), vigorous (6 to ≤9 METs) and very vigorous (>9 METs) physical activities per day; average activity-related energy expenditure per day; and average METs per day.

2.3.iv. Pulmonary function testing. Spirometry, plethysmography and D_LCO were performed in all participants using automated equipment (BodyBox 5500; Medisoft, Sorinnes, Belgium) and recommended techniques [105-107], as previously described by Landry et al.[30] Measurements were expressed as percentages of their predicted normal values.[108]

2.3.v. Cardiopulmonary exercise testing. Exercise tests were (i) completed by 29 BPD, 26 PRE and 32 TERM participants, (ii) conducted on an electronically braked cycle ergometer (Ergoselect 200; Ergoline GmbH, Blitz, Germany) using a computerized CPET system (Vmax

Encore^{TM}; CareFusion, Yorba Linda, CA, USA) and (iii) consisted of a steady-state rest period of 3-min followed by 20 W increases in power output (starting at 20 W) every 2-min to the point of symptom-limitation (i.e., volitional fatigue) and/or until the participant was unable to maintain a pedal cadence of ≥50 rev/min.

Standard respiratory and gas exchange parameters were collected breath-by-breath (Vmax Encore^{TM}) while participants breathed through a rubber mouthpiece and low-resistance flow transducer with nasal passages occluded by a nose clip. Heart rate (HR) was monitored continuously by 12-lead electrocardiography (GE Marquette's CardioSoft® 12-lead ECG system), while oxyhemoglobin saturation (SpO_2) was monitored by finger pulse oximeter (Masimo Radical^{TM}; Masimo Corp., Irvine, CA, USA). Inspiratory capacity (IC) maneuvers were performed at rest, within the last 30-sec of every 2-min interval during CPET, and at end-exercise. Assuming that total lung capacity does not change during exercise,[109] changes in IC and inspiratory reserve volume (IRV = IC - V_T) reflect changes in dynamic end-expiratory and end-inspiratory lung volume, respectively. Using Borg's modified 0-10 category-ratio scale,[110] participants rated the intensity of their perceived breathlessness and perceived leg discomfort at rest, within the last 30-sec of every 2-min interval during CPET, and at end-exercise. Participants verbalized their main reason(s) for stopping exercise: breathlessness; leg discomfort; breathlessness + leg discomfort; unable to maintain pedal cadence ≥50 rev/min; other.

2.3.vi. Analysis of exercise endpoints. Physiological parameters were averaged over the last 30-sec of the 3-min steady-state rest period and linked with symptom ratings and IC-derived

measurements collected immediately after this period and before the start of CPET. Physiological parameters were averaged over the first 30-sec of the 2nd minute of every 2-min interval during CPET and linked with symptom ratings and IC-derived measurements collected during the last 30-sec of the same minute. Peak exercise was defined as the last 30-sec of loaded pedaling: physiological parameters averaged over this time period were linked with symptom ratings and IC-derived measurements collected at the symptom-limited peak of CPET. Peak power output (PPO) was defined as the highest power output that the participant was able to sustain for ≥30-sec.

The $\dot{V}_E/\dot{V}CO_2$ (ventilatory equivalent for CO_2) nadir was identified for each participant as the lowest 30-sec average data point recorded during CPET and used as an index of exercise ventilatory efficiency.

In keeping with recommendations made by the American Thoracic Society and American College of Chest Physicians,[111] measured parameters were compared between groups at standardized submaximal power outputs referenced to DXA-derived estimates of total lean body mass (LBM) so that exercise physiological and symptom responses would be largely independent of age, sex and body size/composition. To this end, measured parameters corresponding to standardized power outputs 0.5, 1.0, 1.5 and 1.9 W/kg LBM (where 1.9 W/kg LBM represents the highest equivalent LBM specific power output (iso-PO_{LBM}) achieved during CPET performed by all 92 participants) were calculated by linear interpolation between adjacent measurement points for each participant.

2.3.vii. Statistical analyses. Continuous variables measured at rest (e.g., age, MRC dyspnea scores, SF36v2^{TM} scores, birth weight, gestational age, APGAR scores, anthropometric parameters, pulmonary function test parameters) and with the physical activity monitor were compared between-groups using a one-way analysis of variance (ANOVA) with Tukey's HSD post-hoc test. Categorical variables (e.g., demographic and past medical history data, reason(s) for stopping exercise) were compared between-groups using a chi-squared test. Between-group comparisons of the $\dot{V}_E/\dot{V}CO_2$ nadir were made using a one-way ANOVA with Tukey's HSD post-hoc test. A two-way repeated measures ANOVA with Tukey's HSD post-hoc test was used to examine group, time (e.g., rest, iso-PO_{LBM}, peak exercise) and group*time effects on physiological and symptom parameters during incremental CPET. Pearson correlation coefficients were calculated between PPO and the peak rate of O_2 consumption ($\dot{V}O_{2peak}$) and selected independent variables. All analyses were performed using SigmaStat® (Version 3.5; Systat® Software, San Jose, CA, USA) and statistical significance was set at $p<0.05$. Data are presented as means (SD) unless otherwise stated.

2.4. RESULTS

2.4.i. Participants. A detailed summary of our participants' characteristics is available in Landry et al.,[30] with key outcome parameters relevant to the current study reprinted here in **Table 2.1**. BPD, PRE and TERM groups were well matched for age, sex and body size/composition. Gestational age and birth weight were (i) significantly lower in BPD vs. both PRE and TERM and (ii) significantly lower in PRE vs. TERM.

2.4.ii. Pulmonary function. A detailed summary of our participants' baseline pulmonary function test results is available in Landry et al.,[30] with key outcome parameters relevant to the current study reprinted here in **Table 2.2**. Spirometric pulmonary function test parameters and D_LCO were significantly lower, while residual volume (RV) was significantly higher in BPD vs. both PRE and TERM. Baseline pulmonary function test parameters were not significantly different between PRE and TERM.

2.4.iii. Physical activity monitoring. Daytime physical activity levels were consistently lower in both BPD and PRE vs. TERM (**Table 2.3**), with statistically significant differences observed between (i) BPD and TERM for average daily activity-related energy expenditure, step count and time spent in vigorous activity and (ii) PRE and TERM for average daily step count and time spent in vigorous activity.

Table 1.1 Participant Characteristics

Parameter	BPD	PRE	TERM
Age, years [range]	22.0 (1.9) [19-26]	21.5 (1.7) [19-25]	22.4 (2.0) [18-25]
Male, n [%]	11 [35]	6 [23]	11 [31]
Gestational age, days‡	192 (18)+*	229 (22)#	277 (9)
Birth weight, kg†	1.1 (0.4)+*	2.2 (0.8)#	3.5 (0.4)
Body height, cm	167 (9)	166 (8)	168 (9)
Total body mass, kg	67.6 (17.0)	67.4 (14.7)	64.6 (10.5)
BMI, kg/m^2	24.3 (6.0)	24.4 (4.8)	22.8 (3.3)
FFMI, kg/m^2 ¶	17.1 (2.8)	16.9 (2.5)	16.8 (2.1)
Lean body mass, kg ¶	45.3 (10.6)	43.9 (9.3)	45.2 (8.5)
Lean body mass, % total body mass ¶	71.3 (10.7)	69.3 (10.7)	73.4 (8.6)
Fat mass, kg ¶	19.2 (11.3)	20.4 (10.8)	16.6 (6.8)
Fat mass, % total body mass ¶	27.7 (10.5)	29.6 (10.4)	25.6 (8.3)

Values are means (SD) unless otherwise stated.

+p<0.05 BPD vs. PRE; *p<0.05 BPD vs. TERM; #p<0.05 PRE vs. TERM

‡Gestational age for TERM participants who did not know the exact number of weeks of birth was assumed to be 40 wks.

†Birth weight from health booklet or chart. Birth weight missing from 1 of 35 TERM participants.

¶Dual energy X-ray absorptiometry scan data missing for 2 of 31 BPD and 2 of 35 TERM participants

Abbreviations: BPD, preterm birth with bronchopulmonary dysplasia (*n*=31); PRE, preterm birth without BPD (*n*=26); TERM, full-term birth (*n*=35); BMI, body mass index; FFMI, Fat free mass index.

Table 2.2 Baseline pulmonary function test parameters

Parameter	BPD	PRE	TERM
FEV_1, % predicted	80 (18)+*	94 (14)	98 (9)
FEV_1/FVC, %	70 (12)+*	79 (7)	79 (7)
$FEF_{25-75\%}$, % predicted	68 (26)+*	89 (26)	96 (19)
TLC, % predicted	114 (13)	111 (9)	113 (12)
FRC, % predicted	121 (22)	114 (15)	120 (16)
RV, % predicted	157 (43)+*	133 (34)	125 (26)
D_LCO, % predicted	86 (11)+*	98 (18)	99 (10)

Values are means (SD)

+p<0.05 BPD vs. PRE; *p<0.05 BPD vs. TERM; #p<0.05 PRE vs. TERM

Abbreviations: BPD, preterm birth with bronchopulmonary dysplasia group (*n*=31); PRE, preterm birth without BPD group (*n*=26); TERM, full-term birth group (*n*=35); FEV_1, forced expiratory volume in 1-sec; FEV_1/FVC, FEV_1-to-forced vital capacity ratio; $FEF_{25-75\%}$, forced expiratory flow between 25% and 75% of FVC maneuver; TLC, total lung capacity; FRC, functional residual capacity; RV, residual volume; D_LCO, diffusing capacity of the lung for carbon monoxide.

Table 2.2 Physical activity parameters [†]

Parameter	BPD	PRE	TERM
Daily wear time, hrs/day	23.2 (0.6)	22.9 (1.0)	22.5 (1.4)
Activity-related energy expenditure, kJ/day	1,620 (1,067)*	1,748 (1,069)	2,581 (1,579)
Average number of steps per day	8,620 (3,277)*	9,194 (2,457)[#]	11,192 (3,839)
Average METs per day	1.48 (0.28)	1.48 (0.20)	1.65 (0.27)
Sedentary activity, min/day	1,301 (73)	1,278 (80)	1,250 (89)
Moderate physical activity, min/day	84.2 (53.4)	88.8 (45.3)	111.0 (59.9)
Vigorous activity, min/day	5.6 (6.0)*	5.9 (13.9)[#]	14.2 (11.5)
Very vigorous activity, min/day	0.2 (0.4)	0.3 (1.0)	1.4 (3.5)

Values are means (SD)

[+]p<0.05 BPD vs. PRE; *p<0.05 BPD vs. TERM; [#]p<0.05 PRE vs. TERM

[†]Activity monitoring data were available from 19 of 31 BPD, 19 of 26 PRE and 24 of 35 TERM participants.

Abbreviations: BPD, preterm birth with bronchopulmonary dysplasia group; PRE, preterm birth without BPD group; TERM, full-term birth group; METs, metabolic equivalents (as estimated by activity monitor)

2.4.iv. Physiological responses to exercise. Cardio-metabolic and gas exchange responses at rest and during CPET are displayed in **Fig. 2.1** and summarized in **Table 2.4**. Peak exercise tolerance was consistently lower in BPD and PRE vs. TERM, with statistically significant differences observed between (i) BPD and TERM for PPO (expressed in W and W/kg LBM) and $\dot{V}O_{2peak}$ (expressed in L/min, ml/kg/min and ml/kg LBM/min) and (ii) PRE and TERM for $\dot{V}O_{2peak}$ (expressed in L/min, ml/kg/min and ml/kg LBM/min). A statistically significant difference for $\dot{V}O_{2peak}$ (expressed in ml/kg LBM/min) was also observed between BPD and PRE. With the exception of isolated differences in the respiratory exchange ratio and HR between BPD and TERM groups at ISO-PO_{LBM}, cardio-metabolic responses during submaximal exercise were similar between-groups (**Figs. 2.1A-C**). Peak SpO_2 was modestly but significantly lower (by ~2-

3%) in BPD vs. both PRE and TERM, otherwise SpO_2 responses during submaximal exercise were similar between-groups (**Fig. 2.1D**). Although the differences were not statistically significant

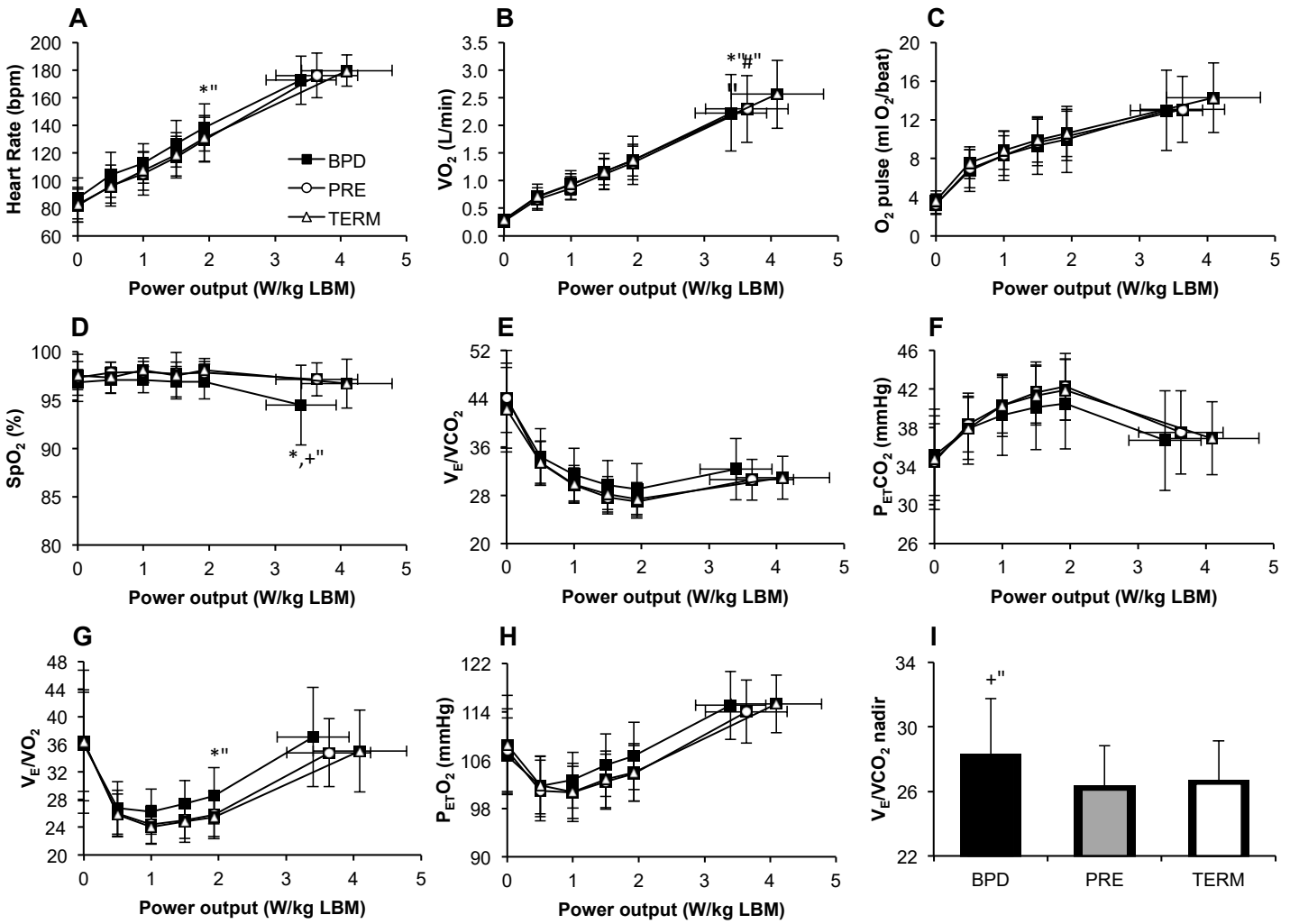

Figure 2.1. Cardio-metabolic and gas exchange responses to incremental cycle exercise testing in young adult survivors of preterm birth with bronchopulmonary dysplasia (BPD), young adult survivors of preterm birth without bronchopulmonary dysplasia (PRE) and young adults born at term with no neonatal respiratory complications (TERM). Values are mean (SD). $^{+}p<0.05$ BPD vs. PRE; *p<0.05 BPD vs. TERM; $^{\#}p<0.05$ PRE vs. TERM. *Abbreviations*: W, watts; LBM, total lean body mass; VO_2, rate of O_2 consumption; SpO_2, oxyhemoglobin saturation; V_E/VCO_2, ventilatory equivalent for CO_2; $P_{ET}CO_2$, end-tidal CO_2 tension; V_E/VO_2, ventilatory equivalent for O_2; $P_{ET}O_2$, end-tidal O_2 tension.

Table 2.4 Physiological and perceptual parameters at rest, during incremental cycle exercise testing at the highest equivalent lean body mass specific power output (ISO-PO_{LBM}) and at the symptom-limited peak of incremental cycle exercise testing

	REST			ISO-PO_{LBM}			PEAK		
Parameter	**BPD**	**PRE**	**TERM**	**BPD**	**PRE**	**TERM**	**BPD**	**PRE**	**TERM**
Power output, W	-	-	-	87 (20)	85 (18)	86 (16)	151 (38)*	158 (35)	182 (42)
Power output, W/kg LBM	-	-	-	1.9 (0.0)	1.9 (0.0)	1.9 (0.0)	9.1 (1.6)*	10.0 (1.9)	11.0 (1.8)
$\dot{V}O_2$, L/min	0.28 (0.08)	0.26 (0.06)	0.29 (0.07)	1.37 (0.44)	1.32 (0.30)	1.47 (0.29)	2.23 (0.68)*	2.30 (0.60)$^{\#}$	2.56 (0.62)
$\dot{V}O_2$, ml/kg/min	4.2 (0.9)	3.9 (0.8)	4.6 (1.4)	20.3 (3.1)	19.0 (3.3)	21.2 (2.9)	33.4 (8.5)*	34.7 (8.1)$^{\#}$	39.8 (7.7)
$\dot{V}O_2$, ml/kg LBM/min	6.2 (1.1)	6.0 (0.7)	6.7 (2.05)	20.0 (4.3)	30.3 (3.2)	30.7 (3.0)	48.6 (8.5)$^{+*}$	52.3 (8.9)$^{\#}$	57.3 (9.3)
$\dot{V}CO_2$, L/min	0.23 (0.06)	0.21 (0.05)	0.25 (0.07)	1.36 (0.46)	1.27 (0.32)	1.28 (0.28)	2.54 (0.74)*	2.61 (0.71)$^{\#}$	2.88 (0.65)
$\dot{V}CO_2$, ml/kg/min	3.4 (0.6)	3.2 (0.8)	3.9 (1.3)	20.0 (3.6)	19.1 (3.4)	19.8 (2.9)	38.1 (9.6)*	39.5 (9.5)$^{\#}$	44.7 (8.7)
$\dot{V}CO_2$, ml/kg LBM/min	5.0 (0.9)	4.9 (0.7)	5.7 (1.6)	29.7 (5.3)	28.9 (3.6)	28.6 (3.1)	55.5 (9.8)+*	59.4 (10.6)$^{\#}$	64.6 (10.4)
RER	0.82 (0.10)	0.82 (0.11)	0.86 (0.15)	0.99 (0.08)*	0.96 (0.06)	0.93 (0.06)	1.14 (0.07)	1.14 (0.07)	1.13 (0.09)
Heart rate, bpm	87 (15)	82 (12)	83 (13)	138 (17)*	130 (16)	131 (17)	173 (17)	176 (16)	180 (11)
O_2 pulse, ml O_2/beat	3.3 (1.1)	3.3 (1.0)	3.6 (1.0)	10.0 (3.4)	10.3 (2.5)	10.6 (2.4)	13.0 (4.1)	13.1 (3.4)	14.3 (3.6)
$\dot{V}_E/\dot{V}CO_2$	43.9 (8.1)	44.1 (5.7)	42.2 (7.0)	29.0 (4.2)	26.8 (2.8)	27.3 (2.8)	32.2 (5.0)	30.6 (3.4)	30.9 (3.5)
$\dot{V}_E/\dot{V}O_2$	35.9 (8.1)	36.4 (7.2)	36.4 (10.4)	28.6 (4.1)*	26.0 (3.4)	25.5 (2.8)	37.0 (7.1)	34.8 (4.9)	35.0 (5.9)
$P_{ET}CO_2$, mmHg	35.1 (4.1)	34.4 (4.0)	34.7 (5.2)	40.4 (4.7)	42.2 (3.5)	41.9 (3.1)	36.6 (5.1)	37.5 (4.3)	36.9 (3.8)
$P_{ET}O_2$, mmHg	106.7 (6.3)	107.6 (6.9)	108.5 (8.2)	106.7 (5.6)	103.8 (4.6)	104.0 (4.7)	115.0 (5.5)	114.0 (5.2)	115.3 (4.8)
SpO_2, %	96.8 (1.3)	97.3 (2.5)	97.5 (1.5)	96.9 (1.8)	97.8 (1.2)	98.1 (1.2)	94.5 (4.1)$^{+*}$	97.1 (1.7)	96.7 (2.5)
$\dot{V}_E$, L/min	9.6 (1.8)	9.4 (2.5)	10.6 (3.9)	38.4 (11.9)	33.9 (7.9)	34.7 (7.2)	79.8 (19.3)*	80.2 (24.5)$^{\#}$	89.4 (21.7)
$\dot{V}_E$, %MVV	10.0 (3.2)	8.1 (2.1)	8.7 (3.0)	39.8 (15.7)$^{+*}$	27.7 (9.9)	28.7 (8.1)	80.7 (19.9)$^{+*}$	68.2 (18.1)	72.3 (16.4)
V_T, L	0.58 (0.13)	0.57 (0.13)	0.70 (0.31)	1.34 (0.35)	1.35 (0.37)	1.38 (0.27)	1.74 (0.48)*	1.97 (0.54)	2.04 (0.43)
V_T, %FVC	14.0 (3.0)	13.4 (2.8)	15.8 (6.9)	32.0 (6.0)	31.4 (5.4)	31.0 (5.5)	41.5 (7.7)*	45.0 (7.1)	45.1 (6.5)
f_R, breaths/min	17.1 (3.9)	16.8 (3.7)	16.0 (4.6)	29.6 (8.3)*	25.9 (6.4)	25.5 (5.3)	47.1 (9.0)$^{+}$	41.6 (9.8)	44.8 (8.8)
IC, L	2.80 (0.74)	2.75 (0.59)	2.98 (0.73)	2.78 (0.60)	2.95 (0.62)	3.02 (0.54)	2.69 (0.62)	2.88 (0.57)	3.03 (0.61)
IC, %FVC	66.6 (12.4)	64.1 (9.0)	66.6 (14.9)	66.4 (10.2)	68.9 (10.4)	67.3 (7.7)	64.9 (13.3)	67.6 (10.9)	67.2 (9.4)
Δ IC from rest, L	-	-	-	-0.02 (0.34)	0.20 (0.27)	0.04 (0.60)	-0.11 (0.61)$^{+*}$	0.14 (0.44)	0.05 (0.71)
IRV, L	2.22 (0.69)	2.18 (0.55)	2.28 (0.73)	1.44 (0.42)	1.59 (0.51)	1.64 (0.39)	0.97 (0.46)	0.94 (0.40)	0.99 (0.43)
IRV, %FVC	52.6 (11.7)	50.7 (9.0)	50.8 (15.4)	34.5 (9.1)	37.5 (11.1)	36.3 (6.1)	22.3 (13.1)	22.6 (10.1)	22.1 (8.8)
Breathlessness, Borg units	0.1 (0.2)	0.1 (0.2)	0.0 (0.1)	1.6 (1.6)	1.9 (1.2)	1.4 (1.1)	5.3 (2.6)$^{+*}$	6.5 (2.6)	6.0 (1.9)
Leg discomfort, Borg units	0.2 (0.5)	0.3 (0.5)	0.2 (0.6)	2.3 (1.8)*	2.2 (1.6)	1.5 (1.2)	6.7 (2.6)$^{+}$	7.5 (1.9)	7.0 (1.8)
Reason(s) for stopping exercise									
Breathlessness, %	-	-	-	-	-	-	0	11	6

Leg discomfort, %	-	-	-	-	-	-	60	44	58
Breathlessness + leg discomfort, %	-	-	-	-	-	-	13	19	18
Pedal cadence <50 rpm, %	-	-	-	-	-	-	20	26	15
Other, %	-	-	-	-	-	-	7	0	3

Values are means (SD) unless stated otherwise

$^{+}p<0.05$ BPD vs. PRE; $^{*}p<0.05$ BPD vs. TERM; $^{\#}p<0.05$ PRE vs. TERM

†Cardiopulmonary exercise test data were collected from 29 of 31 BPD, 26 of 26 PRE and 32 of 35 TERM participants.

Abbreviations: BPD, preterm birth with bronchopulmonary dysplasia group; PRE, preterm birth without BPD group; TERM, full-term birth group; LBM, lean body mass; $\dot{V}O_2$ and $\dot{V}CO_2$, rate of O_2 consumption and CO_2 production, respectively; RER, respiratory exchange ratio; $\dot{V}_E/\dot{V}CO_2$ and $\dot{V}_E/\dot{V}O_2$, ventilatory equivalent for CO_2 and O_2, respectively; $P_{ET}CO_2$ and $P_{ET}O_2$, end-tidal CO_2 and O_2 tension, respectively; SpO_2, oxyhemoglobin saturation; Δ, change; $\dot{V}_E$, minute ventilation; MVV, maximal voluntary ventilation estimated as the forced expiratory volume in 1-sec x 35; V_T, tidal volume; FVC, forced vital capacity; IC, inspiratory capacity; f_R, respiratory frequency; IRV, inspiratory reserve volume.

(with the exception of the ventilatory equivalent for O_2 [$\dot{V}_E/\dot{V}O_2$] being higher in BPD vs. TERM at iso-PO_{LBM}), perusal of **Figs. 2.1E-H** shows that $\dot{V}_E/\dot{V}CO_2$ and $\dot{V}_E/\dot{V}O_2$ were modestly but consistently elevated (with attendant lower and higher end-tidal CO_2 [$P_{ET}CO_2$] and O_2 tensions [$P_{ET}O_2$], respectively) at any standardized submaximal power output during CPET in BPD vs. both PRE and TERM. In keeping with these observations, the $\dot{V}_E/\dot{V}CO_2$ nadir was higher in BPD vs. both PRE and TERM, although statistical significance was only observed between BPD and PRE (**Fig. 2.1I**).

Ventilation, breathing pattern and dynamic operating lung volume responses at rest and during CPET are displayed in **Fig. 2.2** and summarized in **Table 2.4**. Compared with TERM, peak $\dot{V}_E$ was significantly lower in both BPD and PRE, consequent to their significantly lower $\dot{V}O_{2peak}$ and peak $\dot{V}CO_2$ (rate of CO_2 production); that is, peak $\dot{V}_E/\dot{V}CO_2$ and peak $\dot{V}_E/\dot{V}O_2$ were not significantly different between-groups (**Figs. 2.1E-F**). Otherwise, $\dot{V}_E$ responses during submaximal exercise were similar between-groups (**Fig. 2.2A**). By contrast, the $\dot{V}_E$-to-maximal voluntary ventilation ratio ($\dot{V}_E$/MVV) was significantly higher during CPET at power outputs ≥1.0 W/kg LBM in BPD vs. both PRE and TERM (**Fig. 2.2B**). Respiratory frequency (f_R) was consistently higher throughout CPET in BPD vs. both PRE and TERM, with statistically significant differences observed between (i) BPD and TERM at 1.5 W/kg LMB and iso-PO_{LBM} and (ii) BPD and PRE at 1.0 W/kg LBM, 1.5 W/kg LBM and at peak exercise (**Fig. 2.2C**). With the exception of peak V_T (expressed in L and as a percentage of forced vital capacity [FVC]), which was significantly lower in BPD vs. TERM, there were no between group differences in the V_T response to CPET (**Fig. 2.2D**). As illustrated in **Figs. 2.2E-H**, mean values of IC and IRV (expressed in L and as a percentage of FVC) were similar between groups throughout CPET when examined in relation

to both LBM-specific power output and $\dot{V}_E$. However, the change in IC from rest to peak exercise was significantly different in BPD vs. both PRE and TERM, with IC decreasing by 0.11 (0.61) L in BPD and increasing by 0.14 (0.44) L in PRE and by 0.05 (0.71) L in TERM (**Table 2.4**).

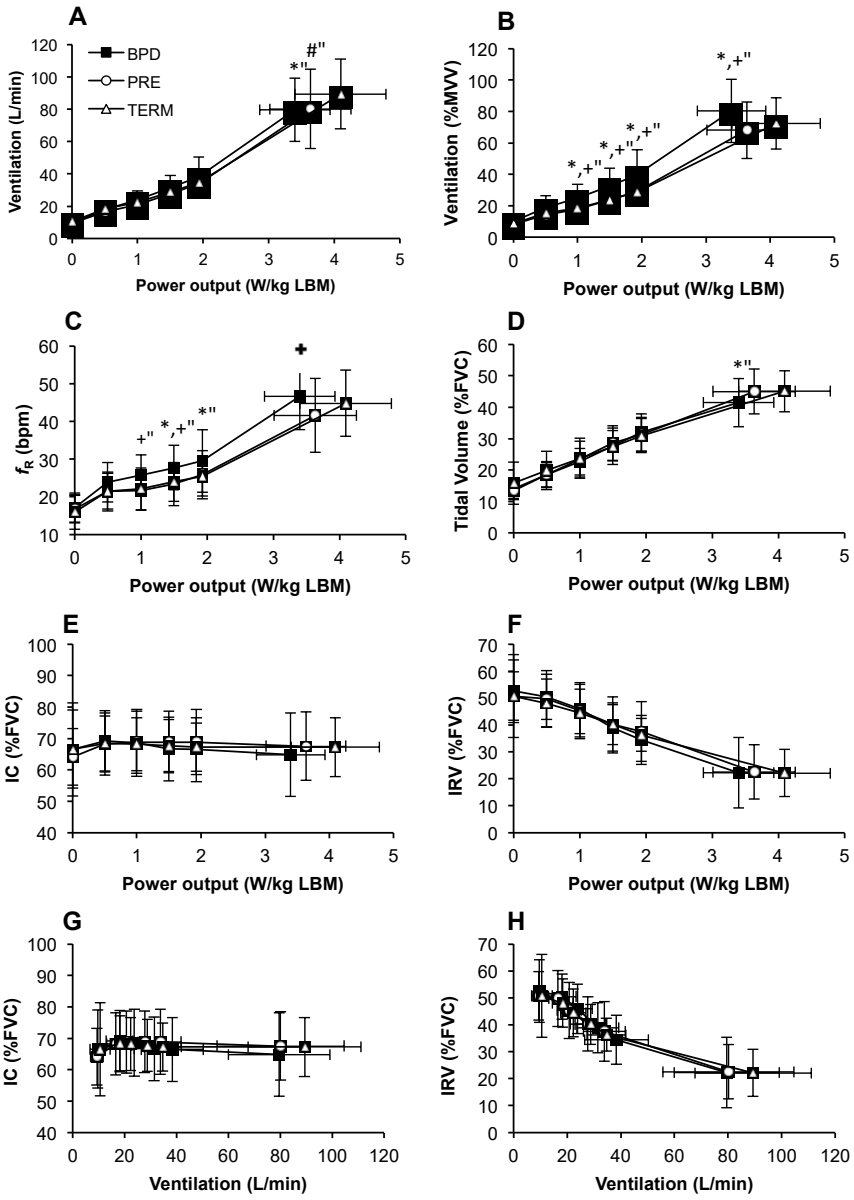

Figure 2.2. Ventilation, breathing pattern and dynamic operating lung volume responses to incremental cycle exercise testing in young adult survivors of preterm birth with bronchopulmonary dysplasia (BPD), young adult survivors of preterm birth without bronchopulmonary dysplasia (PRE) and young adults born at term with no neonatal respiratory complications (TERM). Values are mean (SD). $^{+}$p<0.05 BPD vs. PRE; *p<0.05 BPD vs. TERM; $^{\#}$p<0.05 PRE vs. TERM. *Abbreviations*: W, watts; LBM, total lean body mass; MVV, maximal voluntary ventilation calculated as the forced expiratory volume in 1-sec x 35; f_R, respiratory frequency; FVC, forced vital capacity; IC, inspiratory capacity; IRV, inspiratory reserve volume.

2.4.v. Symptom responses to exercise. Symptom responses at rest and during CPET are displayed in **Fig. 2.3** and summarized in **Table 2.4**. The reasons for stopping exercise were not significantly different between groups, with the majority of participants in each group stopping because of intolerable leg discomfort. Intensity ratings of leg discomfort were (i) significantly lower at end-exercise in BPD vs. PRE and (ii) elevated during CPET at and above iso-PO_{LBM} in both BPD and PRE vs. TERM, although statistical significance was only observed between BPD and TERM at iso-PO_{LBM} (**Fig. 2.3A**). Intensity ratings of breathlessness were (i) significantly lower at end-exercise in BPD vs. both PRE and TERM and (ii) not significantly different during CPET at any standardized submaximal LBM-specific power output between groups (**Fig. 2.3B**). As illustrated in **Figs. 2.3C-D**, breathlessness-$\dot{V}_E$, breathlessness-$\dot{V}_E$/MVV and breathlessness-IRV%FVC relationships were similar between groups. In fact, **Fig. 2.3D** reveals a rightward shift of the breathlessness-$\dot{V}_E$/MVV relationship throughout exercise in BPD vs. both PRE and TERM, such that breathlessness intensity ratings were lower at any given $\dot{V}_E$/MVV during exercise in BPD vs. both PRE and TERM, particularly near the limits of tolerance.

2.4.vi. Correlates of peak exercise capacity. Statistically significant correlations were observed between $\dot{V}O_{2peak}$ (expressed in ml/kg LBM/min) and each of the following parameters within the pooled data: activity-related energy expenditure (**Fig. 2.4A**); number of steps per day (**Fig. 2.4B**); % predicted FEV_1 (**Fig. 2.4C**); % predicted $FEF_{25-75\%}$ (**Fig. 2.4D**); % predicted RV (**Fig. 2.4E**); % predicted D_LCO (**Fig. 2.4F**); and the $\dot{V}_E/\dot{V}CO_2$ nadir (**Fig. 2.4G**), which in turn correlated with % predicted D_LCO (**Fig. 2.4H**). Statistically significant correlations were also observed between PPO (expressed in W/kg LBM) and each of the following parameters within the pooled data:

activity-related energy expenditure (Pearson r=0.454, p<0.001); number of steps per day (Pearson r=0.393, p=0.002); % predicted FEV_1 (Pearson r=0.261, p=0.015); % predicted RV (Pearson r=-0.257, p=0.012); % predicted D_LCO (Pearson r=0.311, p=0.003); and the $\dot{V}_E/\dot{V}CO_2$ nadir (Pearson r=-0.266, p=0.013).

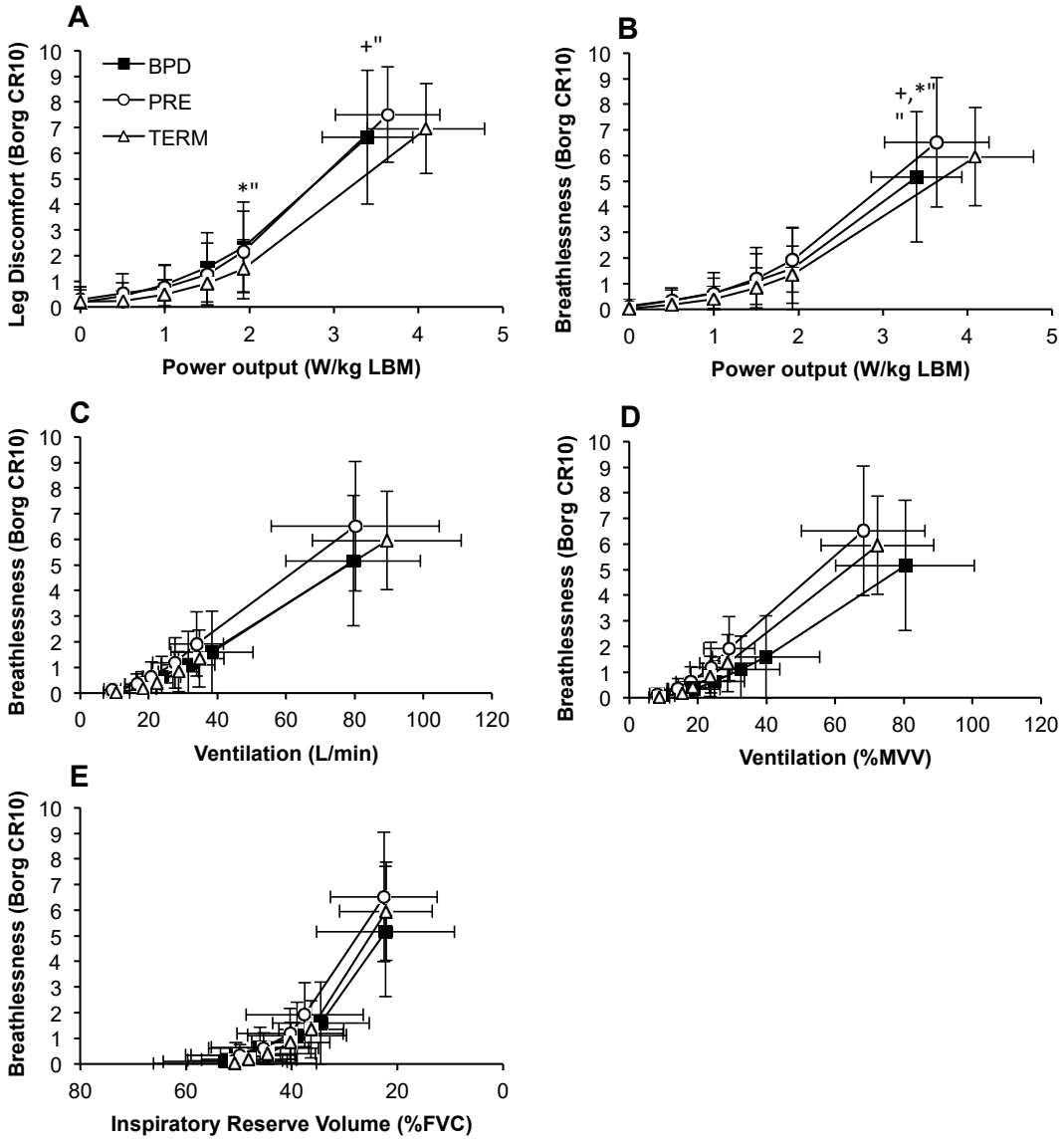

Figure 2.3. Symptom responses to incremental cycle exercise testing in young adult survivors of preterm birth with bronchopulmonary dysplasia (BPD), young adult survivors of preterm birth without bronchopulmonary dysplasia (PRE) and young adults born at term with no neonatal respiratory complications (TERM). Values are mean (SD). $^{+}$p<0.05 BPD vs. PRE; *p<0.05 BPD vs. TERM; $^{\#}$p<0.05 PRE vs. TERM. *Abbreviations*: W, watts; LBM, total lean body mass; CR10, modified 0-10 category ratio scale; MVV, maximal voluntary ventilation calculated as the forced expiratory volume in 1-sec x 35; FVC, forced vital capacity.

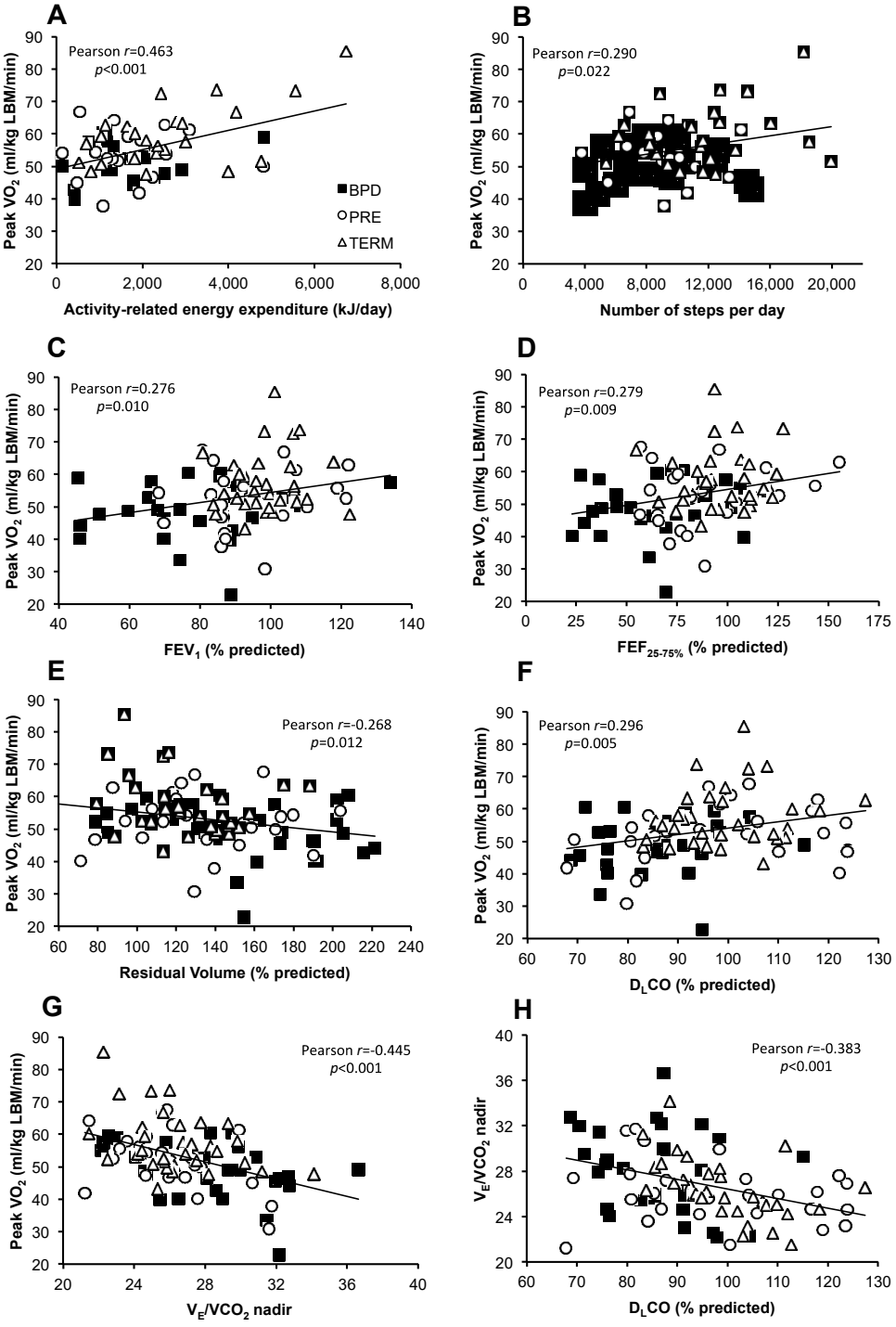

Figure 2.4. Correlates of the peak rate of O_2 consumption (VO_2) on incremental cycle exercise testing in young adult survivors of preterm birth with bronchopulmonary dysplasia (BPD), young adult survivors of preterm birth without bronchopulmonary dysplasia (PRE) and young adults born at term with no neonatal respiratory complications (TERM). *Abbreviations*: LBM, total lean body mass; FEV_1, forced expiratory volume in 1-sec; $FEF_{25-75\%}$, forced expiratory flow from 25% to 75% of the forced vital capacity maneuver; D_LCO, diffusing capacity of the lung for carbon monoxide; V_E/VCO_2, ventilatory equivalent for CO_2.

2.5. DISCUSSION

In this relatively large observational cohort study, we confirmed earlier reports[26, 27, 30, 62, 63] of impaired baseline pulmonary function and exercise tolerance (aerobic working capacity) in adult survivors of preterm birth with a history of BPD. We found that objective measures of daytime physical activity levels (DPALs) were significantly lower in adult survivors of preterm birth with and without BPD compared with healthy term-born controls. We also provided evidence that the impaired exercise tolerance of adult BPD survivors cannot be explained by exertional breathlessness associated with abnormal restrictive constraints on V_T expansion, but that it may reflect cardiovascular and locomotor muscle deconditioning due to abnormally low DPALs.

The adverse effect of preterm birth complicated by BPD on spirometric and plethysmographic baseline pulmonary function test parameters, namely FEV_1, FEV_1/FVC, $FEF_{25-75\%}$ and RV, were confirmed by the results of our study. We also observed statistically significant, though weak, univariate correlations between FEV_1, $FEF_{25-75\%}$ and RV and each of PPO and $\dot{V}O_{2peak}$ within the pooled data. The physiological and/or clinical significance of these correlations are difficult to interpret in as much as (i) abnormal restrictive constraints on V_T expansion could not account for the impaired exercise tolerance of our adult BPD survivors (*see below*), despite FEV_1 and $FEF_{25-75\%}$ being significantly lower and RV being significantly higher in BPD vs. TERM; and (ii) $\dot{V}O_{2peak}$ was significantly lower in PRE vs. TERM, even though FEV_1, $FEF_{25-75\%}$ and RV were not significantly different between-groups. For these reasons, it is unlikely that abnormalities in baseline pulmonary function contributed meaningfully to the impaired exercise tolerance of our young adult BPD survivors aged 19-26 years.

Consistent with the results of previous studies in children, adolescent and adult survivors of preterm birth with BPD,[54, 63, 64] we found that adult BPD survivors adopted a more rapid (tachypneic) breathing pattern during exercise compared with both PRE and TERM. We also found that IC decreased by 0.11 L from rest to peak exercise in adult BPD survivors (reflecting the existence of dynamic lung hyperinflation [DH]), which was in contrast to our PRE and TERM participants who increased their respective IC values from rest to peak exercise by 0.14 L and 0.05 L. From these findings, it could be argued that DH contributed, at least in part, to the impaired exercise tolerance of our adult BPD survivors. However, an important study by Guenette et al.[112] found that the symptom-limited peak cycle exercise performance of adults with moderate-to-severe chronic obstructive pulmonary disease (COPD) was (i) independent of the presence of DH during exercise and (ii) closely related to the behavior of dynamic IRV, which has emerged as the most proximate measure of restrictive mechanical constraints on V_T expansion during exercise relevant to breathlessness and exercise tolerance in patients chronic pulmonary disorders.[102, 103] We contend that, in the presence of DH during exercise, our adult BPD survivors adopted a more tachypneic breathing pattern so as to allow their V_T to expand normally and without greater erosion of their dynamic IRV at any given power output and $\dot{V}_E$ during exercise compared with PRE and TERM. It is reasonable to assume that, under these circumstances, V_T expansion occurred on a similar portion of each group's sigmoid respiratory pressure-volume curve, resulting in similar levels of elastic loading, functional weakening and neural activation of the inspiratory pump muscles (e.g., diaphragm) at any given power output and $\dot{V}_E$ during exercise. In view of our current understanding of the physiological mechanisms of exertional breathlessness in health and chronic pulmonary diseases,[103, 113] it

follows that the relationship between exercise-induced increases in ratings of perceived breathlessness and each of power output and $\dot{V}_E$ were comparable in BPD vs. both PRE and TERM. In other words (and as predicted by the relatively preserved breathlessness-IRV%FVC relationships during exercise in BPD vs. PRE and TERM), breathlessness intensity ratings were not higher at any given power output and $\dot{V}_E$ during exercise in BPD vs. PRE and TERM because dynamic IRV%FVC was not lower at any given power output and $\dot{V}_E$ during exercise in BPD vs. PRE and TERM. On the basis of these observations, we concluded that the impaired exercise tolerance of our adult BPD survivors could not be explained by breathlessness associated with abnormal restrictive constraints on V_T expansion during exercise. Indeed, breathlessness intensity ratings were significantly lower at the symptom-limited peak of exercise in BPD compared with both PRE and TERM (consequent to adult BPD survivors' correspondingly lower PPO, $\dot{V}O_{2peak,}$ peak $\dot{V}CO_2$ and peak $\dot{V}_E$, and despite their higher peak $\dot{V}_E$/MVV) and not a single one of our adult BPD survivors identified intolerable breathlessness as their main exercise-limiting symptom.

The results of recent reports by MacLean et al.,[64] Caskey et al.,[27] and Hestnes et al.[54] suggest that an abnormally high $\dot{V}_E/\dot{V}CO_2$ response to exercise (reflecting abnormally low exercise ventilatory efficiency) may contribute to the impaired exercise tolerance of children, adolescent and adult survivors of preterm birth complicated by BPD. In keeping with these observations, we found that (i) both $\dot{V}_E/\dot{V}CO_2$ and $\dot{V}_E/\dot{V}O_2$ were uniformly elevated throughout exercise in BPD compared with both PRE and TERM, although the differences were not statistically significant between-groups; (ii) the $\dot{V}_E/\dot{V}CO_2$ nadir was modestly higher in adult BPD survivors vs. PRE (p=0.049) and TERM (p=0.108); and (iii) within the pooled data, the $\dot{V}_E/\dot{V}CO_2$

nadir was inversely related to both PPO and $\dot{V}O_{2peak}$ as well as to D_LCO, which in turn was inversely related to both PPO and $\dot{V}O_{2peak}$. Taken together, these findings support the existence of an elevated physiological dead space with attendant greater dead space (wasted) ventilation during exercise in our adult BPD survivors, a likely consequence of structural pulmonary abnormalities like emphysema.[78] However, the extent to which exercise ventilatory inefficiency contributed to the impaired exercise tolerance of our adult BPD survivors is difficult to interpret in as much as (i) breathlessness intensity ratings were not significantly higher for any given power output during exercise in BPD vs. PRE and TERM, which is in contrast to the effects of dead space loading on exertional breathlessness in healthy adults;[99, 114] (ii) cardiometabolic responses to incremental cycle exercise testing were comparable in BPD, PRE and TERM; and (iii) $\dot{V}O_{2peak}$ was significantly lower in PRE vs. TERM, even though D_LCO, the $\dot{V}_E/\dot{V}CO_2$ nadir and $\dot{V}_E/\dot{V}CO_2$-power output relationships were comparable between-groups. It is well established that an abnormally high $\dot{V}_E/\dot{V}CO_2$ response to exercise independently predicts adverse health outcomes such as mortality among patients with hearth failure, pulmonary arterial hypertension, idiopathic pulmonary fibrosis and COPD.[115-118] Whether abnormalities in exercise ventilatory efficiency observed in children, adolescent and young adults survivors of preterm birth complicated by BPD become clinically important (i.e., predict adverse health outcomes) with advancing age should be a focus of further research.

Our study is among the first to demonstrate that objective estimates of DPALs were significantly lower among adult survivors of preterm birth with and without BPD compared to TERM. To this end, average daily activity-related energy expenditure, average daily step count and average daily time spent participating in vigorous activities were 32-37%, 18-23% and 58-

61% lower in both BPD and PRE compared with TERM, respectively. We also found weak but statistically significant univariate correlations between activity-monitor derived estimates of average daily activity-related energy expenditure and average daily step count with each of PPO and $\dot{V}O_{2peak}$ within the pooled data. These findings, when viewed in light of the fact that the impaired exercise tolerance of our adult BPD survivors could not be explained by breathlessness due to abnormal static and dynamic breathing mechanics, support the hypothesis that cardiovascular and peripheral locomotor muscle (e.g., quadriceps) deconditioning associated with abnormally low DPALs may be the proximate source of impaired exercise tolerance among our adult survivors of preterm birth both with and without BPD. In keeping with the results of Lovering et al.[63] and in further support of this hypothesis, we found that (i) intensity ratings of perceived leg discomfort were consistently higher during exercise at standardized submaximal power outputs of ≥1.9 W/kg LBM in both BPD and PRE vs. TERM; (ii) intensity ratings of perceived leg discomfort were similar at the symptom-limited of exercise in BPD vs. TERM, even though PPO and $\dot{V}O_{2peak}$ were significantly lower (by 15-17%) in the former; and (iii) intolerable leg discomfort was identified as the main exercise limiting symptom in the majority of participants, regardless of birth and BPD history. The factors responsible for the abnormally low DPALs in BPD and PRE could not be elucidated from our study and thus remain unclear, although physical activity-activity breathlessness associated with pathophysiological abnormalities in static and dynamic breathing mechanics is not likely responsible, at least not according the results of our study. It is possible that socio-emotional and/or neuro-developmental factors present during childhood and adolescence are associated

with habituation to physical activity avoidance that persists into adulthood.[30, 84, 119] Further research is needed in this regard.

2.5.i Methodological considerations

The main limitation of the current study is the cross-sectional nature of the study design. Even with age, sex, and BMI-matched control subjects, there may be other factors that had a role in the decrease exercise capacity of BPD subjects that were not measured at the time the study was conducted. Namely, direct assessment of specific cardiovascular responses to exercise, specifically cardiac output and a-vO_2 difference, were not taken during exercise and thus are not part of the analysis. Furthermore, there is no measurement of peripheral muscle strength and/or in the subject populations, preventing the comparison of these important outcomes between groups. The lack of this information has implications in the root cause of abnormally low DPALs in BPD subjects, as the current mechanism is unknown and speculative. However, this study does provide the basis for future studies into the mechanisms of abnormally low DPALs in young adults living with BPD, and a more detailed assessment of the cardiovascular and peripheral locomotor muscle response to exercise in this population.

2.5.ii Conclusion

In conclusion, the collective results of the current study suggest that the abnormally low exercise tolerance of young adult survivors of preterm birth with a history of BPD cannot be explained by exertional breathlessness associated with abnormal restrictive constraints on V_T expansion, but that it may reflect the consequences of cardiovascular and peripheral locomotor muscle deconditioning associated with abnormally low daytime physical activity levels. This should bring positive reinforcement to young adults afflicted by BPD and to their healthcare

providers because daytime physical activity levels and, by extension, exercise tolerance are amenable to targeted exercise/physical activity/lifestyle interventions and may improve clinical and patient reported outcomes in this population.

REFERENCES

1. Tracy, S.K., et al., *Spontaneous preterm birth of liveborn infants in women at low risk in Australia over 10 years: a population-based study.* BJOG, 2007. **114**(6): p. 731-5.
2. Blencowe, H., et al., *National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications.* Lancet, 2012. **379**(9832): p. 2162-72.
3. O'Reilly, M., F. Sozo, and R. Harding, *Impact of preterm birth and bronchopulmonary dysplasia on the developing lung: long-term consequences for respiratory health.* Clin Exp Pharmacol Physiol, 2013. **40**(11): p. 765-73.
4. de Jong, F., et al., *Systematic review and meta-analysis of preterm birth and later systolic blood pressure.* Hypertension, 2012. **59**(2): p. 226-34.
5. Hofman, P.L., et al., *Premature birth and later insulin resistance.* N Engl J Med, 2004. **351**(21): p. 2179-86.
6. Lewandowski, A.J., et al., *Right ventricular systolic dysfunction in young adults born preterm.* Circulation, 2013. **128**(7): p. 713-20.
7. Northway, W.H., Jr., et al., *Late pulmonary sequelae of bronchopulmonary dysplasia.* N Engl J Med, 1990. **323**(26): p. 1793-9.
8. Hilgendorff, A. and M.A. O'Reilly, *Bronchopulmonary dysplasia early changes leading to long-term consequences.* Front Med (Lausanne), 2015. **2**: p. 2.
9. Northway, W.H., Jr., R.C. Rosan, and D.Y. Porter, *Pulmonary disease following respirator therapy of hyaline-membrane disease. Bronchopulmonary dysplasia.* N Engl J Med, 1967. **276**(7): p. 357-68.
10. Walsh, M.C., et al., *Safety, reliability, and validity of a physiologic definition of bronchopulmonary dysplasia.* J Perinatol, 2003. **23**(6): p. 451-6.
11. Jobe, A.H. and E. Bancalari, *Bronchopulmonary dysplasia.* Am J Respir Crit Care Med, 2001. **163**(7): p. 1723-9.
12. Medicine, I.o., *Preterm Birth: Causes, Consequences, and Prevention*, ed. R.E. Behrman and A.S. Butler. 2007, Washington, DC: The National Academies Press. 790.
13. Santuz, P., et al., *Factors limiting exercise performance in long-term survivors of bronchopulmonary dysplasia.* Am J Respir Crit Care Med, 1995. **152**(4 Pt 1): p. 1284-9.
14. Fanaroff, A.A., et al., *Trends in neonatal morbidity and mortality for very low birthweight infants.* Am J Obstet Gynecol, 2007. **196**(2): p. 147 e1-8.
15. Farstad, T., et al., *Bronchopulmonary dysplasia - prevalence, severity and predictive factors in a national cohort of extremely premature infants.* Acta Paediatr, 2011. **100**(1): p. 53-8.
16. Trembath, A. and M.M. Laughon, *Predictors of bronchopulmonary dysplasia.* Clin Perinatol, 2012. **39**(3): p. 585-601.
17. Kobaly, K., et al., *Outcomes of extremely low birth weight (<1 kg) and extremely low gestational age (<28 weeks) infants with bronchopulmonary dysplasia: effects of practice changes in 2000 to 2003.* Pediatrics, 2008. **121**(1): p. 73-81.
18. Bhandari, A. and S. McGrath-Morrow, *Long-term pulmonary outcomes of patients with bronchopulmonary dysplasia.* Semin Perinatol, 2013. **37**(2): p. 132-7.

19. Hintz, S.R., et al., *Predicting time to hospital discharge for extremely preterm infants.* Pediatrics, 2010. **125**(1): p. e146-54.
20. Rojas, M.A., et al., *Changing trends in the epidemiology and pathogenesis of neonatal chronic lung disease.* J Pediatr, 1995. **126**(4): p. 605-10.
21. Smith, V.C., et al., *Trends in severe bronchopulmonary dysplasia rates between 1994 and 2002.* J Pediatr, 2005. **146**(4): p. 469-73.
22. Leaver, S.K. and T.W. Evans, *Acute respiratory distress syndrome.* BMJ, 2007. **335**(7616): p. 389-94.
23. Gough, A., et al., *Impaired lung function and health status in adult survivors of bronchopulmonary dysplasia.* Eur Respir J, 2014. **43**(3): p. 808-16.
24. Bhandari, A. and H.B. Panitch, *Pulmonary outcomes in bronchopulmonary dysplasia.* Semin Perinatol, 2006. **30**(4): p. 219-26.
25. Hennessy, E.M., et al., *Respiratory health in pre-school and school age children following extremely preterm birth.* Arch Dis Child, 2008. **93**(12): p. 1037-43.
26. Gough, A., et al., *General and respiratory health outcomes in adult survivors of bronchopulmonary dysplasia: a systematic review.* Chest, 2012. **141**(6): p. 1554-67.
27. Caskey, S., et al., *Structural and Functional Lung Impairment in Adult Survivors of Bronchopulmonary Dysplasia.* Ann Am Thorac Soc, 2016. **13**(8): p. 1262-70.
28. Joshi, S., et al., *Exercise-induced bronchoconstriction in school-aged children who had chronic lung disease in infancy.* J Pediatr, 2013. **162**(4): p. 813-818 e1.
29. Rogers, M., et al., *Aerobic capacity, strength, flexibility, and activity level in unimpaired extremely low birth weight (<or=800 g) survivors at 17 years of age compared with term-born control subjects.* Pediatrics, 2005. **116**(1): p. e58-65.
30. Landry, J.S., et al., *Lung Function and Bronchial Hyperresponsiveness in Adults Born Prematurely. A Cohort Study.* Ann Am Thorac Soc, 2016. **13**(1): p. 17-24.
31. Gien, J. and J.P. Kinsella, *Pathogenesis and treatment of bronchopulmonary dysplasia.* Curr Opin Pediatr, 2011. **23**(3): p. 305-13.
32. Baraldi, E. and M. Filippone, *Chronic lung disease after premature birth.* N Engl J Med, 2007. **357**(19): p. 1946-55.
33. Kwinta, P. and J.J. Pietrzyk, *Preterm birth and respiratory disease in later life.* Expert Rev Respir Med, 2010. **4**(5): p. 593-604.
34. Smith, L.J., et al., *Normal development of the lung and premature birth.* Paediatr Respir Rev, 2010. **11**(3): p. 135-42.
35. Speer, C.P., *Inflammation and bronchopulmonary dysplasia: a continuing story.* Semin Fetal Neonatal Med, 2006. **11**(5): p. 354-62.
36. Dollner, H., et al., *Histologic chorioamnionitis and umbilical serum levels of pro-inflammatory cytokines and cytokine inhibitors.* BJOG, 2002. **109**(5): p. 534-9.
37. Paananen, R., et al., *Blood cytokines during the perinatal period in very preterm infants: relationship of inflammatory response and bronchopulmonary dysplasia.* J Pediatr, 2009. **154**(1): p. 39-43 e3.
38. Weaver, M., N.R. Dunn, and B.L. Hogan, *Bmp4 and Fgf10 play opposing roles during lung bud morphogenesis.* Development, 2000. **127**(12): p. 2695-704.

39. Benjamin, J.T., et al., *NF-kappaB activation limits airway branching through inhibition of Sp1-mediated fibroblast growth factor-10 expression.* J Immunol, 2010. **185**(8): p. 4896-903.
40. Kotecha, S., et al., *Increase in the concentration of transforming growth factor beta-1 in bronchoalveolar lavage fluid before development of chronic lung disease of prematurity.* J Pediatr, 1996. **128**(4): p. 464-9.
41. Ichiba, H., M. Saito, and T. Yamano, *Amniotic fluid transforming growth factor-beta1 and the risk for the development of neonatal bronchopulmonary dysplasia.* Neonatology, 2009. **96**(3): p. 156-61.
42. Tin, W. and U. Wariyar, *Giving small babies oxygen: 50 years of uncertainty.* Semin Neonatol, 2002. **7**(5): p. 361-7.
43. Bonikos, D.S., K.G. Bensch, and W.H. Northway, Jr., *Oxygen toxicity in the newborn. The effect of chronic continuous 100 percent oxygen exposure on the lungs of newborn mice.* Am J Pathol, 1976. **85**(3): p. 623-50.
44. Saugstad, O.D., *Oxygen and oxidative stress in bronchopulmonary dysplasia.* J Perinat Med, 2010. **38**(6): p. 571-7.
45. Czarna, M. and W. Jarmuszkiewicz, *[Role of mitochondria in reactive oxygen species generation and removal; relevance to signaling and programmed cell death].* Postepy Biochem, 2006. **52**(2): p. 145-56.
46. Pham-Huy, L.A., H. He, and C. Pham-Huy, *Free radicals, antioxidants in disease and health.* Int J Biomed Sci, 2008. **4**(2): p. 89-96.
47. Proud, D. and R. Leigh, *Epithelial cells and airway diseases.* Immunol Rev, 2011. **242**(1): p. 186-204.
48. Dasgupta, C., et al., *Hyperoxia-induced neonatal rat lung injury involves activation of TGF-{beta} and Wnt signaling and is protected by rosiglitazone.* Am J Physiol Lung Cell Mol Physiol, 2009. **296**(6): p. L1031-41.
49. Stenmark, K.R. and S.H. Abman, *Lung vascular development: implications for the pathogenesis of bronchopulmonary dysplasia.* Annu Rev Physiol, 2005. **67**: p. 623-61.
50. Bhatt, A.J., et al., *Disrupted pulmonary vasculature and decreased vascular endothelial growth factor, Flt-1, and TIE-2 in human infants dying with bronchopulmonary dysplasia.* Am J Respir Crit Care Med, 2001. **164**(10 Pt 1): p. 1971-80.
51. Lassus, P., et al., *Pulmonary vascular endothelial growth factor and Flt-1 in fetuses, in acute and chronic lung disease, and in persistent pulmonary hypertension of the newborn.* Am J Respir Crit Care Med, 2001. **164**(10 Pt 1): p. 1981-7.
52. Maniscalco, W.M., et al., *Hyperoxic injury decreases alveolar epithelial cell expression of vascular endothelial growth factor (VEGF) in neonatal rabbit lung.* Am J Respir Cell Mol Biol, 1997. **16**(5): p. 557-67.
53. Le Cras, T.D., et al., *Treatment of newborn rats with a VEGF receptor inhibitor causes pulmonary hypertension and abnormal lung structure.* Am J Physiol Lung Cell Mol Physiol, 2002. **283**(3): p. L555-62.
54. Hestnes, J., et al., *Ventilatory Efficiency in Children and Adolescents Born Extremely Preterm.* Front Physiol, 2017. **8**: p. 499.
55. Balasubramaniam, V., et al., *Hyperoxia reduces bone marrow, circulating, and lung endothelial progenitor cells in the developing lung: implications for the pathogenesis of*

bronchopulmonary dysplasia. Am J Physiol Lung Cell Mol Physiol, 2007. **292**(5): p. L1073-84.
56. Borghesi, A., et al., *Circulating endothelial progenitor cells in preterm infants with bronchopulmonary dysplasia.* Am J Respir Crit Care Med, 2009. **180**(6): p. 540-6.
57. Mahmoud, R.A., C.C. Roehr, and G. Schmalisch, *Current methods of non-invasive ventilatory support for neonates.* Paediatr Respir Rev, 2011. **12**(3): p. 196-205.
58. Kraybill, E.N., et al., *Risk factors for chronic lung disease in infants with birth weights of 751 to 1000 grams.* J Pediatr, 1989. **115**(1): p. 115-20.
59. Bjorklund, L.J., et al., *Manual ventilation with a few large breaths at birth compromises the therapeutic effect of subsequent surfactant replacement in immature lambs.* Pediatr Res, 1997. **42**(3): p. 348-55.
60. Mokres, L.M., et al., *Prolonged mechanical ventilation with air induces apoptosis and causes failure of alveolar septation and angiogenesis in lungs of newborn mice.* Am J Physiol Lung Cell Mol Physiol, 2010. **298**(1): p. L23-35.
61. Gupta, S., S.K. Sinha, and S.M. Donn, *Ventilatory management and bronchopulmonary dysplasia in preterm infants.* Semin Fetal Neonatal Med, 2009. **14**(6): p. 367-73.
62. Landry, J.S., et al., *Long-term impact of bronchopulmonary dysplasia on pulmonary function.* Can Respir J, 2011. **18**(5): p. 265-70.
63. Lovering, A.T., et al., *Ventilatory and sensory responses in adult survivors of preterm birth and bronchopulmonary dysplasia with reduced exercise capacity.* Ann Am Thorac Soc, 2014. **11**(10): p. 1528-37.
64. MacLean, J.E., et al., *Altered breathing mechanics and ventilatory response during exercise in children born extremely preterm.* Thorax, 2016. **71**(11): p. 1012-1019.
65. Welsh, L., et al., *The EPICure study: maximal exercise and physical activity in school children born extremely preterm.* Thorax, 2010. **65**(2): p. 165-72.
66. Lowe, J., et al., *Physical activity in school-age children born preterm.* J Pediatr, 2015. **166**(4): p. 877-83.
67. Vardar-Yagli, N., et al., *Pulmonary and extrapulmonary features in bronchopulmonary dysplasia: a comparison with healthy children.* J Phys Ther Sci, 2015. **27**(6): p. 1761-5.
68. Fewtrell, M.S., et al., *Prematurity and reduced body fatness at 8-12 y of age.* Am J Clin Nutr, 2004. **80**(2): p. 436-40.
69. Kriemler, S., et al., *Aerobic and lung performance in premature children with and without chronic lung disease of prematurity.* Clin J Sport Med, 2005. **15**(5): p. 349-55.
70. Blayney, M., et al., *Bronchopulmonary dysplasia: improvement in lung function between 7 and 10 years of age.* J Pediatr, 1991. **118**(2): p. 201-6.
71. Doyle, L.W., et al., *Changes in lung function between age 8 and 14 years in children with birth weight of less than 1,501 g.* Pediatr Pulmonol, 1999. **27**(3): p. 185-90.
72. Mitchell, S.H. and W.G. Teague, *Reduced gas transfer at rest and during exercise in school-age survivors of bronchopulmonary dysplasia.* Am J Respir Crit Care Med, 1998. **157**(5 Pt 1): p. 1406-12.
73. Korhonen, P., et al., *Respiratory outcome in school-aged, very-low-birth-weight children in the surfactant era.* Acta Paediatr, 2004. **93**(3): p. 316-21.

74. Lovering, A.T., et al., *Normal pulmonary gas exchange efficiency and absence of exercise-induced arterial hypoxemia in adults with bronchopulmonary dysplasia.* J Appl Physiol (1985), 2013. **115**(7): p. 1050-6.
75. Narang, I., et al., *Longitudinal evaluation of airway function 21 years after preterm birth.* Am J Respir Crit Care Med, 2008. **178**(1): p. 74-80.
76. Thannickal, V.J., et al., *Blue journal conference. Aging and susceptibility to lung disease.* Am J Respir Crit Care Med, 2015. **191**(3): p. 261-9.
77. Aukland, S.M., et al., *Neonatal bronchopulmonary dysplasia predicts abnormal pulmonary HRCT scans in long-term survivors of extreme preterm birth.* Thorax, 2009. **64**(5): p. 405-10.
78. Wong, P.M., et al., *Emphysema in young adult survivors of moderate-to-severe bronchopulmonary dysplasia.* Eur Respir J, 2008. **32**(2): p. 321-8.
79. Calder, N.A., et al., *Absence of ventilatory responses to alternating breaths of mild hypoxia and air in infants who have had bronchopulmonary dysplasia: implications for the risk of sudden infant death.* Pediatr Res, 1994. **35**(6): p. 677-81.
80. Bates, M.L., et al., *Ventilatory control in infants, children, and adults with bronchopulmonary dysplasia.* Respir Physiol Neurobiol, 2013. **189**(2): p. 329-37.
81. Katz-Salamon, M., B. Jonsson, and H. Lagercrantz, *Blunted peripheral chemoreceptor response to hyperoxia in a group of infants with bronchopulmonary dysplasia.* Pediatr Pulmonol, 1995. **20**(2): p. 101-6.
82. Blanco, C.E., et al., *The response to hypoxia of arterial chemoreceptors in fetal sheep and new-born lambs.* J Physiol, 1984. **351**: p. 25-37.
83. Bates, M.L., E.T. Farrell, and M.W. Eldridge, *Abnormal ventilatory responses in adults born prematurely.* N Engl J Med, 2014. **370**(6): p. 584-5.
84. Svedenkrans, J., et al., *Long-term impact of preterm birth on exercise capacity in healthy young men: a national population-based cohort study.* PLoS One, 2013. **8**(12): p. e80869.
85. Lowe, J., et al., *Physical Activity and Sedentary Behavior in Preterm-Born 7-Year Old Children.* PLoS One, 2016. **11**(5): p. e0155229.
86. Svien, L.R., *Health-related fitness of seven- to 10-year-old children with histories of preterm birth.* Pediatr Phys Ther, 2003. **15**(2): p. 74-83.
87. Basterfield, L., et al., *Longitudinal study of physical activity and sedentary behavior in children.* Pediatrics, 2011. **127**(1): p. e24-30.
88. Saigal, S., et al., *Comparison of current health, functional limitations, and health care use of young adults who were born with extremely low birth weight and normal birth weight.* Pediatrics, 2007. **119**(3): p. e562-73.
89. Jacob, S.V., et al., *Exercise ability in survivors of severe bronchopulmonary dysplasia.* Am J Respir Crit Care Med, 1997. **155**(6): p. 1925-9.
90. Zavorsky, G.S., et al., *Exercise capacity of children with pediatric lung disease.* Clin Invest Med, 2009. **32**(6): p. E302.
91. Tsopanoglou, S.P., et al., *Functional capacity during exercise in very-low-birth-weight premature children.* Pediatr Pulmonol, 2014. **49**(1): p. 91-8.
92. Smyth, J.A., et al., *Pulmonary function and bronchial hyperreactivity in long-term survivors of bronchopulmonary dysplasia.* Pediatrics, 1981. **68**(3): p. 336-40.

93. Rideau Batista Novais, A., et al., *Hyperventilation during exercise in very low birth weight school-age children may implicate inspiratory muscle weakness.* J Pediatr, 2012. **160**(3): p. 415-420 e1.
94. Moss, T.J., *Respiratory consequences of preterm birth.* Clin Exp Pharmacol Physiol, 2006. **33**(3): p. 280-4.
95. Bonamy, A.K., et al., *Lower skin capillary density, normal endothelial function and higher blood pressure in children born preterm.* J Intern Med, 2007. **262**(6): p. 635-42.
96. Schubert, U., et al., *Aortic growth arrest after preterm birth: a lasting structural change of the vascular tree.* J Dev Orig Health Dis, 2011. **2**(4): p. 218-25.
97. Vrijlandt, E.J., et al., *Lung function and exercise capacity in young adults born prematurely.* Am J Respir Crit Care Med, 2006. **173**(8): p. 890-6.
98. Mendonca, C.T., et al., *Physiological mechanisms of dyspnea during exercise with external thoracic restriction: role of increased neural respiratory drive.* J Appl Physiol (1985), 2014. **116**(5): p. 570-81.
99. O'Donnell, D.E., H.H. Hong, and K.A. Webb, *Respiratory sensation during chest wall restriction and dead space loading in exercising men.* J Appl Physiol, 2000. **88**(5): p. 1859-69.
100. Kotrach, H.G., J. Bourbeau, and D. Jensen, *Does nebulized fentanyl relieve dyspnea during exercise in healthy man?* J Appl Physiol (1985), 2015. **118**(11): p. 1406-14.
101. Harty, H.R., et al., *External thoracic restriction, respiratory sensation, and ventilation during exercise in men.* J Appl Physiol, 1999. **86**(4): p. 1142-50.
102. Faisal, A., et al., *Common Mechanisms of Dyspnea in Chronic Interstitial and Obstructive Lung Disorders.* Am J Respir Crit Care Med, 2016. **193**(3): p. 299-309.
103. O'Donnell, D.E., et al., *Mechanisms of activity-related dyspnea in pulmonary diseases.* Respir Physiol Neurobiol, 2009. **167**(1): p. 116-32.
104. Landry, J.S., D. Croitoru, and D. Menzies, *Validation of ICD-9 diagnostic codes for bronchopulmonary dysplasia in Quebec's provincial health care databases.* Chronic Dis Inj Can, 2012. **33**(1): p. 47-52.
105. Miller, M.R., et al., *Standardisation of spirometry.* Eur Respir J, 2005. **26**(2): p. 319-38.
106. Macintyre, N., et al., *Standardisation of the single-breath determination of carbon monoxide uptake in the lung.* Eur Respir J, 2005. **26**(4): p. 720-35.
107. Wanger, J., et al., *Standardisation of the measurement of lung volumes.* Eur Respir J, 2005. **26**(3): p. 511-22.
108. Kuster, S.P., et al., *Reference equations for lung function screening of healthy never-smoking adults aged 18-80 years.* Eur Respir J, 2008. **31**(4): p. 860-8.
109. Stubbing, D.G., et al., *Pulmonary mechanics during exercise in normal males.* J Appl Physiol, 1980. **49**(3): p. 506-10.
110. Borg, G.A., *Psychophysical bases of perceived exertion.* Med Sci Sports Exerc, 1982. **14**(5): p. 377-81.
111. American Thoracic, S. and P. American College of Chest, *ATS/ACCP Statement on cardiopulmonary exercise testing.* Am J Respir Crit Care Med, 2003. **167**(2): p. 211-77.
112. Guenette, J.A., K.A. Webb, and D.E. O'Donnell, *Does dynamic hyperinflation contribute to dyspnoea during exercise in patients with COPD?* Eur Respir J, 2012. **40**(2): p. 322-9.

113. Jensen, D., D. Ofir, and D.E. O'Donnell, *Effects of pregnancy, obesity and aging on the intensity of perceived breathlessness during exercise in healthy humans.* Respir Physiol Neurobiol, 2009. **167**(1): p. 87-100.
114. Jensen, D., et al., *Effects of dead space loading on neuro-muscular and neuro-ventilatory coupling of the respiratory system during exercise in healthy adults: implications for dyspnea and exercise tolerance.* Respir Physiol Neurobiol, 2011. **179**(2-3): p. 219-26.
115. Neder, J.A., et al., *Exercise Ventilatory Inefficiency Adds to Lung Function in Predicting Mortality in COPD.* COPD, 2016: p. 1-9.
116. Schwaiblmair, M., et al., *Ventilatory efficiency testing as prognostic value in patients with pulmonary hypertension.* BMC Pulm Med, 2012. **12**: p. 23.
117. Sue, D.Y., *Excess ventilation during exercise and prognosis in chronic heart failure.* Am J Respir Crit Care Med, 2011. **183**(10): p. 1302-10.
118. Vainshelboim, B., et al., *The Prognostic Role of Ventilatory Inefficiency and Exercise Capacity in Idiopathic Pulmonary Fibrosis.* Respir Care, 2016.
119. Montagna, A. and C. Nosarti, *Socio-Emotional Development Following Very Preterm Birth: Pathways to Psychopathology.* Front Psychol, 2016. **7**: p. 80.