Clinical and Physiological Aspects of Preterm Lung Disease

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Abstract

This thesis explores three aspects of preterm lung disease, with a focus on physiological assessment and outcomes.

Nasal high flow (HF) is widely used in preterm infants, but the optimal approach to weaning HF is unclear. A longitudinal cohort study involving 40 preterm infants was performed exploring changes in diaphragm electrical activity (Edi), an objective measure of respiratory muscle effort, that occur during weaning. HF was weaned according to a standardized protocol, and Edi measured serially. Edi did not change significantly with flow rate reduction steps, but significantly increased when discontinuing HF. This study provides a safe and effective framework for weaning HF in preterm infants, supported by physiological data, and identified Edi as a useful measure of respiratory muscle effort for future study.

Preterm infants requiring ongoing positive pressure support near term are a particularly high-risk subgroup, but little is known about the specific characteristics and outcomes of these infants. A national surveillance study of life-threatening bronchopulmonary dysplasia, defined as need for positive pressure respiratory support or pulmonary vasodilator therapy at ≥38 weeks corrected gestation, was performed via the British Paediatric Surveillance Unit. Significant morbidity and mortality were identified in this group, along with marked variation in practice, particularly in key areas of postnatal steroid use and pulmonary hypertension management.

Longer term, children born preterm have lung function abnormalities and an altered ventilatory response to exercise that persist with age. Expiratory flow limitation leading to dynamic hyperinflation during exercise has been proposed as a contributory mechanism, but this is difficult to assess during standard exercise testing. Optoelectronic plethysmography (OEP) is a motion analysis system that non-invasively tracks changes in thoracoabdominal volumes. A feasibility study was performed in a cohort of school-aged children, demonstrating the ability of OEP to measure ventilatory changes during exercise and directly assess for dynamic hyperinflation.

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I am grateful to Tiny Lives, the Newcastle neonatal unit charity for funding the high flow study, and to the Newcastle Hospitals Charity for their contribution to the optoelectronic plethysmography work.

Finally, I would like to express sincerest thanks to the infants, children and families who took part in the studies, as without them this work would not be possible.

Declaration

I declare that I undertook the work described in this thesis between September 2018 and March 2022. I performed all aspects of study design, data collection, analysis, and interpretation with the exception of the following points described below.

The life-threatening bronchopulmonary dysplasia study was designed by Dr Sundeep Harigopal and Dr Janet Berrington in collaboration with the British Paediatric Surveillance Unit. Standard lung function tests for school aged children in the optoelectronic plethysmography study were undertaken by Ruth Levy. All other work was performed by myself.

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List of Abbreviations

ATS	American Thoracic Society
a.u.c.	Area under curve
aOR	Adjusted odds ratio
BAPM	British Association of Perinatal Medicine
BiPAP	Bilevel positive airway pressure
BPD	Bronchopulmonary dysplasia
BPSU	British Paediatric Surveillance Unit
CGA	Corrected gestational age
CI	Confidence interval
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CP	Cerebral palsy
CPAP	Continuous positive airway pressure
CT	Computerised tomography
DH	Dynamic hyperinflation
DLCO	Diffusing capacity of the lung for carbon monoxide
DOL	Day of life
ECG	Electrocardiogram
Echo	Echocardiogram
ECMO	Extracoporeal membrane oxygenation
Edi	Electrical activity of the diaphragm
EEVab	End-expiratory volume of the abdomen
EEVcw	End expiratory volume of the chest wall
EEVrc	End expiratory volume of the rib cage
EFL	Expiratory flow limitation
EMG	Electromyography
ERS	European Respiratory Society
$FEF_{25-75\%}$	Forced mid-expiratory flow
FeNO	Fraction of exhaled nitric oxide
FEV_1	Forced expiratory volume in 1-second
FiO_2	Fraction of inspired oxygen
FRC	Functional residual capacity

FVC	Forced vital capacity
GA	Gestational age
GI	Gastrointestinal
GP	General practitioner
HFOV	High frequency oscillatory ventilation
IC	Inspiratory capacity
IMV	Intermittent mandatory ventilation
iNO	Inhaled nitric oxide
INSURE	Intubate, surfactant and rapid extubation
IPPV	Intermittent positive pressure ventilation
IQR	Interquartile range
IVH	Intraventricular haemorrhage
KCO	Carbon monoxide transfer coefficient
LISA	Less invasive surfactant administration
LPM	Litres per minute
LTV	Long term ventilation
MIST	Minimally invasive surfactant administration
NAVA	Neurally adjusted ventilatory assist
NC	Nasal cannula
NDI	Neurodevelopmental impairment
NEC	Necrotising enterocolitis
NEX	Nose, earlobe, xiphisternum
NHS	National Health Service
NICHD	National Institute of Child Health and Human Development
NICU	Neonatal intensive care unit
NIH	National Institute of Health
NIPPV	Nasal intermittent positive pressure ventilation
NNAP	National Neonatal Audit Programme
NNRD	National Neonatal Research Database
O_2	Oxygen
OEP	Optoelectronic plethysmography
OR	Odds ratio
pCO_2	Partial pressure of carbon dioxide

PCR	Polymerase chain reaction
PDA	Patent ductus arteriosus
PEG	Percutaneous endoscopic gastrostomy
PICU	Paediatric intensive care unit
PIE	Pulmonary interstitial emphysema
PMA	Postmenstrual age
PN	Postnatal
pO_2	Partial pressure of oxygen
Poes	Oesophageal pressure
PPROM	Preterm, prolonged ruptured membranes
PPV	Positive pressure ventilation
PROP	Prematurity and respiratory outcomes
PTP	Pressure time product
RA	Room air
RCT	Randomised controlled trial
RDS	Respiratory distress syndrome
RIP	Respiratory inductance plethysmography
ROP	Retinopathy of prematurity
RR	Relative risk
RV	Residual volume
SGA	Small for gestational age
TLC	Total lung capacity
UK	United Kingdom
USA	United States of America
V/Q	Ventilation/perfusion
VCO_2	Volume of carbon dioxide
VE	Minute ventilation
VO_2	Volume oxygen
VT	Tidal volume
W	Watts
YPAG-NE	Young Persons Advisory Group - North East

Chapter 1. Introduction

1.1 Preterm lung disease

Preterm birth is common, with over 11% of births occurring at <37 weeks gestation, and is the leading cause of deaths in children under the age of 5 years globally, predominantly due to associated respiratory disease(Blencowe et al., 2012; WHO, 2022). Rates of preterm birth are generally increasing, and infants are being supported from birth at progressively more immature gestations, therefore the burden of preterm lung disease is set to increase(Stoll et al., 2015).

Normal lung development occurs in a tightly regulated sequence, with simultaneous development of the lung parenchyma, vasculature and surrounding structures producing a highly specialised system for gas exchange that allows most infants to transition easily to ex-utero life. Preterm birth disrupts this process and requires gas exchange to occur in a system not intended to do this for several weeks or months. The primary manifestation of this at birth is respiratory distress syndrome (RDS), which is almost universal in the most extremely preterm infants(Stoll et al., 2010). Structural and functional immaturity of the lung and associated vasculature, along with relative surfactant deficiency, impair gas exchange and reduce pulmonary compliance, presenting with clinical signs of respiratory distress and respiratory failure.

The primary aim of respiratory care for preterm infants is to support transition and maximise survival, whilst minimising complications relating to treatment, such as the development of bronchopulmonary dysplasia. It is increasingly recognised that preterm birth does not only impact respiratory health in childhood but has consequences throughout the life course, therefore continued optimisation and improvement of preterm respiratory care is essential(Gough et al., 2012).

1.2 Bronchopulmonary dysplasia

Bronchopulmonary dysplasia was first described in 1967 by Northway *et al* as a condition affecting relatively mature infants with respiratory distress syndrome exposed to aggressive mechanical ventilation, resulting in diffuse airway damage, inflammation, and fibrosis(Northway et al., 1967). The condition described in this paper is largely

unrecognisable in the modern neonatal intensive care unit (NICU) due to improved respiratory care with widespread use of antenatal steroids, exogenous surfactant, and lung-protective ventilation strategies, but with increasing survival of more immature infants a 'new' pattern BPD has evolved.

Today, BPD predominantly affects the most extremely preterm infants, born during a critical phase of lung development and results from a complex interaction of antenatal, postnatal, and genetic stressors on an immature lung. Although primarily a respiratory disorder, BPD has multisystem effects, associated with neurodevelopmental delay, poor growth, pulmonary hypertension, and respiratory morbidity that persist throughout childhood and into adulthood(Islam et al., 2015; Cheong & Doyle, 2019). This section will describe the clinical features, epidemiology, aetiology, and short-term outcomes of BPD.

1.2.1 Defining BPD

The definition of BPD has undergone significant evolution in recent decades, in line with changes in clinical practice (Figure 1.1). BPD is unusual in that it is a diagnosis based on management strategies, namely the need for supplementary oxygen and/or positive pressure support at a set timepoint.

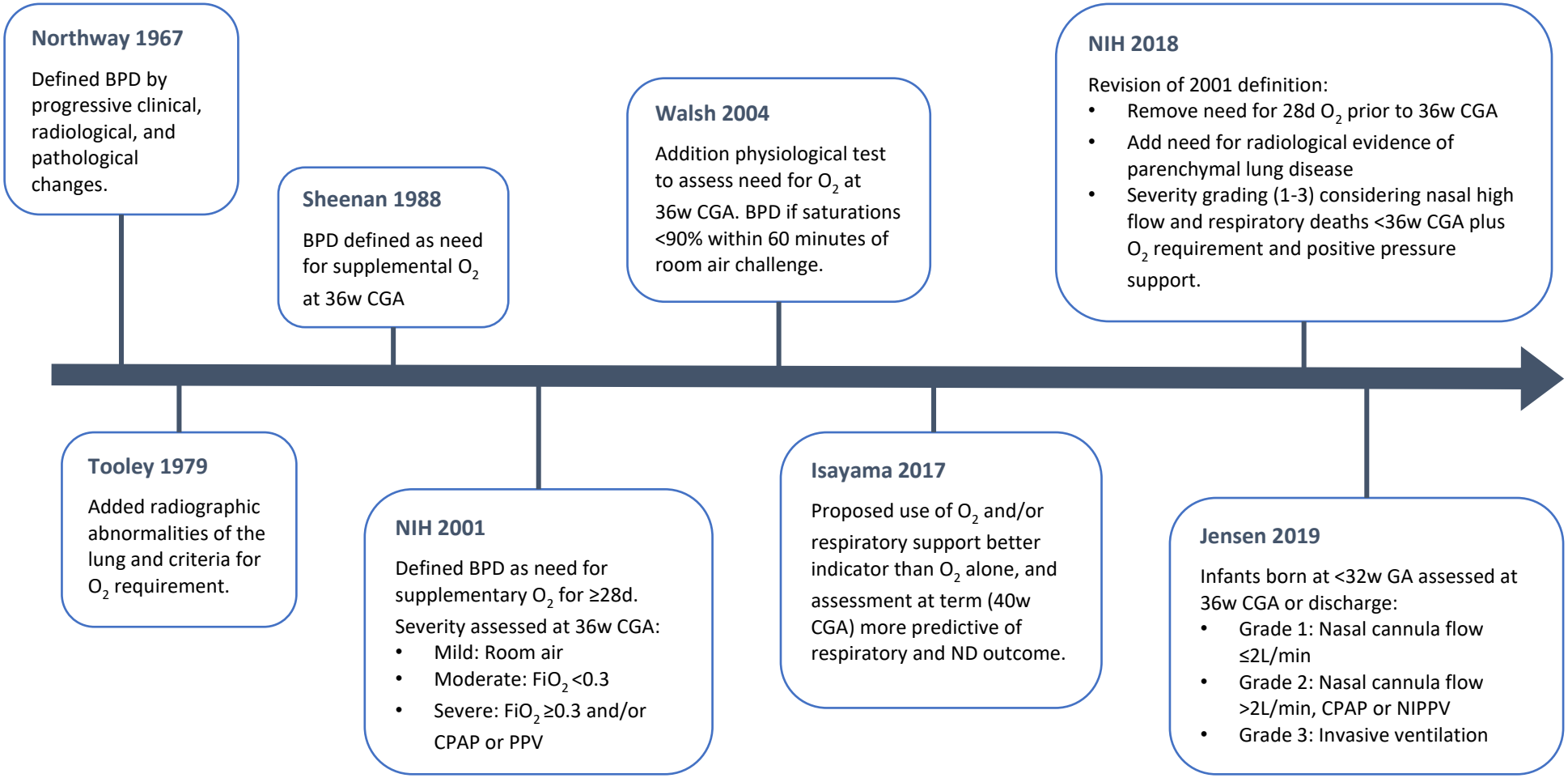

Figure 1.1 Evolution of definitions of bronchopulmonary dysplasia. BPD: Bronchopulmonary dysplasia. O_2: Oxygen. w: Weeks. CGA: Corrected gestational age. d: Days. FiO_2: Fraction of inspired oxygen. NIH: National Institutes of Health. CPAP: Continuous positive airway pressure. PPV: Positive pressure ventilation. ND: Neurodevelopmental. GA: Gestational age. L/min: Litres per minute. NIPPV: Nasal intermittent positive pressure ventilation. Adapted with permission from Gilfillan *et al* 2021.

Currently, the most widely used definition of BPD in the clinical and research setting is the 2001 NIH workshop consensus definition (Table 1.1). BPD is diagnosed if an infant receives at least 28 days of supplementary oxygen, and assessment of respiratory support at 36 weeks corrected gestational age (CGA) determines severity(Jobe & Bancalari, 2001). Although widely cited, the relevance of this to current UK practice is limited: oxygen is generally delivered via nasal cannula at a set flow rate (rather than percentage), there is no standardised approach to assessing need for oxygen, and nasal high flow therapy, now widely used in most neonatal units, is not categorised in this definition. Furthermore, the definition of 'severe' BPD is broad, including infants requiring 31% oxygen via low flow nasal cannula together with those requiring high levels of invasive mechanical ventilation, therefore the predictive value of this classification is limited.

	<32 weeks gestation	**≥ 32 weeks gestation**
Time of assessment	36 weeks CGA or discharge home (whichever first)	>28 days but <56 days postnatal age or discharge home (whichever first)
Treatment with oxygen >21% for at least 28 days plus:		
Mild BPD	Breathing room air	Breathing room air
Moderate BPD	Need for <30% oxygen	Need for <30% oxygen
Severe BPD	Need for ≥30% oxygen and/or positive pressure (PPV or CPAP)	Need for ≥30% oxygen and/or positive pressure (PPV or CPAP)

Table 1.1 The 2001 National Institutes of Health (NIH) consensus definition of bronchopulmonary dysplasia (BPD). CGA: Corrected gestational age. PPV: Positive pressure ventilation. CPAP: Continuous positive airway pressure.

The National Institutes of Health (NIH) definition was updated in 2018 to address some of these challenges (Figure 1.1). This revision takes into account use of nasal high flow therapy, includes the need for radiographic evidence of parenchymal lung disease to differentiate from infants requiring respiratory support for other indications such as problems with control of breathing or upper airway disease, and separately classifies severely affected infants who die from lung disease prior to 36 weeks(Higgins et al., 2018). Although these refinements improve the practical application of this definition, further work is required to assess its ability to predict longer-term outcomes.

The optimal definition of BPD must be pragmatic, easily assessed at the bedside, reflect modern neonatal care, and predict important long-term outcomes. Isayama *et al* investigated the diagnostic criteria and corrected gestational age of assessment with the strongest predictive value for serious respiratory or neurodevelopmental outcome at 18-21 months in infants born at <29 weeks gestation in the Canadian Neonatal Network. Definitions based on need for oxygen and/or respiratory support had a higher predictive value than those based on oxygen alone, and assessment at 40 weeks CGA was the overall best predictor of respiratory and neurosensory morbidity(Isayama et al., 2017).

Similarly, Jensen *et al* assessed the predictive value of 18 classifications of BPD based on mode of respiratory support and/or oxygen requirement for death or serious respiratory morbidity at 2 years using data from infants born at <32 weeks in 18 Neonatal Research Network centres(Jensen et al., 2019). The optimal definition classified BPD according to mode of respiratory support at 36 weeks, irrespective of oxygen requirement (Table 1.2), whilst the definition most similar to the 2001 NIH consensus definition was one of the least accurate predictors of outcome. The markedly increased rate of late death, respiratory morbidity and neurodevelopmental impairment in infants requiring mechanical ventilation at 36 weeks corrected gestational age highlights this as an extremely high-risk subgroup, not discernible using the NIH definition. This is an important definition, as it is easily applicable to clinical practice, has high predictive value taking into account longer-term morbidity and mortality, and has been validated in other populations(Vyas-Read et al., 2021).

	No BPD n=773	Grade 1 n=1038	Grade 2 n=617	Grade 3 n=249
Respiratory support at 36 weeks CGA	In room air	Low flow nasal cannula	High flow nasal cannula or CPAP	Invasive ventilation
Death after 36 weeks PMA	2%	2%	3%	20%
Late death or serious respiratory morbidity	10%	19%	35%	77%
Late death or moderate/ severe NDI	33%	46%	60%	79%

Table 1.2 Optimal definition of bronchopulmonary dysplasia (BPD) and outcomes proposed by Jensen et al. CGA: Corrected gestational age. CPAP: Continuous positive airway pressure. NDI = Neurodevelopmental impairment. Low flow = ≤2L/min; high flow >2L/min.

Despite this, several limitations in the definition of BPD remain. The decision to provide respiratory support is clinician dependent with marked variation in practice, and not simply based on lung disease, as growth, feeding, frequency of apnoea all contribute to decisions regarding respiratory support. Furthermore, assessment based on respiratory support at a set time point results in a dichotomous 'yes/no' outcome to the presence or absence of disease, and classification of severity. In reality, bronchopulmonary dysplasia represents part of the spectrum of preterm lung disease with a continuum of severity, therefore arbitrarily categorising this based on a single assessment may be of limited value. Although BPD is a pragmatic marker of disease severity and prognosis, it does not replace comprehensive clinical assessment and follow-up.

1.2.2 Incidence of BPD

Bronchopulmonary dysplasia is now almost exclusively a disease of very preterm infants, with incidence inversely proportional to gestational age and birth weight. Significant BPD, defined as need for oxygen or respiratory support at 36 weeks corrected gestational age, affects 37% of all infants born at <32 weeks gestation in the UK, although marked variation between centres is evident(*National Neonatal Audit Programme (NNAP) 2020 annual Report on 2019 data. RCPCH; London, 2020*). BPD rates >80% are reported in infants ≤24 weeks gestation but this decreases with increasing gestational age(Costeloe et al., 2012; Siffel et al., 2021). Overall rates of BPD have increased in recent years, a finding widely attributed to

increasing survival of the most immature infants, but the influence of changing patterns of respiratory support and lower use of postnatal steroids is not clear(Stoll et al., 2015).

1.2.3 Pathophysiology of BPD

Bronchopulmonary dysplasia is the result of a pathway of lung injury occurring secondary to preterm birth, which interrupts normal pulmonary and vascular development, and exposes the lung to inflammation and injury (Figure 1.2). The aetiology of BPD is multifactorial with a host of antenatal and postnatal factors modulating the susceptibility of the preterm lung to injury and contributing to the development of BPD, which are discussed in detail in the sections below.

The pathology of BPD is heterogeneous, with imaging studies showing variable areas of hyperinflation, atelectasis, and fibrosis throughout the lung(Higano et al., 2018). This results in abnormal patterns of lung compliance and resistance, ventilation/perfusion mismatch, and intrapulmonary shunting with impaired gas exchange. On histological examination alveolar and pulmonary simplification is evident, reducing the alveolar-capillary surface area available for effective gas exchange, and contributing to the development of pulmonary hypertension(Thébaud et al., 2019).

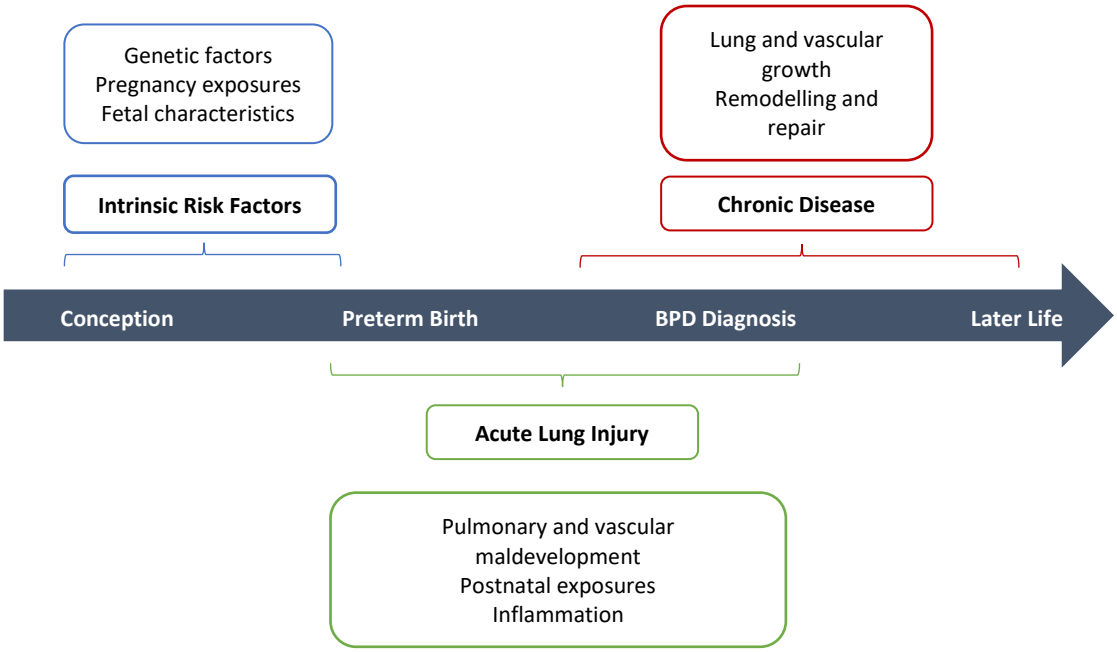

Figure 1.2 Stages and evolution of bronchopulmonary dysplasia (BPD). Antenatal risk factors influence lung development and susceptibility to injury prior to and following preterm birth. Acute lung injury occurs during the neonatal period, leading to chronic disease with remodelling and repair over subsequent years. Adapted with permission from Thébaud *et al* 2019.

1.2.4 Antenatal factors associated with development of BPD

Gestational age and birth weight are two of the strongest predictors of both incidence and severity of BPD. In the National Institute of Child Health and Human Development (NICHD) Neonatal Network, 73% of infants born at 23 weeks gestation developed BPD, of whom 39% had severe disease, whilst at 28 weeks gestation incidence was 23%, only 8% of whom had severe BPD(Stoll et al., 2010). Preterm birth can largely be divided into two main aetiologies: placental insufficiency associated with fetal growth restriction leading to semi-elective, medically indicated delivery, and placental inflammation associated with preterm, prolonged ruptured membranes (PPROM) or chorioamnionitis leading to spontaneous preterm labour. Although both are associated with BPD risk, the pathology and resulting phenotypes differ.

Small for gestational age infants show a 3-fold increase in BPD, along with lower lung function scores at 11 years of age compared to non-growth restricted infants(Bose et al.,

2009; Simpson et al., 2017). Furthermore, hypertensive disorders of pregnancy, particularly maternal pre-eclampsia, are strongly associated with BPD risk, suggesting abnormal placentation and vascular development play a key role. Placental changes consistent with hypoperfusion are more prevalent in extremely preterm infants with BPD, whilst increased placental vessel maldevelopment and lower levels of pro-angiogenic growth factors are found in cord blood of infants who develop BPD-associated pulmonary hypertension(Taglauer et al., 2018). It is therefore likely that factors contributing to abnormal placental vascular development also contribute to the pulmonary vascular abnormalities observed in BPD.

Chorioamnionitis, with associated in-utero inflammation has been variably associated with BPD and RDS risk, but a recent meta-analysis reported a significant positive association between exposure to chorioamnionitis and risk of BPD defined at both 28 days and 36 weeks corrected gestational age (odds ratio 2.32 [1.88-2.86] and 1.29 [1.17-1.42] respectively)(Villamor-Martinez et al., 2019). In this study, infants exposed to chorioamnionitis were born at a significantly lower gestation and birth weight, had higher rates of PPROM, early and late onset sepsis and mortality than non-exposed infants. Covariate analysis confirmed a positive association between chorioamnionitis and BPD, particularly at lower gestational ages and in infants with increased risk of respiratory distress, indicating the complex interplay of these factors. Maternal smoking, another highly pro-inflammatory state, is associated with 2-fold increase in risk of moderate/severe BPD in preterm infants, in addition to longer duration of mechanical ventilation and CPAP requirement, consistent with a role for antenatal inflammation in BPD development(Morrow et al., 2017).

Antenatal steroid administration prior to preterm delivery has been regarded as one of the key advances in perinatal care in recent decades, associated with significant reductions in perinatal and neonatal death, RDS, need for mechanical ventilation, intraventricular haemorrhage (IVH), necrotising enterocolitis (NEC) and early onset infection. Despite the clear respiratory benefits, antenatal steroid use does not appear to reduce rates of BPD, although this may be due to increased survival with antenatal steroid use(Roberts et al., 2017).

1.2.5 Respiratory support and development of BPD

Preterm birth occurs during the late canalicular or early saccular stage of lung development, when alveolarization and surfactant production are just beginning(Joshi & Kotecha, 2007). Extremely preterm infants almost universally develop respiratory distress syndrome requiring respiratory support as gas exchange must occur in a structurally and functionally immature system. The extremely preterm lung is highly susceptible to damage, including volutrauma, barotrauma, atelectotrauma and rheotrauma associated with use of positive pressure respiratory support, and biotrauma associated with supplemental oxygen therapy. Lamb models have shown significant injury can be induced by just a few large volume breaths at delivery, therefore careful use of lung-protective respiratory support strategies is essential(Björklund et al., 1997).

Volume-targeted ventilation significantly reduces the outcome of death or BPD at 36 weeks corrected gestational age in preterm infants compared to traditional pressure-limited ventilation (relative risk 0.73; 95% CI 0.59-0.89), in addition to reducing BPD alone, pneumothorax, significant IVH, and hypocarbia(Klingenberg et al., 2017). Lung compliance changes rapidly during RDS, therefore controlling tidal volume reduces both volutrauma leading to lung damage and BPD, and fluctuations in blood carbon dioxide (CO_2) levels contributing to brain injury, and should be the first-line mode of support when mechanical ventilation is required. High frequency oscillatory ventilation (HFOV) is an alternative ventilatory strategy, in which the lung is held open by a constant distending pressure, and gas exchange occurs using very small tidal volumes delivered at a very high rate. This has the theoretical advantage of avoiding swings in pressure and tidal volume that may cause lung injury. Prophylactic HFOV has been explored as a lung protective strategy in preterm infants, but clear benefits over conventional ventilation have not been shown. On meta-analysis, a small reduction in BPD has been reported with prophylactic use of HFOV (relative risk 0.86; 95% CI 0.78-0.96), but this effect was not consistent and rates of air leak were increased(Cools et al., 2015). Importantly, most studies have compared HFOV to time-cycled, pressure-limited ventilation, rather than modern volume-targeted modes and it is likely the clear benefits of volume-targeted ventilation outweigh this small potential reduction in BPD observed with HFOV.

Duration of invasive ventilation is one of the strongest predictors of BPD and need for home oxygen in preterm infants(Jensen et al., 2015; Dassios et al., 2021). The aetiology of this is likely two-fold, as prolonged duration of ventilation increases exposure of the lung to potential injury from positive pressure support, whilst need for invasive ventilation is a composite marker of risk factors and exposures that independently increase risk of BPD, such as lower gestational age, birth weight and sepsis. Importantly, duration of ventilation is a stronger predictor of BPD than number of ventilation courses, therefore proactive weaning of invasive ventilation and extubation to non-invasive support in a timely manner should be encouraged(Jensen et al., 2015).

Given the risks of mechanical ventilation, avoidance of endotracheal intubation and management with non-invasive support is logical and benefits of this approach are clear. Meta-analysis of three large randomised controlled trials (RCTs) comparing prophylactic CPAP with routine intubation for very preterm infants, showed a significant reduction in death or BPD, BPD alone and need for mechanical ventilation with CPAP(Subramaniam et al., 2016). In these studies, approximately 50% of infants did not require mechanical ventilation highlighting that initial CPAP with rescue intubation and surfactant is likely superior to routine intubation. Nasal high flow has recently been investigated as an alternative mode of primary support for infants with RDS, but two large RCTs and meta-analysis have shown higher rates of treatment failure when compared to CPAP(Roberts et al., 2016; Manley et al., 2019; Conte et al., 2018). Rates of BPD did not differ, but these studies included relatively mature infants where baseline risk of BPD is low, and importantly, no RCTs have assessed use of nasal high flow for primary support in preterm infants born at <28 weeks. Given the advantages of CPAP, namely more consistent distending pressure delivery and reduced rates of treatment failure, use of nasal high flow as primary support for RDS in very preterm infants cannot be recommended(Liew et al., 2020). The physiological effects and clinical role of high flow in preterm infants are discussed further in section 1.3-1.4.

Despite prophylactic non-invasive respiratory support, some infants will inevitably require escalation of treatment and surfactant administration. Traditionally, surfactant administration required intubation and delivery via an endotracheal tube, but in further efforts to reduce exposure to mechanical ventilation, alternative strategies for surfactant delivery have been explored. Intubation, surfactant and rapid extubation (INSURE) reduces the composite outcome of death or BPD, but still requires premedication and a period of

positive pressure ventilation(Isayama et al., 2017). Less or minimally invasive surfactant administration (LISA/MIST) involves surfactant delivery via a thin catheter, while the infant breathes independently on non-invasive support. Network meta-analysis of non-invasive ventilation strategies ranked LISA as the highest probability of being the best strategy, showing lower rates of death or BPD compared to both mechanical ventilation and nasal CPAP, along with reduced rates of BPD alone and severe IVH compared to mechanical ventilation(Isayama et al., 2016). Nebulised surfactant has been explored as a truly non-invasive option for surfactant administration, but clinical trials have yet to show convincing benefit, likely due to inconsistent drug delivery using this approach(Härtel et al., 2021; Dani et al., 2022).

In summary, avoidance of mechanical ventilation with prophylactic CPAP and selective, less invasive surfactant administration should be preferred mode of respiratory support in preterm infants to minimise BPD. Inevitably some infants will still require mechanical ventilation, in which case, a volume-targeted mode should be used.

1.2.6 Oxygen therapy and development of BPD

Supplemental oxygen is widely used in supporting preterm infants after birth, however fetal development usually occurs in a relatively hypoxic *in utero* environment. As a result, preterm birth may create significant oxidative stress for the infant. Administration of high concentrations of oxygen leads to free radical formation, with toxic effects on the newborn lung, brain, eyes, and other organs. Preterm infants seem to be particularly susceptible to oxidative stress due to lack of maternal antioxidant transfer and impaired antioxidant responses, therefore oxygen use must be carefully considered to minimise these complications(Weinberger et al., 2002; Tipple & Ambalavanan, 2019).

The Neonatal Oxygenation Prospective Meta-analysis (NeOProM) collaboration performed an individual patient data meta-analysis of five randomised controlled trials comparing the outcomes of infants randomised to a lower (85-89%) or higher (91-95%) target saturation range(Askie et al., 2018). This large meta-analysis included data from 4965 preterm infants born at <28 weeks gestation. No significant difference in the primary outcome of death or major disability was observed at 18-24 months (RR 1.04 [95% CI, 0.98 to 1.09]), however, infants randomised to the lower saturation target group showed significantly higher rates of

death and severe necrotising enterocolitis. In this study, fewer infants randomised to the lower saturation target group required supplemental oxygen at 36 weeks, which is to be expected given the lower target saturation range, but means fewer infants would be diagnosed with BPD. This highlights the difficulty in defining BPD according to oxygen requirement and in balancing conflicting outcomes, but given the clear increase in death and necrotising enterocolitis observed in the low target group, oxygen target saturations of 91-15% are generally recommended for preterm infants.

Recently, automated oxygen control systems have become available using inbuilt servo-controlled feedback mechanisms to automatically adjust delivered oxygen concentration according to an infant's saturations. A number of small studies have consistently shown that use of automated oxygen control systems increases the proportion of time spent in the target saturation range during both invasive and non-invasive support, but no reduction in BPD has been demonstrated(Nair et al., 2022). This may reflect lack of power due to the small sample size of studies to date, and further large, multi-centre studies to fully explore the clinical utility of this technology is required.

1.2.7 Infection and inflammation in development of BPD

Inflammation is the key common pathway in the pathogenesis of BPD, with initial respiratory support and oxygen causing tissue damage, further exacerbated by other inflammatory exposures such as infection and necrotising enterocolitis. As discussed above, this inflammatory cascade may start in utero with exposure to chorioamnionitis. *Ureaplasma* is a common commensal organism in the urogenital tract, easily transferred from mother to fetus, therefore colonisation is common in preterm infants. Pulmonary colonisation with *Ureaplasma* is significantly associated with BPD in preterm infants, increasing risk >2-fold on meta-analysis (OR 2.22 [95% CI 1.42-3.47])(Lowe et al., 2014). Azithromycin is highly effective against *Ureaplasma*, and has additional anti-inflammatory properties that may modulate the development of BPD(Parnham et al., 2014). A recent meta-analysis of trials addressing the role of azithromycin in reducing bronchopulmonary dysplasia showed significantly lower BPD or death with azithromycin therapy in *Ureaplasma* positive infants, but no difference when all infants combined irrespective of *Ureaplasma* status suggesting risk stratification and targeted therapy may be beneficial(Razak & Alshehri, 2020).

Sepsis and necrotising enterocolitis are common complications of prematurity, associated with systemic inflammation, and widely reported to increase risk of BPD(Klinger et al., 2010; Zozaya et al., 2020). A quality improvement initiative to reduce rates of late onset sepsis in 129 Californian neonatal units was associated with a significant reduction in BPD rates, and in this cohort adjusted hospital rates of BPD correlated positively with rates of late onset sepsis, suggesting this is an important modifiable risk factor(Lapcharoensap et al., 2017). Similarly, a large multicentre cohort study using data from >25,000 infants in the Spanish Neonatal Networks database showed significantly higher rates of BPD in infants with both medically (OR 1.44 [95% CI 1.18-1.77]) and surgically (OR 2.0 [95% CI 1.71-2.33]) managed NEC(Zozaya et al., 2020). NEC typically presents with abdominal distention and multi-organ failure, requiring higher levels of respiratory support which indirectly increases BPD risk; however it is likely that systemic inflammation associated with ischaemia, bacterial translocation and alterations in the microbiome also contribute directly to lung inflammation and BPD development(Willis & Ambalavanan, 2021).

1.2.8 Postnatal corticosteroids in BPD

Given the key role of inflammation in development of BPD, postnatal corticosteroids are a logical strategy for prevention and treatment of BPD, although concerns regarding neurodevelopmental impairment and increased rates of cerebral palsy (CP) following steroid exposure have significantly reduced use in recent decades(Stoll et al., 2015). It is now apparent that steroids do have a role in prevention and treatment of BPD, but identifying the optimal treatment strategy and targeting the infants most likely to benefit is key(Doyle et al., 2014). Early use of dexamethasone (≤7 days of age) significantly reduces BPD, but does not improve mortality and is associated with significant side effects including increased gastrointestinal (GI) perforation and increased risk of cerebral palsy, therefore is not recommended(Doyle et al., 2021a). In contrast, late dexamethasone (>7 days of age) use shows clear respiratory benefits including lower rates of death or BPD, BPD alone and home oxygen use. Short term side effects include hyperglycaemia, hypertension and increased severe retinopathy of prematurity (ROP) but not blindness, but importantly there is no increase in adverse neurological outcomes at follow-up(Doyle et al., 2021b). Despite this, the optimal timing, dosing, and regime of steroid remain unclear. A recent network meta-analysis comparing postnatal steroid regimes identified moderately early (8-14 days), medium cumulative dose (2-4mg/kg) dexamethasone as the regime most likely to reduce

BPD, although the overall quality of the evidence included was low(Ramaswamy et al., 2021).

Early hydrocortisone has recently become a promising strategy for prevention of BPD in preterm infants. The PREMILOC study recruited infants born at 24^{+0}-27^{+6} weeks gestation in French NICU's and randomised to 10 days of hydrocortisone or placebo. The hydrocortisone group showed significantly higher survival without BPD, extubation at the end of the treatment period and weaning from oxygen at 36 weeks CGA. Rates of late onset sepsis were higher in the 24-25 week gestation subgroup exposed to hydrocortisone, but there were no significant differences in other side effects including GI perforation, NEC, need for insulin or hypertension(Baud et al., 2016). Importantly, at 2 year follow-up, no significant difference in neurodevelopmental impairment, CP or other major neurological impairment was noted overall, but the 24-25 week subgroup exposed to hydrocortisone showed lower rates of moderate/severe neurodevelopmental impairment or developmental quotient scores <70 than the placebo group(Baud et al., 2017, 2019). Consistent with this, meta-analysis of studies assessing early hydrocortisone for prevention of BPD showed significantly increased BPD-free survival and increased survival without moderate/severe neurodevelopmental impairment. Increased GI perforation with hydrocortisone is a concern and, although not evident in the PREMILOC study, this is evident on meta-analysis. However, all studies that showed an increase in GI perforation with early hydrocortisone used concurrent ibuprofen or indomethacin to treat a patent ductus arteriosus (PDA), and this association is not evident in studies that excluded use(Morris et al., 2019). Given the lack of convincing benefit for routine early closure of the PDA, and the observation that early hydrocortisone use is associated with less need for PDA treatment, it may be appropriate to delay PDA treatment in favour of early hydrocortisone going forward.

Use of hydrocortisone after 7 days of age appears ineffective, with no significant difference in BPD-free survival on meta-analysis(Morris et al., 2019). Inhaled steroids have been investigated, in an attempt to deliver steroid directly to the lung and minimise systemic side-effects. A recent Cochrane review suggested early inhaled steroid use reduced death or BPD at 36 weeks corrected gestational age, however the upper limit of the confidence interval for number needed to benefit is infinity, therefore the clinical relevance of this is unclear(Shah et al., 2017). Furthermore, follow-up of the Neurosis trial, the largest study assessing early inhaled budesonide for prevention of BPD, showed a significantly higher 2-year mortality in

infants exposed to budesonide than controls(Bassler et al., 2018). Although this may be a chance finding, given the lack of convincing benefit, inhaled steroids are not recommended routinely for prevention of BPD. Intratracheal steroids, administered together with surfactant, have shown potential benefit in small studies, and larger multicentre RCT's are underway to assess this further(Yeh et al., 2016). Although topical administration of steroid to target the anti-inflammatory effect on the lung seems logical, it is possible that some of the benefits of systemic steroids are secondary to their glucocorticoid action, with increased blood pressure improving haemodynamic stability and cerebral blood flow, which may limit the effectiveness of targeted steroid delivery.

1.2.9 Role of other respiratory medications in BPD

Respiratory medication use in extremely preterm infants is common but highly variable between centres, largely due to the lack of definitive evidence for most interventions. Caffeine is one of the few medications with clear evidence of benefit with reduced BPD, reduced duration of respiratory support, and improved neurodevelopmental outcomes at 11 years of age(Schmidt et al., 2006; Mürner-Lavanchy et al., 2018). As a result, caffeine use should be universal in neonatal units today.

Diuretics are widely used in BPD to reduce pulmonary oedema which occurs secondary to lung injury with increased capillary permeability, and volume overload associated with a PDA. Both thiazides and furosemide improve pulmonary mechanics in the short term, increasing lung compliance and reducing airway resistance, but there is no evidence of long-term benefit in reducing death or BPD and complications including electrolyte imbalance and nephrocalcinosis are common(Stewart et al., 2011; Stewart & Brion, 2011). Despite this, 58% of infants born at <29 weeks gestation in the multicentre US prematurity and respiratory outcomes (PROP) cohort received diuretics during their neonatal admission(Greenberg et al., 2020). Similarly, inhaled bronchodilators, received by 32% of the PROP cohort, improve lung compliance, tidal volume and reduce airway resistance in BPD, but convincing evidence of clinical benefit is lacking(Ng et al., 2016).

Inhaled nitric oxide (iNO) is a selective pulmonary vasodilator, widely used to improve oxygenation and reduce need for extracorporeal membrane oxygenation (ECMO) in term infants with hypoxic respiratory failure. In addition to its potent vasodilator effects,

laboratory studies have shown iNO reduces inflammation and oxidant stress, whilst increasing lung growth and alveolarisation, leading to investigation of prophylactic iNO to reduce BPD. However, clinical studies and meta-analysis have not shown any improvement in BPD or neurodevelopmental outcomes in preterm infants with routine, prophylactic use of iNO, therefore it is not recommended(Barrington et al., 2017; Kinsella et al., 2016).

1.2.10 Patent ductus arteriosus and development of BPD

Management of the PDA and its role in development of BPD is a controversial, and highly debated topic in neonatology. A PDA is present in up to 70% of infants born at <28 weeks gestation, with spontaneous closure occurring at a median age of 8 days in infants born at 28-29 weeks gestation, and 71 days in infants <26 weeks(Semberova et al., 2017). Figure 1.3 outlines the mechanisms by which a PDA may contribute to the development of BDP. A left to right ductal shunt increases pulmonary blood flow resulting in higher pulmonary arterial and venous pressures and fluid transudation into the interstitium. This, compounded by increased vascular permeability and reduced lymphatic drainage due to pulmonary inflammation, results in pulmonary oedema with reduced lung compliance, ventilation/ perfusion mismatch and hypoxia. As a result, increasing levels of respiratory support and oxygen supplementation are required, inducing further lung damage.

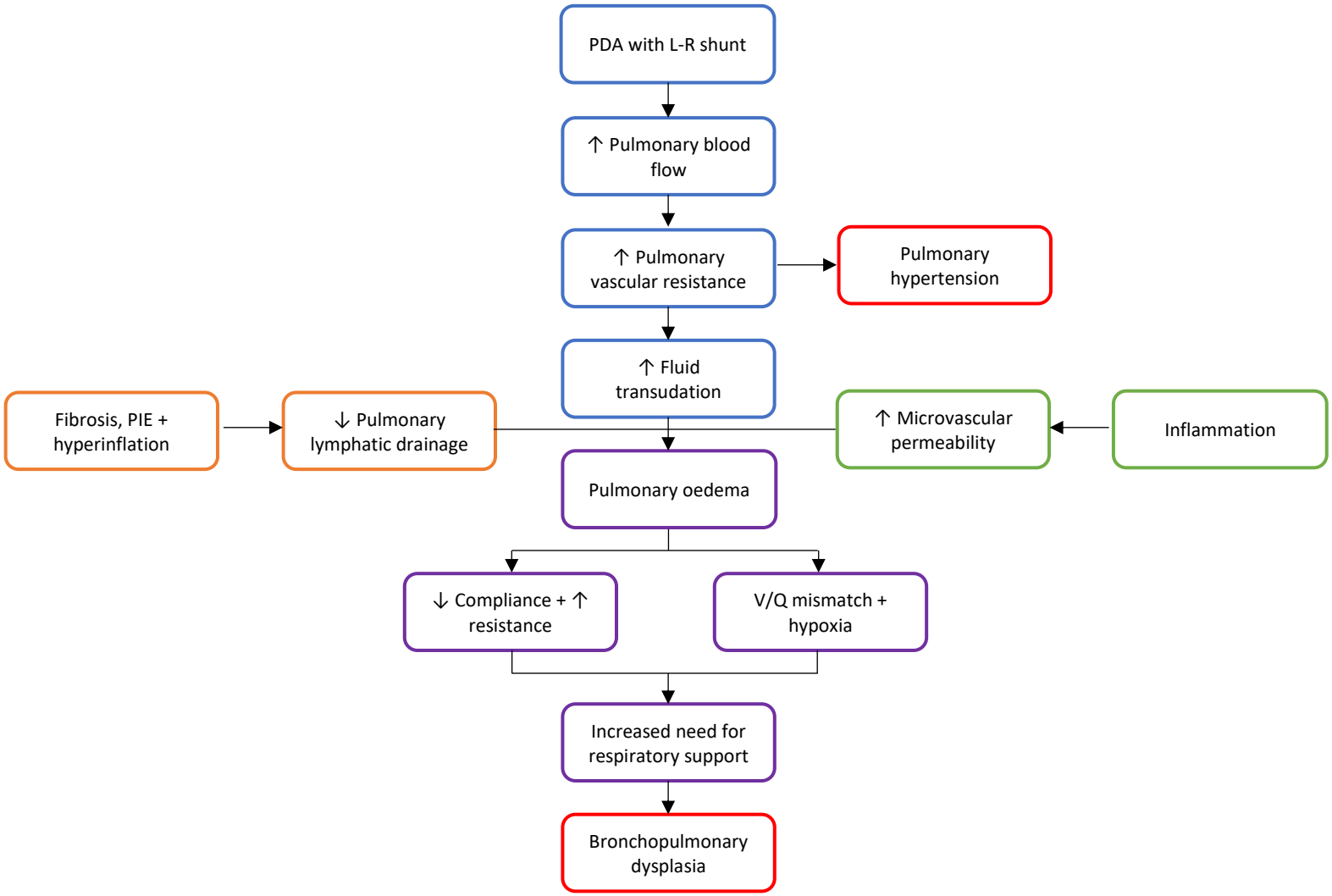

Figure 1.3 Pathophysiology of patent ductus arteriosus (PDA) in development of bronchopulmonary dysplasia. L-R: Left to right. PIE: Pulmonary interstitial emphysema. V/Q: Ventilation/perfusion.

Retrospective, observational studies have suggested an association between the presence of a PDA and BPD. Clyman et al reported in infants born at <28 weeks, presence of a moderate or large PDA at 7 days was associated with a 2-3 fold higher risk of BPD than a small/no PDA, however data from the NICHD network suggested prophylactic treatment does not alter rates of BPD alone or death/BPD(Clyman, 2018; Jensen et al., 2017).

There is currently no convincing evidence from clinical trials that routine, early closure of a PDA is effective at reducing BPD. A recent Cochrane review concluded that although prophylactic ibuprofen reduced the risk of PDA at days 3-4 and need for subsequent medical or surgical treatment, it does not reduce BPD, mortality or IVH. Significant side effects including oliguria and GI bleeding are more common with prophylactic treatment, therefore routine early PDA treatment is not recommended(Ohlsson & Shah, 2020).

Selective closure of haemodynamically significant PDA is likely to be a safer, more effective strategy, although the precise timing and treatment criteria remain unclear. The PDA-TOLERATE trial compared routine treatment of a moderate to large PDA at the end of the first week of life with a conservative approach, only treating if specific haemodynamic or respiratory rescue criteria were met. Median age of PDA closure was 8 days in the routine treatment group and 30 days in the conservative treatment group, but no difference was observed in rates of BPD or death/BPD between groups(Clyman et al., 2019). Trials assessing the clinical impact of PDA treatment are difficult due to high rates of spontaneous ductal closure, variable definitions of haemodynamic significance, and lack of control for confounding factors such as ventilation strategy, positive end expiratory pressure, inotropes and fluid regimens that significantly influence the haemodynamic effect of a duct. Future trials ideally need to address these issues to delineate the true relevance of the PDA to development of BPD and other important neonatal outcomes.

1.2.11 Pulmonary Hypertension in BPD

Abnormalities of pulmonary vascular structure and function are common in BPD, and a subset of infants develop clinical pulmonary hypertension. Incidence of pulmonary hypertension is related to BPD severity affecting just 6% of infants with mild disease, but 39% of those with severe BPD. Pulmonary hypertension can be a late occurrence in BPD, with 65% of cases diagnosed after a normal echocardiogram at 4-6 weeks of age, therefore

routine screening near term is essential to identify and treat this potentially reversible complication. BPD with associated pulmonary hypertension has a mortality rate of 16% pre-discharge and 40% by 2-years of age, highlighting this as an important prognostic factor(Arjaans et al., 2018).

The pathogenesis of pulmonary hypertension in BPD is multifactorial, with abnormal vascular development, vessel remodelling and altered vasoreactivity contributing. Pre-eclampsia and intrauterine growth restriction are associated with increased rates of pulmonary hypertension, even in infants with no or mild BPD, suggesting vascular maldevelopment begins in fetal life in some infants(Berkelhamer et al., 2018). Clinical factors associated with increased risk of pulmonary hypertension in preterm infants include lower gestational age and birth weight, longer duration of respiratory support, infection, NEC and the presence of a PDA(Arjaans et al., 2018). Excessive pulmonary blood flow from a left to right shunt may lead to pulmonary vascular remodelling, whilst lung disease itself may increase pulmonary vascular resistance as hyperinflation and gas trapping overstretch small pulmonary arterioles, atelectasis collapses pulmonary vessels, and hypoxia or hypercarbia induce vasoconstriction(Mourani & Abman, 2015).

Optimisation of respiratory support and elimination of exacerbating factors is therefore first line management of BPD-associated pulmonary hypertension. Home oxygen therapy or long-term ventilation to avoid hypoxia and hypercarbia, treatment of reflux to prevent recurrent micro-aspiration, and addressing any structural airway abnormalities including tracheo- or bronchomalacia, subglottic stenosis or vocal cord anomalies is essential(Hilgendorff et al., 2016). Pulmonary vein stenosis is present in approximately 5% of infants with severe BPD, and contributes to increased pulmonary vascular resistance, therefore anatomical cardiovascular abnormalities should be looked for and addressed(Swier et al., 2016). Diuretic therapy preferentially using spironolactone and a thiazide is recommended if evidence of volume overloaded, as the mineralocorticoid effects of spironolactone may have additional benefits in the presence of right ventricular hypertrophy and pulmonary hypertension.

If pulmonary hypertension persists despite optimal respiratory management, pulmonary vasodilator therapy may be required. Sildenafil is the most widely used drug in infants, although there is little evidence to guide therapy. Small retrospective case series suggest a reduction in pulmonary hypertension and improved right ventricular function with sildenafil,

although this data is limited(Mourani et al., 2009; Kadmon et al., 2017). Given its ease of administration, good tolerance, and lack of evidence for alternative therapies, oral sildenafil is recommended as the first line pulmonary vasodilator for BPD-associated pulmonary hypertension.

1.2.12 Short-term outcomes of BPD

Although the majority of infants are weaned off positive pressure respiratory support prior to discharge, need for home oxygen post-discharge is common. In a population-based study of infants born at <28 weeks from 2014-2018 in the United Kingdom, 3,477 infants (29.4% of total) were discharged on home oxygen(Dassios et al., 2021). This is a significant burden on families and healthcare resources, with infants requiring home oxygen significantly more likely to receive respiratory medications and require re-admission for a respiratory issue post-discharge(Álvarez-Fuente et al., 2017; DeMauro et al., 2019). A smaller number of infants require long-term positive pressure support, with or without a tracheostomy due to BPD. Rates of tracheostomy placement vary widely between centres, and this is generally regarded as a negative outcome due to the high burden of responsibility for families and the association with mortality and neurodevelopmental impairment(Cuevas Guaman et al., 2015; DeMauro et al., 2014). However, it is increasingly recognised that earlier tracheostomy placement in infants with severe BPD may be beneficial, as this is associated with improved growth and short-term development, likely due to more stable positive pressure delivery than with non-invasive interfaces(DeMauro et al., 2014; Luo et al., 2018).

Infants with BPD have a longer initial hospital admission, and are significantly more likely to require readmission for a respiratory illness during the first 2 years of life than those without BPD(Cotten et al., 2005; Ralser et al., 2012). Infant pulmonary function tests consistently show features of airflow obstruction and gas trapping in BPD, however given the technical difficulties performing infant lung function measurements this is generally confined to the research setting therefore the predictive value of this is limited(Islam et al., 2015). Higher rates of significant neurodevelopmental impairment are evident at 2-years of age in children with BPD, particularly in those with severe disease(Malavolti et al., 2018). Furthermore, significantly lower health-related quality of life scores in relation to both physical and psychosocial health have been reported in preterm infants with severe BPD compared to

term and preterm cohorts, highlighting the importance of multidisciplinary follow-up and support post-discharge(Brady et al., 2019).

1.3 Nasal high flow in preterm infants

1.3.1 Delivery of nasal high flow therapy

Historically, nasal CPAP was the principal mode of non-invasive respiratory support in preterm infants used for primary support of respiratory distress syndrome in infants not requiring invasive ventilation and for post-extubation support(Subramaniam et al., 2016; Sweet et al., 2019). CPAP delivers a set distending pressure to the infant via a nasal mask or prongs, which requires a tight seal to ensure adequate pressure delivery. Whilst an effective mode of support, CPAP does have some disadvantages as the interfaces are bulky, require highly skilled nursing care to maintain an adequate seal, and are associated with nasal trauma(Fischer et al., 2010).

In recent years, use of nasal high flow as an alternative mode of non-invasive respiratory support has increased significantly(Shetty, Sundaresan, et al., 2016). Nasal high flow therapy provides heated and humidified gas at flow rates of >1L/min, which is delivered to the infant via loose-fitting nasal prongs(Wilkinson et al., 2016). Flow rates in infants are generally 2-8L/min, and use of blended air and oxygen allows controlled delivery of a target fraction of inspired oxygen. Due to its ease of use, high flow was initially used clinically without good evidence of safety and efficacy, but in recent years a number of physiological studies and several large randomised controlled trials have increased our understanding of the mechanisms of action of high flow in preterm infants and helped refine its role in clinical practice.

1.3.2 Physiological effects of nasal high flow

The mechanism of action of high flow is multifactorial, involving four key aspects: generation of positive distending pressure, washout of the nasopharyngeal dead space, reduced inspiratory resistance, and gas conditioning (Figure 1.4).

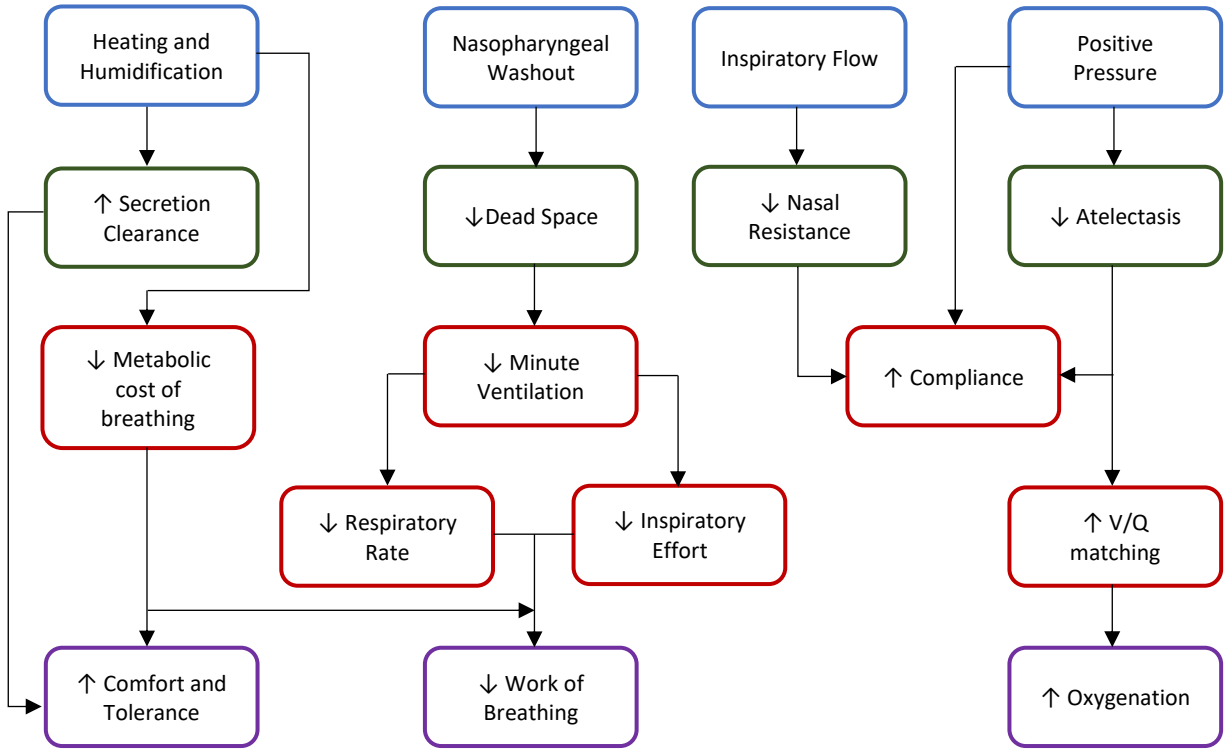

Figure 1.4 Physiological effects of nasal high flow therapy. V/Q = Ventilation perfusion. (Modified from Goligher & Slutsky, 2017).

1.3.3 Positive pressure generation

High flow systems deliver a set gas flow which provides some distending pressure, but unlike CPAP systems, the pressure delivered is not measured or controlled. The positive distending pressure delivered by high flow is linearly related to flow rate, however the absolute pressures generated are highly variable and unpredictable(Wilkinson et al., 2008; Iyer & Mhanna, 2016; Liew et al., 2020).

Wilkinson et al and Liew et al both studied pharyngeal pressure in preterm infants receiving high flow at 2-8L/min, and reported a similar linear increase in pressure generated with increasing flow rate with an average increase of 0.8cmH_2O and 0.6cmH_2O per 1L/min increase in flow rate respectively(Wilkinson et al., 2008; Liew et al., 2020). Significant variation in pressure delivery was observed, particularly at higher flow rates (Figure 1.5). At flow rates >6L/min, pharyngeal pressures ranging from 2.4-13.5cmH_2O and oesophageal pressures from 5-15cmH_2O have been reported(Liew et al., 2020; Iyer & Mhanna, 2016).

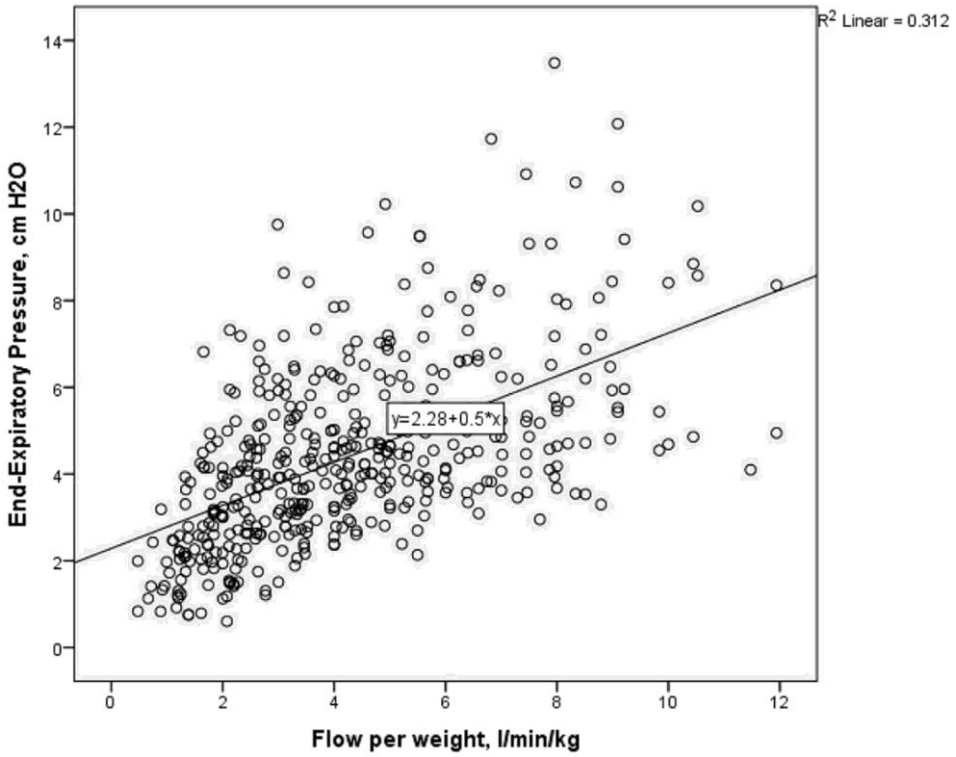

Figure 1.5 Scatterplot showing relationship between measured pharyngeal end-expiratory pressure and flow weight in preterm infants receiving high flow. Figure demonstrates high variation in delivered end-expiratory pressure at flow rates >6L/min/kg(Reproduced with permission: Liew et al., 2020).

Lampland et al similarly measured end-expiratory oesophageal pressure in preterm infants receiving high flow at 1-6L/min. Although delivered pressure did increase with flow rate, huge intra- and inter-individual variation was observed with coefficients of variation of 180% and 1885% respectively(Lampland et al., 2009).

The positive pressure generated by high flow is influenced by infant weight, showing a negative correlation such that generated pressure is higher in smaller infants at all flow rates. Wilkinson reported an average 1.4cmH_2O reduction in pharyngeal pressure per 1kg increase in infant weight, whilst Liew reported an average reduction of 0.7cmH_2O/kg(Wilkinson et al., 2008; Liew et al., 2020). In clinical practice, weight-adjusted flow rates are not routinely considered in neonatology, but potentially an important source of variation in the distending pressure delivered, and clinical efficacy of high flow observed.

Unlike CPAP, which requires a tight seal at the patient interface creating a close system, high flow is an open system with a variable degree of leak around the nasal prongs which also influences pressure delivery. In a simulated model, Sivieri demonstrated that with the mouth open, increasing the nare: prong ratio was associated with an increase in airway pressure, generating dangerously high pressures of up to 24cmH_2O at 6L/min flow with nare: prong ratio >0.9(Sivieri et al., 2013). Similarly, in a lung injury model using newborn piglet lungs injured with oleic acid, Frizzola recorded significantly higher tracheal pressures when nasal prongs occluded the nares than with a leak(Frizzola et al., 2011). In preterm infants, Locke et al found no change in oesophageal pressure with 2mm nasal prongs, but a linear increase in oesophageal pressure with increasing flow rate when 3mm nasal prongs were used(Locke et al., 1993). It is currently recommended that nasal cannula occlude <50% of the nostril to avoid excessive pressure generation and allow sufficient egress of gas(Roehr et al., 2016). Notably, many studies exploring pressure generation with high flow did not match prong size to the infant which may account for some of the marked variation in pressure delivery observed.

Mouth position is another factor that influences ‘leak’ in the system, therefore may influence distending pressure generated. Consistent with this, Kubicka found that in infants receiving high flow at 1-5L/min, no pressure was generated with the mouth open at any flow rate, but a linear relationship between flow rate and maximum oral cavity pressure was observed in infants ≤1500g when the mouth was closed(Kubicka et al., 2008). Similarly, Liew

et al studied pharyngeal pressure generated in 44 preterm infants receiving high flow at 2-8L/min, and found delivered end expiratory pressure was significantly higher with the mouth closed at all flow rates (difference 0.2-2.3cmH_2O at flow rates of 2-8L/min)(Liew et al., 2020). In clinical practice, mouth position is not controlled in infants receiving high flow, contributing to the high variability in positive pressures generated and effectiveness of high flow support.

In summary, the pressure delivered by high flow increases with flow rate, but varies considerably within and between individuals due to the effect of infant weight and varying leak at the mouth and nose. It is not possible to measure or control the pressure delivered by high flow in clinical practice, therefore clinicians must be aware of the potential for dangerously high pressure generation, particularly in the smallest infants.

1.3.4 Washout of nasopharyngeal dead space

The anatomical dead space is the volume of gas between the nasal cavity and the terminal bronchioles, containing end-expiratory gas with a higher concentration of CO_2 and lower concentration of O_2 than inspired air. This reduces the efficiency of gas exchange as it is drawn into the lungs in advance of fresh gas, particularly in infants where the dead space to tidal volume ratio is high. Washout of the nasopharynx by high flow may reduce this dead space and improve gas exchange by reducing residual CO_2 and allowing a larger proportion of the minute ventilation to reach the alveoli to participate in gas exchange.

In a lung injury animal model, high flow delivered at 2-8L/min improved gas exchange and lowered arterial CO_2 independently of changes in airway pressure and minute ventilation suggesting an important role for this washout mechanism(Frizzola et al., 2011). Similarly, in a 3D-printed infant airway model, increased CO_2 washout with increasing flow rate was observed, and a single cannula high flow system produced greater CO_2 washout despite lower airway pressures than a dual prong system at all flow rates, likely due to increased washout with greater leak(Nieves et al., 2019).

This washout mechanism was clearly demonstrated by Liew et al who measured nasopharyngeal end-expiratory CO_2 concentration in infants receiving nasal high flow therapy at 2-8L/min. A strong, negative correlation between end-expiratory CO_2 and weight-adjusted flow rate was observed, and end-expiratory CO_2 was lower when the mouth was

open than closed(Liew et al., 2020). This is consistent with the findings of simulated models, suggesting leak is important to this washout effect, and the oral route may provide an easier pathway for this to occur(Sivieri et al., 2017).

1.3.5 Reduced upper airway resistance

The large surface area of the nasopharynx facilitates humidification and warming of inspired gas, but may result in significant resistance to gas flow, increasing work of breathing. During high flow therapy, gas is provided at, or above, the peak inspiratory flow rate of the patient, which may help overcome this resistance and reduce work of breathing(Dysart et al., 2009). This effect is difficult to quantify as an infant's work of breathing is dependent on multiple factors, therefore there is little in vivo data specifically supporting this mechanism of action in preterm infants. Salsow et al reported no difference in work of breathing between CPAP 6cmH_2O and HF at 3-5L/min, despite lower oesophageal pressures with high flow, suggesting that a mechanism other than distending pressure affects work of breathing on high flow therapy(Saslow et al., 2006). Nasal high flow therapy has been shown to reduce peak electrical activity of the diaphragm, which reflects inspiratory effort, but not the minimum electrical activity of the diaphragm during expiration, which is influenced by positive end-expiratory pressure, supporting reduced inspiratory resistance as a key mechanism of action(Oda et al., 2019).

1.3.6 Gas conditioning

Heating and humidification of inspired gases is a normal function of the nasal mucosa but is associated with energy consumption and evaporative heat loss, providing an additional metabolic burden to preterm infants. Delivery of unconditioned, dry may result in mucosal injury, with thicker secretions and impaired mucociliary function increasing risk of infection, and impaired respiratory function with reduced pulmonary compliance and functional residual capacity(Kopelman & Holbert, 2003; Roberts & Hodgson, 2017). Woodhead et al randomised 30 preterm infants to receive heated and humidified high flow therapy or unheated, unhumidified 'high flow' via standard nasal cannula post-extubation. Infants randomised to heated and humidified high flow showed lower respiratory distress scores, less nasal mucosal damage, and significantly lower rates of treatment failure (0/15

compared to 7/15), clearly showing the clinical benefit of optimal gas conditioning with high flow therapy(Woodhead et al., 2006).

1.4 Clinical evidence for use of high flow in preterm infants

1.4.1 Use of high flow for primary support of respiratory distress

There is now clear clinical evidence from several large randomised controlled trials and meta-analyses that use of high flow therapy for primary support of respiratory distress syndrome is associated with significantly higher rates of treatment failure than CPAP, therefore cannot be recommended. The largest study comparing high flow and CPAP exclusively in preterm infants was the HIPSTER trial, an international, multicentre randomised controlled trial involving 564 preterm infants (≥28 weeks gestation), published in 2016(Roberts et al., 2016). Recruitment to this trial was stopped early at the recommendation of the safety monitoring committee due to significantly higher rates of treatment failure in the high flow group (71/278; 25.5%) than the CPAP group (38/286; 13.3%), with a risk difference of 12.3% (95% CI 5.8-18.7). The rate of intubation at 72 hours did not differ between the groups, as infants failing high flow therapy could switch to CPAP as a 'rescue' modality prior to intubation. The same investigators subsequently performed the HUNTER trial, randomising 754 preterm infants (≥31 weeks gestation) in non-tertiary special care nurseries to high flow or CPAP for primary support(Manley et al., 2019). This was a more mature group of infants with a mean gestational age of 36.9 weeks and birth weight of 2.9kg, but similarly showed significantly higher rates of treatment failure with high flow (risk difference 10.3% [95% CI 5.2-15.5]). In contrast, Lavizzari *et al* randomised 316 infants 29-36^{+6} weeks gestation with respiratory distress syndrome to either high flow or CPAP for primary support, and reported no difference in the primary outcome of treatment failure(Lavizzari et al., 2016). However, in this single-centre study, INSURE (intubate, surfactant administration and rapid extubation) was widely used such that >40% of infants in each group received surfactant, limiting the generalisability of this study.

A recent systematic review and meta-analysis involving data from 1830 infants in 10 different studies, showed an overall 34% increase in risk of treatment failure with high flow compared to CPAP (relative risk 1.34 (95% CI 1.01-1.68), with no influence of gestational age, birth weight, high flow rate, type of CPAP generator or use of surfactant on meta-

regression(Bruet et al., 2022). It is important to note that very few infants <28 weeks gestation were included in this analysis, as they are excluded from most studies, therefore data on this vulnerable group is extremely limited and use of high flow for primary support should be avoided. Interestingly, the authors of this review concluded that, as intubation rates are not different with use of rescue CPAP and high flow is associated with less nasal trauma, high flow should be used for primary support of RDS. Given the clear increase in treatment failure associated with a period of physiological instability in preterm infants, vulnerable to the effects of de-recruitment, atelectotrauma and fluctuations in O_2/CO_2, plus the additional cost of switching devices, caution is required in applying this approach in clinical practice. Consistent with this, national and international guidelines continue to recommend CPAP as first line respiratory support for respiratory distress syndrome(National Institute for Health and Care Excellence., 2019; Sweet et al., 2019).

1.4.2 Use of high flow for post-extubation support

A Cochrane review published in 2016 included data from over 900 preterm infants in 6 randomised controlled trials and showed no difference in overall rates of treatment failure, reintubation, death or bronchopulmonary dysplasia, but lower rates of nasal trauma with use of high flow compared to CPAP. The authors concluded that high flow is a safe alternative to CPAP in this situation, however, as for trials of primary support, the number of extremely preterm infants <28 weeks included in these studies was very limited. The largest study comparing CPAP and high flow for post-extubation support to date was performed by Manley et al in three Australian neonatal intensive care units and included 303 very preterm infants (<32 weeks gestation). Although no statistically significant difference in treatment failure rate was observed in this study overall (risk difference 8.4% [95% CI -1.9-18.7%]), in the small subgroup of infants <26 weeks included (63 infants), treatment failure rates markedly higher using high flow, with a 20% risk difference in favour of CPAP.

In a more recent study comparing high flow with CPAP or non-invasive positive pressure ventilation (NIPPV) in 372 infants born at <34 weeks showed significantly higher rates of treatment failure in the high flow group (overall risk difference 14.9% [95% CI 6.2-23.3]), with lower corrected gestational age at the start of treatment independently associated with high flow failure. This study differs in that NIPPV was permitted in the comparison group, limiting its generalisability as this mode of support is not available in all units, however it

supports the finding that likelihood of success of high flow is dependent on gestational age. As a result, high flow cannot be recommended as first line respiratory support post-extubation in extremely preterm infants, but may be considered in more mature infants.

1.4.3 Use of high flow as a weaning modality

High flow may also be used as a weaning modality, to transition convalescing infants from CPAP. This practice is based on the belief that high flow is a step down from CPAP in degree of respiratory support delivered, and these infants will benefit from the smaller nasal prongs and less invasive interface than CPAP. There are limited trial data assessing the efficacy of high flow for this indication, and the few published studies available show conflicting results, likely due to differences in study population and design.

Abdel-Hady et al randomised 60 preterm infants born at ≥28 weeks, stable on CPAP 5cmH_2O to wean directly from CPAP or transition to high flow for weaning. Infants that received high flow had a longer duration of oxygen therapy (median 14 v 5 days) and respiratory support (median 18 v 10.5 days) than those weaned directly from CPAP (Abdel-Hady et al., 2011). In contrast, Badiee et al reported a significantly shorter duration of oxygen therapy (mean 20.6 v 49.6 hours) and hospital stay (11.3 v 14.8 days) in a study of 88 preterm infants randomised to high flow for weaning(Badiee et al., 2015). The marked difference in average duration of oxygen therapy between these studies suggest the populations and/or weaning protocols are not comparable, and their relevance to current clinical practice is limited, as both excluded infants born at <28 weeks gestation, and used maximal high flow rates of 2L/min which is not consistent with current practice. These limitations were addressed in a study by Soonsawad et al, who randomised 101 infants born at <32 weeks, stable on CPAP 6cmH_2O to wean directly from CPAP or to transition to high flow (4-6L/min according to weight) for weaning. No difference in the primary outcome of time to wean from respiratory support was reported in this study (median 11 days in both groups), but significantly less nasal trauma occurred in the high flow group.

A recent systematic review and meta-analysis of strategies for withdrawal of CPAP reported a stepdown strategy to high flow resulted in an almost 3-week reduction in duration of CPAP, but was associated with a significantly longer duration of oxygen supplementation (median difference 7.8 days [95% CI 5.31-10.28]) than directly discontinuing CPAP(Van Delft

et al., 2020). It is unclear whether this reflects differences in the respiratory support provided, as it is feasible that the unstable positive pressure delivered by high flow may result in periods of barotrauma and/or atelectotrauma, contributing to lung disease, or differences in weaning strategy, as optimal high flow weaning strategies are not clear and an area for future study.

1.4.4 Advantages of high flow use in preterm infants

The main driver in the rapid increase in use of high flow in preterm infants is its ease of use and perception of increased comfort and tolerance by infants, making it popular with clinical staff and parents. This is clearly evident in UK national survey data where clinicians report a clear preference for high flow with regards to infant comfort, access to the infant, ease of skin to skin care, and to facilitate oral feeding(Shetty, Sundaresan, et al., 2016). Although expert clinician experience is important, much of this is anecdotal and not supported by trial evidence.

Using an objective neonatal pain and discomfort scale, Klingenberg et al showed no difference in patient comfort in preterm infants receiving CPAP or high flow, whilst Osman et al reported higher pain scores and higher salivary cortisol levels, a marker of pain and stress, in infants receiving CPAP than those receiving high flow(Klingenberg et al., 2014; Osman et al., 2015). These differences are likely due to use of different pain scores, and the difficulty in objectively assessing comfort in preterm infants but importantly, on parental assessment infant satisfaction was rated significantly higher with high flow than CPAP(Klingenberg et al., 2014).

A retrospective, observational cohort study by Shetty et al reported earlier attainment of full oral feeds in infants requiring respiratory support beyond 34 weeks corrected gestational age who received high flow compared to those who remained on CPAP(Shetty, Hunt, et al., 2016). However, due to the retrospective nature of this study, differences in the study population and approach to feeding contribute to this observation, as infants were not offered oral feeds on CPAP. One small single centre randomised controlled trial has specifically assessed the duration to reach full oral feeds in infants receiving high flow or CPAP. In this study of 44 infants requiring respiratory support beyond 32 weeks corrected gestation, average time to reach full oral feeds was not different between the groups

suggesting that oral feeding on CPAP is feasible and transitioning to high flow does not expedite this(Glackin et al., 2017).

One clear advantage of high flow, shown consistently across clinical trials, is reduced rates of nasal trauma compared to CPAP. Although this is generally reported as a secondary outcome, and classification systems for nasal trauma differ, this benefit is reproducibly shown. A recent meta-analysis of seven studies showed that high flow was associated with a significantly reduced rate of nasal trauma compared to CPAP with a risk ratio 0.46 (95% CI 0.37-0.58; number needed to treat 7)(Imbulana et al., 2018).

1.4.5 Disadvantages of high flow use in preterm infants

As discussed above, a major concern with the use of high flow is uncontrolled and unregulated pressure generation, with the potential to generate high airway pressures, particularly in the smallest infants. Case reports of infants with air leak syndromes added to this concern, however data from randomised controlled trials is reassuring with no evidence of pneumothorax risk with high flow(Hegde & Prodhan, 2013; Iglesias-Deus et al., 2017; Wilkinson et al., 2016).

A number of retrospective studies have raised concerns about the impact of high flow on respiratory outcomes, particularly associating the introduction of high flow with a longer duration of respiratory support and increased rates of BPD(Hoffman et al., 2016; Taha et al., 2016; Sand et al., 2022). However, differences in infant characteristics and changes in practice between study periods make it difficult to draw definitive conclusions from this data. It is possible that high flow provides less effective respiratory support than CPAP, with variation in distending pressure contributing to further barotrauma, atelectotrauma, and lung damage. However, high flow is commonly used in infants requiring prolonged respiratory support; it is therefore also feasible that infants receiving high flow have the most severe lung disease, necessitating longer support. Alternatively, exposure to prolonged respiratory support may reflect differences in clinicians weaning practice as, due to its perceived comfort and tolerance, there is less drive to wean high flow aggressively. A recent meta-analysis of randomised controlled trials reporting rates of BPD in infants randomised to high flow or CPAP for various indications reported no difference in BPD between groups (relative risk 1.1 [95% CI 0.9-1.34]), but the quality of evidence in this study was low and BPD

reported as secondary outcome in all included studies. No prospective studies have been adequately powered to assess the impact of exposure to high flow on bronchopulmonary dysplasia, and ultimately further work is required to explore this.

1.4.6 Weaning high flow in preterm infants

As discussed above, a large body of clinical evidence has helped to refine the use of high flow in preterm infants, particularly understanding its mechanisms of action and indications for use, however there is little clinical evidence to guide weaning of high flow and marked variation in practice is evident. Excessively slow weaning may contribute to the prolonged duration of respiratory support observed in some retrospective studies of high flow use, in addition to prolonging hospital admissions and healthcare costs, whilst weaning too quickly risks destabilising the infant and worsening their clinical condition(Hoffman et al., 2016; Taha et al., 2016). A Cochrane review published in 2014 aiming to assess strategies for discontinuing high flow in preterm infants found no studies suitable for inclusion, which remains the case to date(Farley et al., 2015).

A UK national survey of high flow practice in 2015 showed clear variation in weaning practice between clinicians, with reported lowest flow rates ranging from 1-4L/min, with no consensus in optimal flow rate change or timing of change(Shetty, Sundaresan, et al., 2016). An expert opinion statement on the use of high flow in preterm infants showed similar variation in opinion, with little agreement in approach to weaning(Yoder et al., 2017). Weaning was typically recommended in decrements of 0.5-1L/min when fraction of inspired oxygen was <0.3-0.35, but there was no consensus on the timing of weaning or the role of other clinical factors such as CO_2 monitoring and clinical examination in indicating readiness to wean. Furthermore, marked variation in opinion on discontinuing high flow was evident, with some investigators discontinuing flow from 4L/min, others from 2L/min and some recommending flow rates as low as 1L/min in extremely low birth weight infants. Trials investigating approaches to discontinuation of high flow therapy in preterm infants were recommended by this group, and this remains an important area for future study.

Protocolisation of weaning has been shown to improve success and reduce length of stay in infants in the paediatric intensive care setting, highlighting the importance of a structured approach to weaning(Petrillo-Albarano et al., 2014; Garcia-Jacques et al., 2017). Abobakr et

al recently explored the impact of a protocol-based strategy for weaning high flow in preterm infants, retrospectively comparing outcomes of infants pre- and post-protocol implementation(Abobakr et al., 2020). This took a fairly cautious approach to weaning, specifying a reduction in flow rate of 1L/min when fraction of inspired oxygen <0.25 and respiratory rate <60/minute. Rates of weaning failure were significantly lower in the protocol group than the non-protocol group (4/53 [7.8%] v 15/51 [28.3%), and time to reach full enteral feeding was shorter, however duration of respiratory support was not different. This supports the benefit of a standardised approach to weaning, but a more proactive approach using more liberal weaning criteria may allow a quicker wean.

1.4.7 Summary of clinical use of high flow in preterm infants

In summary, high flow is a widely used and popular mode of respiratory support in preterm infants due to its ease of use, increased infant comfort and reduced nasal trauma. It is however evident that it not interchangeable with CPAP, and careful consideration of the indication for high flow and infant selection is required. There is very little clinical evidence supporting the use of high flow in extremely preterm infants <28 weeks, therefore it cannot be recommended in this group at present. Further work is required to clarify the impact of exposure to high flow on important respiratory outcomes such as bronchopulmonary dysplasia, and to assess optimal high flow weaning strategies.

1.5 Assessment of work of breathing in preterm infants

1.5.1 Assessment of work of breathing

The term ‘work’ technically refers to a force applied over a distance, or in respiratory physiology, a pressure changing a volume. This is calculated as the integral of the pressure-volume curve, and is represented graphically by the Campbell diagram(Cabello & Mancebo, 2006). However, this does not necessarily reflect the overall energy consumption of breathing as measurement relies on volume displacement therefore does not take into account isometric muscle contraction, or the duration of contraction. The term ‘work of breathing’ is therefore generally used to refer to a broader concept of respiratory muscle effort, and will be used in this way throughout this thesis.

The aim of any form of respiratory support is to share the effort of breathing with the patient, until they recover and are able to perform this independently. Titration and weaning of respiratory support in preterm infants generally rely on clinical examination and observation to assess effort and efficacy of breathing, however this is subjective and provides little information regarding the metabolic work of breathing. Whilst excessive patient effort with under-support may be detrimental, increasing metabolic demands of the infant and potentially aggravating lung injury, over-support and suppression of a patient's own respiratory drive may also be harmful(Yoshida et al., 2013). Ventilator induced lung injury is well established complication of positive pressure ventilation in preterm infants, secondary to the effects of volutrauma, barotrauma and rheotrauma, however diaphragm atrophy and dysfunction can also occur, even with short-term use(Knisely et al., 1988; Powers et al., 2009). Spontaneous breathing during mechanical ventilation reduces diaphragm dysfunction and lung inflammation, but increases ventilation homogeneity and weaning success therefore maintaining an optimum level of intrinsic respiratory muscle effort is beneficial(Jaber et al., 2011; Mauri et al., 2013).

An objective measure of breathing effort may allow better titration of respiratory support to ensure the optimal balance between unloading of the respiratory muscles whilst allowing some patient effort is achieved. The two most widely used techniques to objectively quantify work of breathing, namely oesophageal pressure measurement and diaphragmatic electromyography, will be discussed below.

1.5.2 Oesophageal pressure measurement

During inspiration, contraction of the respiratory muscles generates a negative intrathoracic pressure, which is the driving force for inspiration. It is not possible to directly measure changes in pleural pressure during spontaneous breathing, however it is well-established that changes in oesophageal pressure correlate closely with changes in pleural pressure, therefore can be used as a surrogate(Mauri et al., 2016). Oesophageal pressure (Poes) is generally regarded as the gold-standard reference technique for measuring respiratory muscle effort, and can be measured using an air or water filled catheter, a specific balloon, or a catheter with an integrated pressure transducer.

Although changes in oesophageal and pleural pressure are closely matched during inspiration, absolute values of Poes are influenced by posture, lung volume, and other external factors, therefore do not necessarily match absolute pleural pressures(Pasticci et al., 2020). The agreement between pleural pressure and oesophageal pressure can be assessed using the occlusion technique. During this manoeuvre, change in airway pressure and change in oesophageal pressure are measured during an occluded inspiration. As there is no change in lung volume (hence no change in pleural pressure) the measured change in airway pressure and oesophageal pressure should be identical(Baydur et al., 1982). This has been performed in preterm neonates, but it is not practical to perform this manoeuvre on infants receiving respiratory support, therefore oesophageal pressure swings rather than absolute values are generally considered(Coates et al., 1989).

Respiratory muscle activity can be further quantified using the pressure time product of the oesophageal pressure (PTPoes). This is the product of the pressure developed by the respiratory muscles multiplied by the time of muscle contraction (i.e., the integral of pressure over time), and may be more representative of overall respiratory muscle effort as it takes into account the duration of contraction. Simultaneous measurement of gastric pressure using a modified balloon or dual-tipped pressure transducer can give additional information on expiratory muscle effort.

1.5.3 Clinical application of oesophageal pressure measurement

Despite the clear relationship between changes in oesophageal pressure and pleural pressure, and the objective information this provides about respiratory muscle effort, this technique is seldom used in clinical practice due to the specialist equipment and skills required. In the research setting, oesophageal pressure measurements have shown potential as a useful tool to guide invasive ventilation, assess readiness for extubation and optimise non-invasive respiratory support in children(Vervenioti et al., 2020; Khemani et al., 2017; Khirani et al., 2013). Titration of non-invasive respiratory support is particularly of interest, as there is little objective data available to guide this, and it is largely based subjective clinical judgement. In a study of 12 infants requiring CPAP for bronchopulmonary dysplasia or severe upper airway obstruction, Khirani *et al* asked clinicians to select a CPAP level setting based on clinical assessment and compared this with a physiological CPAP level based on normalisation or maximal reduction of the oesophageal pressure swing. The mean

physiological CPAP level was 2cmH_2O higher than mean clinical CPAP level, and was associated with significantly greater improvement in oesophageal pressure swing and other indices of respiratory effort(Khirani et al., 2013).

One randomised controlled trial has attempted to compare the outcome of preterm infants receiving 'optimal' non-invasive respiratory support, selected based on the greatest reduction in oesophageal pressure swings, to a control group receiving non-invasive respiratory support based on standard clinical assessment. In this study, although mean oesophageal pressure swing was significantly lower in the 'optimal' support group than the control group, this difference was small and not likely to be clinically relevant as both were within normal ranges. Consistent with this, no difference in respiratory outcomes at 36 weeks was observed between groups(Dudoignon et al., 2021). Although titration of non-invasive respiratory support based on oesophageal pressure measurement was not superior to standard clinical assessment in this group, this was a small study (total 30 participants), involving infants with low levels of respiratory distress, with little difference in work of breathing between modes of support or off respiratory support, therefore there was little potential for improvement. Further work is required to prospectively assess the impact of titration of support based on physiological parameters in a wider group of infants with significant respiratory distress, and potential to benefit from this approach.

1.5.4 Electrical activity of the diaphragm

As the main inspiratory muscle, there has been significant interest in monitoring diaphragm activity as a marker of respiratory muscle effort. During spontaneous breathing, efferent signals from the brainstem respiratory centres travel via the phrenic nerve to the diaphragm, electrically activating diaphragm motor units and causing the muscle to contract. The resulting electromyography signal can be continually monitored using transcutaneous electrodes, or a commercially available modified gastric tube containing an array of electrodes positioned in the lower oesophagus. The maximum electrical activity during inspiration (Edi max) reflects neural inspiratory effort and is responsible for the size of a breath, whilst the minimum electrical activity during expiration (Edi min) reflects the tonic activity required to maintain functional residual capacity and prevent atelectasis. Changes in Edi correlate closely with changes in oesophageal pressure, suggesting this is reliable indicator of respiratory muscle effort, and normal ranges for these values have been

described in both term and preterm infants(Essouri et al., 2019; Stein et al., 2012, 2013). This is an attractive alternative to oesophageal pressure measurement as it is minimally invasive, using skin electrodes or a modified feeding tube, therefore better tolerated and more suitable for clinical use.

1.5.5 Clinical application of diaphragm electrical activity monitoring

A major driver in recent interest in electrical activity of the diaphragm has been the development of neurally adjusted ventilatory assist (NAVA) technology, which uses the Edi signal to directly regulate invasive or non-invasive ventilation. Ventilation with NAVA requires an Edi-capable gastric tube, which connects directly to the ventilator and uses the infant's Edi signal to control ventilation. A breath is initiated when a defined increase in Edi (the Edi trigger) is detected, and positive-pressure delivered in a servo-controlled manner in proportion to the Edi during inspiration. As a result, the infant controls the precise timing, size, and duration of the breath (Figure 1.6). Lower peak inspiratory pressures, improved oxygenation and better synchronisation have been reported with both invasive and non-invasive NAVA compared to conventional modes, but currently evidence of clinical benefit from adequately powered, prospective randomised controlled trials in preterm infants is lacking(Longhini et al., 2015; Kallio et al., 2016; Latremouille et al., 2021).

Figure 1.6 Neurally adjusted ventilatory assist (NAVA) screen showing diaphragm electrical activity (Edi) signal (lower pink trace) and delivery of positive pressure, flow, and volume in synchrony with and proportion to this.

In addition to its application in NAVA, the Edi signal can be used as a standalone marker of respiratory muscle effort and neural respiratory drive. Observational studies have shown CPAP and high flow reduce Edi in preterm infants, and a trend towards increased Edi in infants unsuccessfully weaning off, or transitioning between, non-invasive support modes has been observed(Kraaijenga et al., 2017; Oda et al., 2019; De Waal et al., 2017). This tool may allow real-time, individualised titration of support, although further study is required to prospectively assess the clinical impact of this strategy.

Edi monitoring is an attractive tool to guide extubation readiness, as it provides objective information regarding both respiratory drive and effort. In adults and older children, a greater increase in Edi during a spontaneous breathing test, indicating increased respiratory distress, is associated with extubation failure, although in infants this relationship is less clear(Dres et al., 2012). Wolf et al performed an extubation readiness test in 20 ventilated children, and reported a significantly higher tidal volume to Edi ratio in children passing the test than in those failing the test, suggesting that increased diaphragm activity reflects better preservation of diaphragm function(Wolf et al., 2011). Similarly, Iyer et al measured Edi pre- and post-extubation in 20 preterm infants and found a smaller increase in Edi max and Edi delta (Edi max – Edi min) in infants extubated unsuccessfully than those extubated

successfully(Iyer et al., 2017). This may reflect an inability to increase diaphragm activity to meet demand due to diaphragm dysfunction or inadequate respiratory drive, but highlights that findings in adults and older children may not be transferrable to infants.

In addition to assessment of respiratory effort, Edi monitoring provides useful information regarding neural respiratory drive and control of breathing. Preterm infants show immature control of breathing, with frequent episodes of central apnoea and periodic breathing contributing to desaturation and bradycardia events. Although most apnoeic episodes in preterm infants are central in origin, obstructive apnoea do occur and differentiating these is important as management strategies differ. Edi monitoring clearly identifies central and obstructive apnoea, as during periods of central apnoea diaphragm activity is absent and the Edi signal shows a flat line, whilst during obstructive apnoea the infant attempts to breathe against an occluded airway, therefore diaphragm activity is increased. Edi monitoring is superior to standard cardiorespiratory monitoring, plethysmography, and chest impedance in classification of apnoea, therefore integrating this into monitoring systems may be useful in the future(Kraaijenga et al., 2018). Caffeine administration has been shown to significantly reduce central apnoea and increase both Edi max and Edi min in preterm infants, suggesting its beneficial effect is mediated by increasing both neural respiratory drive and effort(Parikka et al., 2015; Williams et al., 2020). Edi monitoring has also been used to diagnose congenital central hypoventilation syndrome in newborn infants, with periods of absent Edi and increased transcutaneous CO_2 reflecting central apnoea during sleep(Szczapa et al., 2013; Sinclair et al., 2018).

1.5.6 Summary of work of breathing assessment in preterm infants

In summary, objective assessment of respiratory muscle effort using oesophageal pressure or diaphragm electrical activity measurement has the potential to allow personalisation of respiratory support, with optimal titration of support minimising the complications of both over and under-support, and to guide weaning. Oesophageal pressure-based measures are generally regarded as the gold-standard method, but are difficult to perform, limiting application to clinical practice. Electrical activity of the diaphragm is an attractive alternative, as it shows good correlation with oesophageal pressure measurement, but is less invasive and better tolerated, therefore more suitable for clinical practice. The ability of this technology to improve clinical outcomes in preterm infants ultimately requires further study.

1.6 Longer-term respiratory outcomes in children born preterm

1.6.1 Respiratory symptoms

Children born preterm have a higher burden of respiratory symptoms, respiratory medication use and respiratory related hospital admissions in early childhood. This is particularly evident in those with a diagnosis of BPD. In the first year of life, readmission rates of up to 50% are reported for children with a diagnosis of BPD, compared to only 23% of infants of a similar gestational age without BPD, with respiratory infection the most common cause of readmissions(Smith et al., 2004; Ralser et al., 2012). Wheezing, shortness of breath, and nocturnal cough disturbing sleep are all reported more frequently in children with BPD than children born preterm without a history of BPD(Sillers et al., 2020).

At school age, the frequency of respiratory symptoms and readmissions decreases considerably, but remains significantly higher in children born preterm than term-born peers(Kuint et al., 2017). Higher rates of wheeze and asthma diagnosis are consistently reported in preterm cohort studies at school-age(Hennessy et al., 2008; Fawke et al., 2010; Vom Hove et al., 2014; Skromme et al., 2018). A recent meta-analysis of studies exploring the association between preterm birth and wheezing disorders in childhood reported that children born very preterm (<32 weeks) were 3 times more likely to experience wheeze than term-born children(Been et al., 2014). Consistent with this, higher rates of respiratory medication use, particularly inhaled bronchodilators and corticosteroids, are reported in preterm children than term-born children(D'Agostino et al., 2020; Levin et al., 2021).

The impact of a diagnosis of BPD on outcomes in childhood is conflicting, with some studies reporting a higher burden of respiratory disease in those with BPD(Vom Hove et al., 2014), and others no difference between children born preterm with and without a history of BPD(Fawke et al., 2010; Skromme et al., 2018). This likely reflects the limitations of defining BPD, as preterm lung disease is a spectrum of abnormality, with significant overlap between groups, and highlights the need for comprehensive follow-up of all preterm children.

The quality of life of preterm born children, particularly those with BPD is relatively unexplored. In a study of health-related quality of life in children with severe BPD at 18-36 months CGA, parental reported physical and psychological quality of life scores were significantly lower in those with BPD than preterm children without BPD and term

controls(Brady et al., 2019). Interestingly, in a small cohort study of children 11-19 years of age, those with a history of BPD reported similar health-related quality of life as healthy term-born controls, and better health status than controls with a diagnosis of asthma despite significantly lower lung function scores compared to both groups(Bozzetto et al., 2016). This is consistent with the reduction in respiratory symptoms with age and suggests lower lung function does not cause functional limitation in preterm-born children.

1.6.2 Lung function in childhood

Children born preterm show lung function abnormalities, particularly features of airflow limitation and gas exchange abnormalities that persist with age. Spirometry consistently shows an obstructive pattern, with lower forced expiratory volume in 1-second (FEV_1) and forced mid-expiratory flow ($FEF_{25-75\%}$) but a normal forced vital capacity (FVC), most marked in those with a neonatal diagnosis of BPD(Islam et al., 2015). Meta-analysis of studies reporting FEV_1 in school-aged children born preterm in the surfactant era showed average FEV_1 differed from term-born controls by -18.9% (95% CI -21.1 to -12.4%) in children with a diagnosis of BPD at 36 weeks CGA, and -7.2% (95% CI -8.7% to -5.6%) in preterm children without BPD(Kotecha et al., 2013). This clearly demonstrates that although children with BPD have the highest burden of disease, preterm lung disease is a spectrum of abnormality, and all preterm-born children are at risk of long-term consequences.

Reduced expiratory airflow, leading to this obstructive pattern, may be due to reduced respiratory muscle strength, and/or increased airflow resistance secondary to smaller airways or increased bronchial smooth muscle tone. Few studies have assessed respiratory muscle strength in preterm-born children, however no significant differences have been reported(Jacob et al., 1998). Imaging studies have shown smaller distal airways in children born preterm, and structural changes in the airway with wall thickening and smooth muscle hypertrophy have been reported in children with BPD, suggesting increased airflow resistance is responsible for the observed phenotype(Sarria et al., 2012; Tiddens et al., 2008). Many preterm-born children, particularly those with a history of BPD, show a degree of bronchodilator responsiveness(Kotecha et al., 2015). Fawke *et al* performed spirometry pre- and post- salbutamol in 182 children born at <26 weeks gestation and reported a positive bronchodilator response (defined as an increase in FEV_1 >12%) in 32% of children with a history of BPD, compared to only 16% of preterm children without a history of BPD,

and 8% of controls(Fawke et al., 2010). Fraction of exhaled nitric oxide is not different from healthy, term-born controls suggesting airway obstruction in preterm children is not mediated by eosinophilic inflammation, and persisting structural abnormalities are likely to be responsible for this(Course et al., 2019).

Total lung capacity (TLC) and functional residual capacity (FRC) appear near normal in children born preterm, but increased residual volume (RV) and residual volume to total lung capacity ratio (RV/TLC) have been reported in those with BPD, suggestive of ongoing air trapping(Lum et al., 2011; Ronkainen et al., 2015). Impaired gas exchange, with reduced diffusion capacity of the lung for carbon monoxide (DLCO) is frequently reported in preterm-born children, particularly those with BPD, suggesting abnormalities in alveolar and/or pulmonary vascular structure and function persist into childhood(Islam et al., 2015; Ronkainen et al., 2015). These findings are consistent with imaging studies showing areas of emphysema, bronchial wall thickening and hypoattenuation that persist with age, and correlate with severity of lung function abnormalities(Moschino et al., 2021).

1.6.3 Longitudinal changes in lung function

Relatively few contemporary studies have assessed lung function longitudinally in children and adults born preterm, however it is evident these lung function abnormalities are not static but deteriorate with time(Um-Bergström et al., 2017; Simpson et al., 2018; Doyle et al., 2019). Simpson *et al* followed up 200 very preterm children with and without BPD with serial assessments of lung function from 4-12 years of age, and a chest CT at 9-12 years of age. Preterm born children showed lower lung function scores than healthy controls at all time points, and this worsened with age. In children with BPD, FEV_1, FEV_1/FVC and $FEF_{25-75\%}$ all declined by at least 0.1 z-score per year, and DLCO showed a small but statistically significant decline with time. FEV_1/FEV and $FEF_{25-75\%}$ z-scores also decreased over time in preterm children without a diagnosis of BPD, although less rapidly. Increased gestational age and birthweight were associated with improved spirometry z-scores, whereas a more rapid decline was associated with bronchial wall thickening or subpleural opacities on CT and exposure to cigarette smoke, an important modifiable factor(Simpson et al., 2018).

A recent Australian cohort study exploring the outcome of young adults born at <28 weeks or <1000g reported that, at 25 years of age, 1 in 4 preterm-born adults had an FEV_1 <5th

centile and almost half the cohort had $FEF_{25-75\%}$ <5th centile(L. Doyle et al., 2019). Similar patterns of abnormality have been observed in other cohorts, and confirmed on meta-analysis(Caskey et al., 2016; L. W. Doyle et al., 2019). In healthy individuals, lung growth continues into early adulthood, to reach peak lung function in their twenties. Children born preterm clearly do not reach the same physiological peak, therefore this low and early declining, lung function is particularly concerning, suggesting they are at high risk of symptomatic respiratory disease in adulthood (Figure 1.7). Studies of respiratory outcomes in preterm-born adults inevitably reflect neonatal care several decades earlier, therefore ongoing work is required to assess the impact of modern neonatal care and survival at ever lower gestational ages in future cohorts.

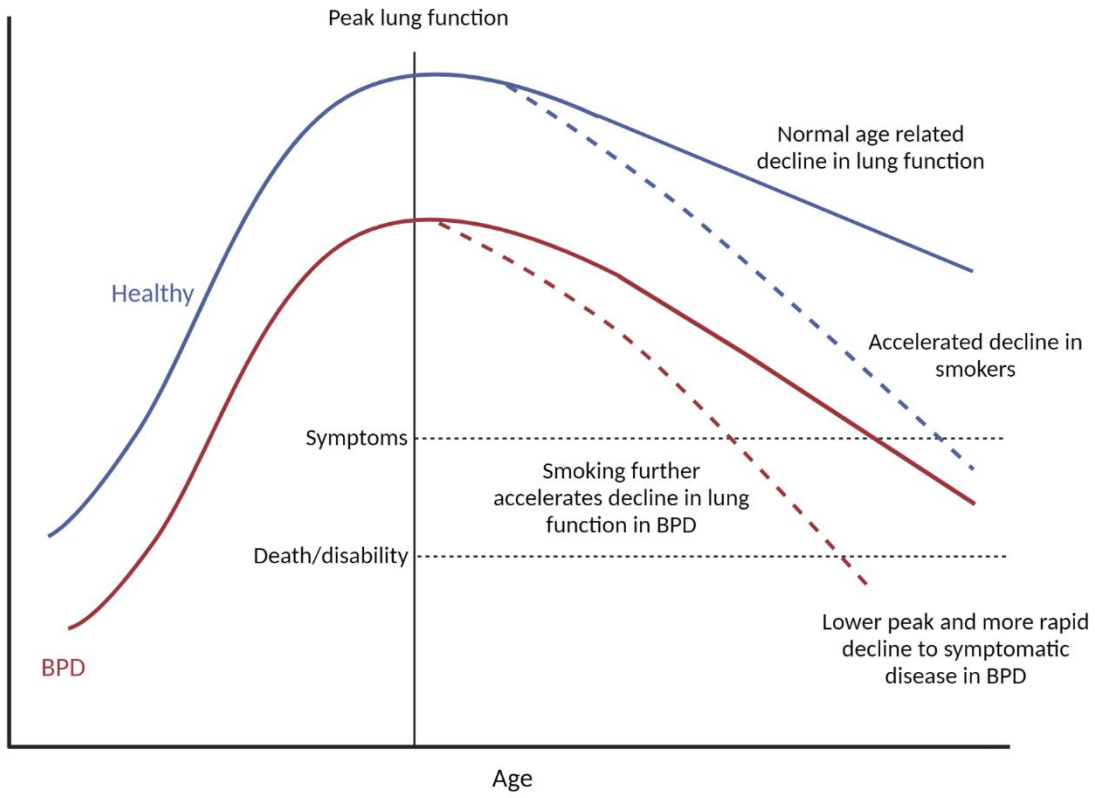

Figure 1.7 Schematic representation of the hypothetical longitudinal change in lung function with age in healthy individuals and those with bronchopulmonary dysplasia (BPD). Adapted from Sillers et al 2020.

1.6.4 Exercise capacity of children born preterm

Preterm birth impacts the respiratory, cardiovascular, and neuromuscular systems, all of which contribute to overall exercise capacity. Oxygen update at maximal exercise (VO_2max) is the gold standard marker of exercise capacity and is influenced by all these systems. Meta-analysis of exercise studies reporting VO_2max showed a small, but statistically significant reduction in VO_2max in all preterm born children compared to healthy controls (mean difference -2.2ml/kg/min [95% CI -3.7 to -0.7]) and those with BPD (mean difference -3.1ml/kg/min [95% CI -5.9 to -0.2]) compared to healthy controls(Edwards et al., 2015). Although the differences reported in this meta-analysis are statistically significant, the functional impact of this is unclear.

Objective assessment of activity levels in preterm-born children using accelerometer data has found little or no difference in baseline activity level between preterm children and controls(Lowe et al., 2016; Welsh et al., 2010; Lowe et al., 2015). However, on self-assessment, preterm children report lower physical activity, exercise capacity and high rates of breathing difficulty during exercise than term-born peers(Welsh et al., 2010; Kilbride et al., 2003; Clemm et al., 2012). Clemm et al assessed physical activity levels, spirometry, and exercise capacity in a cohort of children born at ≤28 weeks at 10- and 18-years of age, compared to term-born controls. Interestingly, in this cohort, VO_2max was not associated with BPD status or FEV_1, but this was positively associated with physical activity level suggesting that they have similar training potential and exercise-based therapy may be beneficial in preterm-born children(Clemm et al., 2015).

1.6.5 Ventilatory response to exercise in preterm children

The ventilatory response to exercise in children born preterm gives insight into the pathophysiology of their ongoing lung disease. Welsh *et al* followed up 38 children born at <26 weeks and found differences in exercise capacity and breathing pattern when compared to healthy term-born children at 11-years of age. The extremely preterm group achieved lower peak workload and a lower VO_2 max during exercise and reached a lower peak minute ventilation (V_E), using a smaller tidal volume (V_T) and a higher respiratory rate than controls(Welsh et al., 2010). Persistent airway obstruction and impaired gas transfer, evidenced by lower FEV_1 and DLCO, were proposed to account for the observed reduction in

VO_2max, whilst increasing respiratory rate rather than tidal volume during exercise may be secondary to an increased dead space to tidal volume ratio, and reduced inspiratory capacity in preterm children.

Similarly, MacLean *et al* performed a peak exercise test using a cycle ergometer in 103 children born extremely preterm at 8-12 years of age. At baseline, preterm children with BPD showed a higher residual volume and residual volume: total lung capacity ratio than term-born controls, indicating increased dead space, and showed an abnormal ventilatory response to exercise with a lower peak minute ventilation and tidal volume than controls. During exercise, children with BPD achieved a lower relative peak VO_2max and showed a higher V_E/VCO_2 slope than healthy controls, which indicates greater ventilatory inefficiency and is consistent with increased dead space ventilation. Although a pulmonary vascular effect cannot be excluded, there were no significant differences in baseline echocardiogram findings between preterm children and healthy controls in this population, suggesting that increased dead space ventilation is responsible for the ventilatory limitation observed(Maclean et al., 2016). Other studies have reported no difference in weight-adjusted minute ventilation and tidal volume in children with BPD compared to controls, although this likely reflects differences in population characteristics and exercise protocols(Prenzel et al., 2020).

1.6.6 Exercise induced bronchoconstriction

Significantly higher rates of exercise induced bronchoconstriction have been reported in children born preterm, particularly those with BPD, compared to healthy term-born controls(Kotecha et al., 2018). Joshi *et al* performed spirometry before and after a maximal exercise test in children 8-12 years of age, and healthy controls. In preterm children with a history of BPD, FEV_1 decreased significantly after exercise (mean change -11%; 95% CI -18 to -4%) and increased significantly after salbutamol (mean change +16%; 95% CI 9 to 23%), whilst in preterm children without BPD and term-born controls more modest changes of <8% were observed. Interestingly, in this cohort, only 10% of children with BPD were receiving bronchodilator treatment, suggesting potential undertreatment of bronchodilator responsive lung disease in this population(Joshi et al., 2013).

1.6.7 Expiratory flow limitation during exercise in children born preterm

The altered breathing pattern observed in preterm-born children during exercise suggests the presence of a mechanical ventilatory constraint limiting exercise capacity. Expiratory flow limitation (EFL) is a feature of obstructive airway disease and occurs when maximal expiratory flow is achieved during tidal breathing(Calverley & Koulouris, 2005). EFL may cause a progressive increase in end-expiratory lung volume, resulting in dynamic hyperinflation, with a corresponding reduction in inspiratory reserve volume and inspiratory capacity (Figure 1.8). This limits the ability to increase tidal volume with exercise and generates intrinsic positive end-expiratory pressure, resulting in functional impairment of the respiratory muscles, increased work of breathing and adverse haemodynamic effects which contribute to the sensation of dyspnoea(Soffler et al., 2017). The mechanisms by which expiratory flow limitation and dynamic hyperinflation cause dyspnoea are summarised in Figure 1.9.

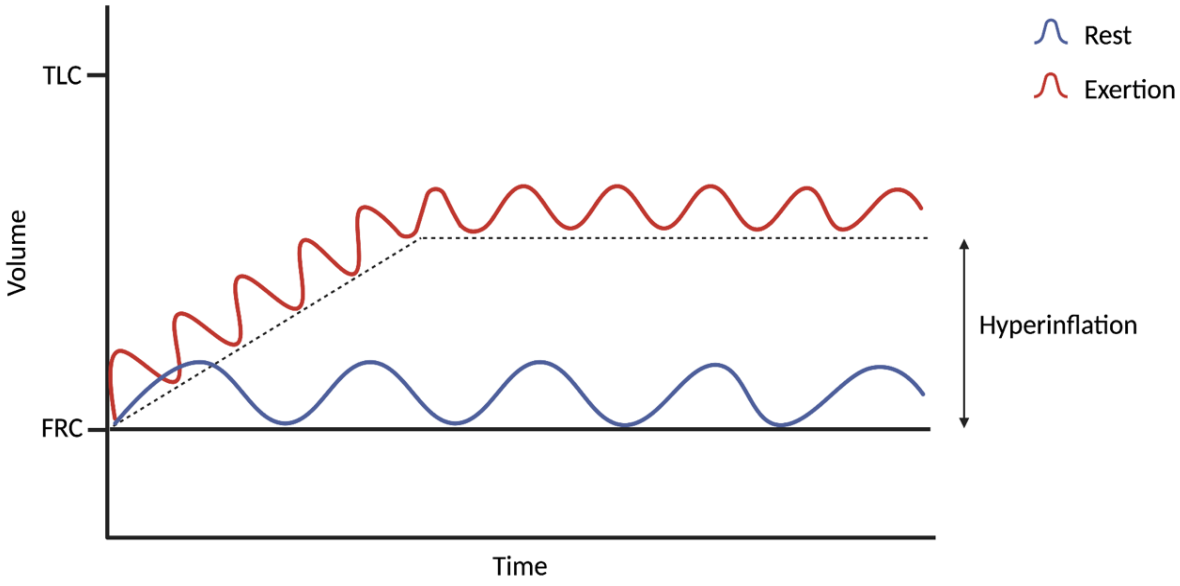

Figure 1.8 Change in end-expiratory lung volume with expiratory flow limitation and dynamic hyperinflation. During normal breathing exhalation occurs to functional residual capacity (solid line). On exertion, end-expiratory lung volume increases (dashed line) with hyperinflation to new steady state. FRC: Functional residual capacity. TLC: Total lung capacity.

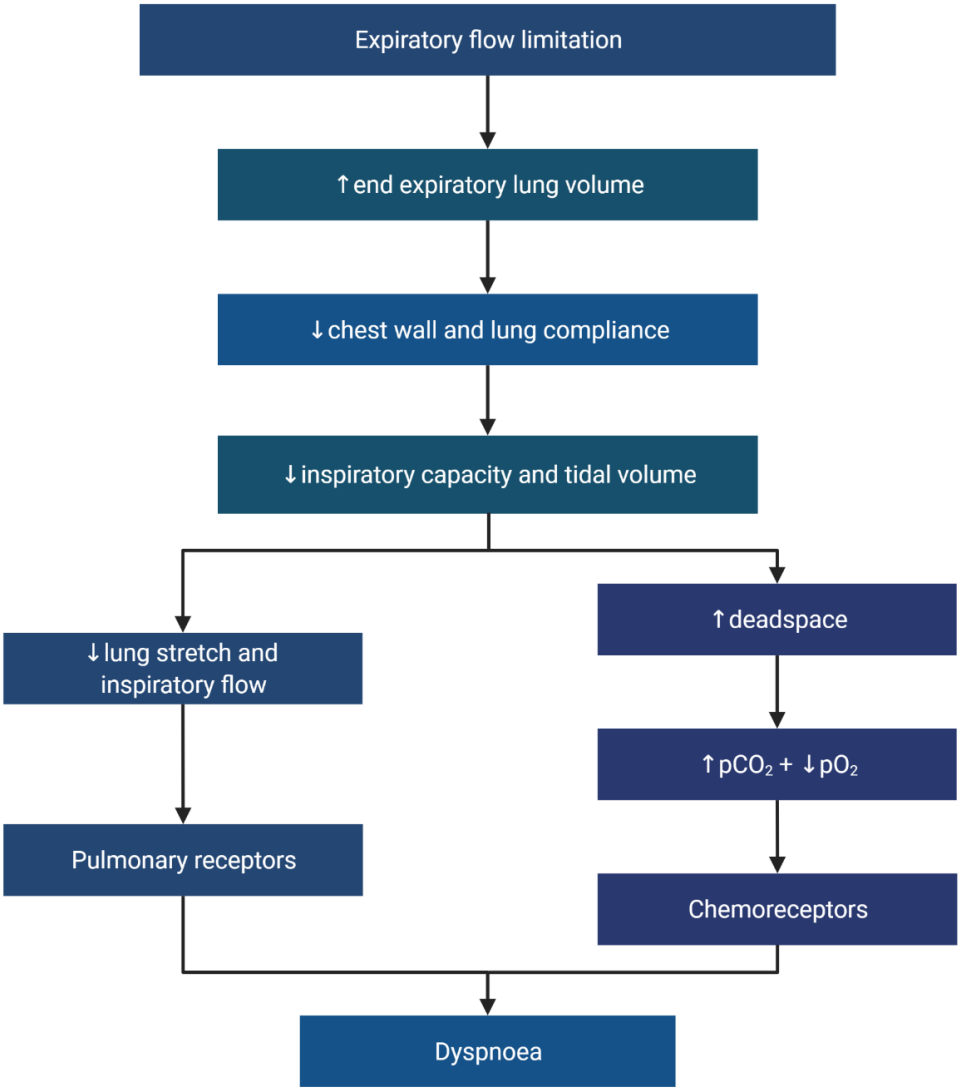

Figure 1.9 Mechanisms by which expiratory flow limitation causes dyspnoea on exertion. pO_2: Partial pressure of oxygen. pCO_2: Partial pressure of carbon dioxide.

At peak exercise, expiratory flow limitation is more common in preterm-born children with BPD than those without BPD and healthy controls. MacLean *et al* found EFL at peak exercise in 47% of extremely preterm children with BPD, compared to only 24% of healthy, term-born controls at 8-12 years of age. In this study, children with BPD reached a lower peak tidal volume during exercise, however there was no difference in inspiratory capacity between groups suggesting dynamic hyperinflation was not present(Maclean et al., 2016). Similarly, O'Dea et al found significantly higher rates of EFL along with a lower peak minute ventilation, tidal volume and increased respiratory rate during exercise in 9 to 12-year-old children with BPD compared to preterm-born children without BPD and term-born controls.

However, inspiratory capacity was not different between groups and there was no difference in tidal volume, minute ventilation or breathing frequency between those with and without EFL during exercise, suggesting EFL and dynamic hyperinflation are not responsible for the altered breathing pattern observed.

Both these studies used standard cardiopulmonary exercise testing (CPET) methodology to assess changes in breathing pattern during exercise and used serial inspiratory capacity manoeuvres to assess changes in operating lung volumes. Standard CPET requires a tight-fitting mask or mouthpiece and nose-clip, which alter normal breathing patterns, and use of serial inspiratory capacity manoeuvres is effort dependent and technically difficult during exercise therefore the reproducibility of these findings is unclear. Optoelectronic plethysmography (OEP) is a motion analysis system that non-invasively measures changes in thoracoabdominal volumes at rest and during exercise using body surface markers. This has the advantage of not requiring a facemask or mouthpiece, therefore allowing more a more normal breathing pattern. Furthermore, this continuously tracks changes in end-expiratory chest wall volume, to allow direct assessment of hyperinflation.

In adults with chronic obstructive pulmonary disease (COPD), who show a similar pattern of obstructive airflow disease, OEP has been used to clearly demonstrate an increase in end-expiratory chest wall volume and dynamic hyperinflation during exercise(Vogiatzis et al., 2005; Massaroni et al., 2017). Similarly in children with asthma, OEP has demonstrated a change in end-expiratory chest wall volume which correlates with change in FEV_1 post-exercise(Feitosa et al., 2018). OEP has not been used during exercise in preterm children, but may be a useful tool to assess changes in end-expiratory chest wall volume and the potential contribution of dynamic hyperinflation in this group, in a non-invasive manner, and is an area for future study.

1.6.8 Summary of respiratory outcomes of preterm children at school age

In summary, preterm born children have lung function abnormalities that persist with age. Airflow obstruction is a key feature, likely due to structural changes in the airway associated with preterm birth but gas exchange abnormalities are also present. This is a spectrum of abnormality, most prominent in those with a history of BPD, reflecting severe neonatal lung disease, but also present in preterm children without BPD. Preterm children show a

reduction in exercise capacity compared to healthy, term-born peers, and an altered ventilatory response to exercise has been observed, suggesting that mechanical ventilatory constraints contribute to this. Further work is required to explore the impact of expiratory flow limitation on lung volumes during exercise, and the relationship between airway obstruction at rest, bronchodilator responsiveness and the ventilatory response to exercise.

1.7 Research aims and objectives

1.7.1 Hypotheses

The work carried out in this PhD aimed to address the following hypotheses:

1. Maximum diaphragm electrical activity will increase when weaning nasal high flow therapy in preterm infants.

2. Preterm infants requiring positive pressure respiratory support or pulmonary vasodilatory therapy at, or beyond, 38 weeks corrected gestation are a distinct subgroup with higher morbidity and mortality than other infants with BPD.

3. Dynamic hyperinflation contributes to exercise limitation in school-aged children born preterm.

1.7.2 Aims and objectives

The specific aims of this work were to:

1. Develop a protocol for weaning nasal high flow support in preterm infants and assess the clinical utility of a weaning protocol.

2. Describe the changes in diaphragm electrical activity that occur when weaning nasal high flow support in preterm infants, and compare this to changes in oesophageal pressure swing.

3. Explore the incidence, clinical characteristics, management, and outcomes of preterm infants with life-threatening bronchopulmonary dysplasia in the United

Kingdom, defined as those requiring positive pressure respiratory support or pulmonary vasodilator therapy at, or beyond, 38 weeks corrected gestational age.

4. Assess the feasibility of using optoelectronic plethysmography to evaluate the ventilatory response to exercise in school-age children.

5. Explore the changes in end-expiratory chest wall volume occurring during exercise in a cohort of children born preterm, specifically assessing for evidence of dynamic hyperinflation.

Chapter 2. Methods

2.1 Overview of studies

This thesis contains three main studies. A brief outline of each study is given below for context, and technical aspects of the methodology are described in this chapter. Full details of the study protocols, recruitment processes, data management and statistics are subsequently reported in the relevant chapters.

2.1.1 Longitudinal cohort study of changes in diaphragm electrical activity with weaning nasal high flow in preterm infants

A longitudinal cohort study assessing changes in diaphragm electrical activity (Edi), a measure of respiratory muscle effort, when weaning nasal high flow support in preterm infants was performed. This study aimed to describe changes in Edi with weaning high flow in preterm infants to optimise weaning protocols and explore the utility of Edi as a marker of readiness to wean. Infants born at <32 weeks gestation were recruited, and their high flow weaned according to a set protocol. Edi, heart rate, saturations and chest and abdominal movement were measured serially before and after each weaning step. Changes in Edi from baseline were measured and the correlation with success of weaning assessed. The utility of oesophageal pressure measurement as an alternative measure of respiratory muscle effort was also explored.

2.1.2 National surveillance study of life-threatening bronchopulmonary dysplasia in the United Kingdom

A prospective national surveillance study of life-threatening bronchopulmonary dysplasia, defined as need for positive pressure respiratory support or pulmonary vasodilator therapy at 38 weeks corrected gestational age, was performed. Data were collected from clinicians across the United Kingdom using a series of data collection questionnaires distributed via the British Paediatric Surveillance Unit. Characteristics of affected infants, antenatal and postnatal exposures, and outcomes were studied.

2.1.3 Lung function and ventilatory response to exercise measured using optoelectronic plethysmography in school age children born preterm

This study explored the feasibility of using optoelectronic plethysmography to assess the ventilatory response to exercise in children born preterm. Children aged 10-15 years born very preterm at <32 weeks gestation were recruited, along with healthy term born controls. Baseline lung function including spirometry, body plethysmography, gas transfer testing and bronchodilator reversibility were assessed and an exercise test using optoelectronic plethysmography to non-invasively measure ventilatory changes was performed.

2.2 Diaphragm electrical activity measurement

2.2.1 Catheter placement

Diaphragm electrical activity was measured using a modified gastric feeding tube containing 10 miniaturised electrodes above the feeding holes, positioned in the lower oesophagus (6F, 50cm Edi catheter, Maquet, Sweden; Figure 2.1).

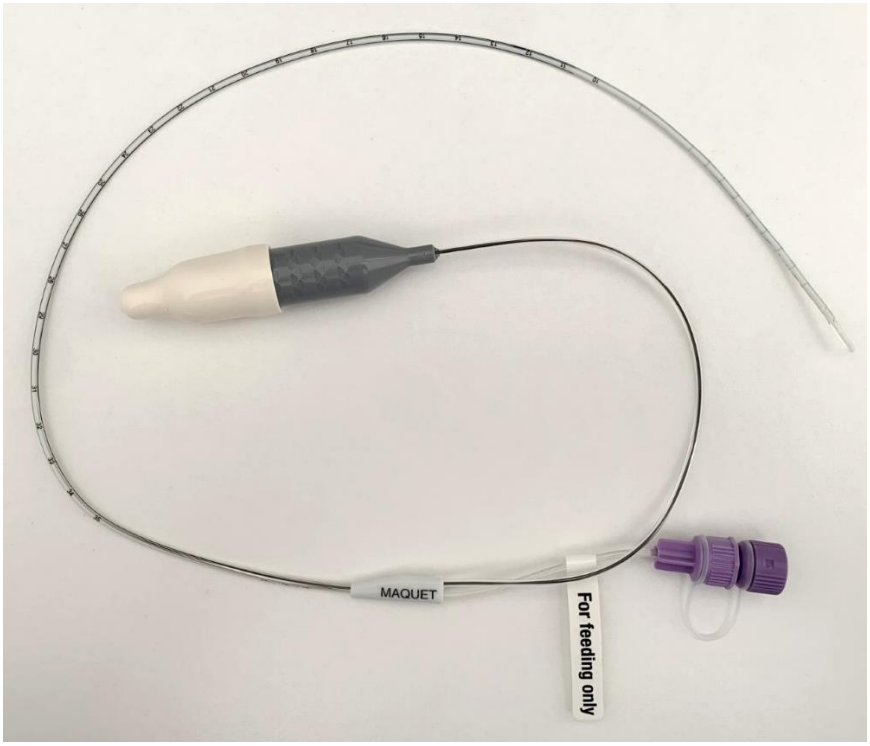

Figure 2.1 Edi catheter used for measuring diaphragm electrical activity.

The expected length of the catheter was estimated by measuring the length from the bridge of the nose, via the earlobe to the xiphisternum (the NEX measurement). The catheter was inserted either via the mouth (orogastric) in infants ≤1750g in infants, or via the nose (nasogastric) in infants >1750g. The catheter was connected using an Edi cable to the Edi module of the Servo-n ventilator (Maquet, Sweden).

Catheter position was refined using the in-built catheter positioning screen. This screen displays the retro-cardiac electrocardiogram (ECG) tracing, with the superimposed Edi signal in pink. The catheter is optimally positioned when the ECG waveform shows the largest P and QRS complexes in the top leads, the P waves have disappeared in the lowest lead, and the pink Edi signal is in the middle of the screen in the 2nd and 3rd leads as displayed in Figure 2.2. Once optimal position was confirmed, the catheter was secured to the infant's face using an adhesive dressing.

Figure 2.2 Edi catheter positioning screen showing optimal catheter position. The ECG signal decreases in amplitude from the upper to lower leads, and the pink EMG signal is highlighted in the central leads.

The inbuilt Maquet Servo-n software processed the raw signal from the electrodes. The signal was filtered to remove electrical interference from the heart, oesophagus and environment, eliminating artefact. Signals from each electrode pair were differentially amplified, digitised, and processed, and the double subtraction technique used to maximise the signal to noise ratio(Sinderby et al., 1997).

2.2.2 Data transfer

The digital Edi signal from the Servo-n ventilator was transferred to a multichannel recorder (Powerlab, ADInstruments) via the RS232 port using a digital to analogue converter, with a sampling frequency of 20Hz.

2.2.3 Edi parameters measured

The Edi signal was analysed on a breath-by-breath basis using LabChart 8 software (ADInstruments). For each breath the following parameters were measured:

- Edi min: The minimum Edi during expiration.
- Edi max: The maximum Edi during inspiration.
- Edi delta: The change in Edi during inspiration (Edi max – Edi min).
- Edi area under curve (a.u.c): Integral of the area subtended by the Edi signal during one breath.

Edi max (the peak Edi measured during inspiration) was used as the primary outcome in this study as this indicates maximal muscle effort, therefore is most reflective of work of breathing. Consistent with this, Edi max has been shown to correlate strongly with the maximal swing in oesophageal pressure in children(Essouri et al., 2019).

In addition, the neural respiratory rate was calculated from the number of Edi cycles during the recording period. The number of central respiratory pauses, defined as a period of >5seconds with Edi amplitude <1μV was also recorded(Beck et al., 2011).

2.3 Oesophageal pressure measurement using a micro-tipped pressure transducer

An oesophageal micro-tipped pressure transducer (CTO-1, Gaeltec, UK) is commonly used to measure oesophageal pressure changes as a measure of respiratory muscle effort, therefore was planned to be used in this study (Figure 2.3). The catheter is 70cm in length and has an external diameter of 2.1mm. A miniature strain gauge transducer is mounted on the tip of the catheter, and measures pressure changes in the lower oesophagus when inserted. The catheter is connected to its associated amplifier (S7D, Gaeltec, UK), connected to a multichannel recorder (PowerLab, ADInstruments) and an analogue signal displayed on the associated software recording screen (LabChart v8, ADInstruments). The catheter was soaked in sterile water for 1 hour before use as per manufacturer's instructions.

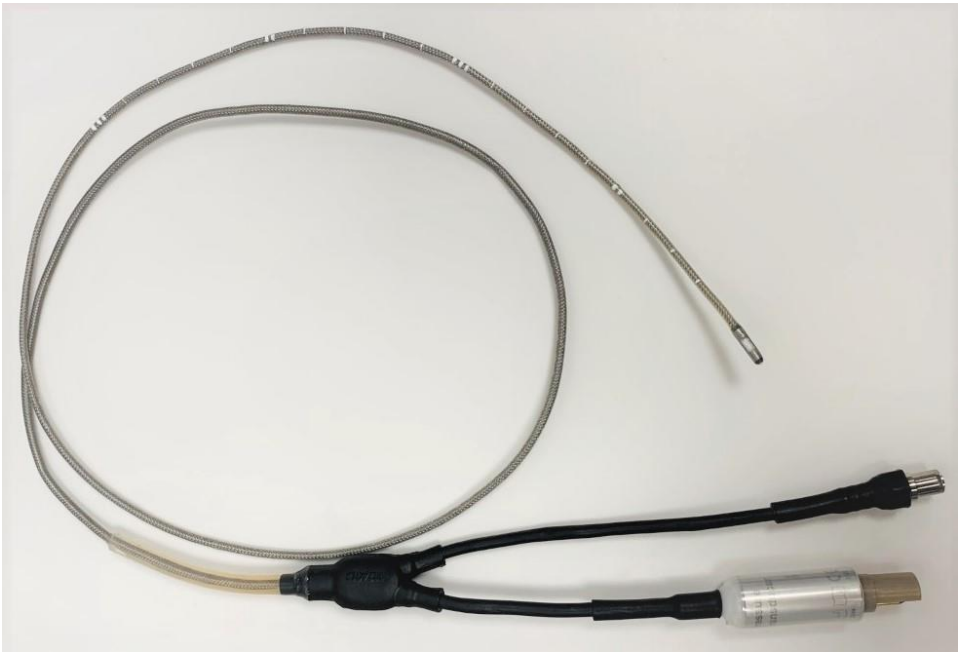

Figure 2.3 Gaeltec CTO-1 oesophageal micro-tipped pressure transducer used for measurement of oesophageal pressure changes.

2.3.1 Calibration of micro-tipped transducer

To calibrate the pressure transducer-amplifier system, the catheter was placed inside an airtight calibration tube and zeroed to atmospheric pressure. A known applied pressure was delivered using a water manometer circuit, and the catheter-amplifier-computer system calibrated using a two-point calibration at ±30cmH_2O.

Linearity of the pressure transducer was tested by connecting the transducer to a water manometer circuit using a three-way tap, and pressures were applied using a syringe in 5cmH_2O increments from -30cmH_2O to +30cmH_2O. The applied pressure measured by the water manometer was plotted against the output from the transducer, converted to digital units by the data acquisition software. The transducer had a linear response over the range ±30cmH_2O (Figure 2.4).

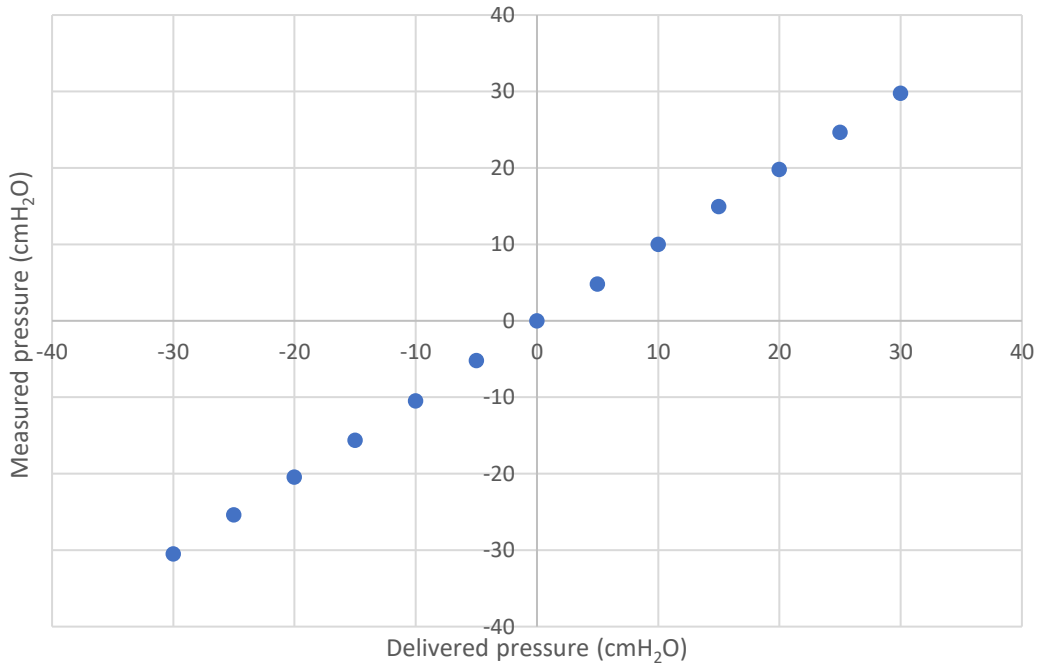

Figure 2.4 Plot showing linearity of Gaeltec micro-tipped pressure sensor.

2.3.2 Stability of micro-tipped transducer

Baseline stability of the micro-tipped pressure transducer was assessed over a 30-minute period. This duration was chosen as the planned duration of recording in the study was 20-minutes. The catheter-amplifier system was zeroed to atmospheric pressure, and the catheter left open to atmospheric pressure for 30-minutes, during which time pressure was continuously recorded. This showed a change of -0.44cmH_2O over a 30-minute period.

In using oesophageal pressure to assess respiratory muscle effort, absolute values are not of interest, but the swing in oesophageal pressure from baseline to maximal inspiration is required. The stability of measuring pressure swings from ±30cmH_2O was therefore also assessed over a 30-minute period (Figure 2.5). This showed increasing inaccuracy over time, with an average error of 1.46cmH_2O measuring ±30cmH_2O at 30-minutes (1.65cmH_2O at +30cmH_2O; 1.27cmH_2O at -30cmH_2O).

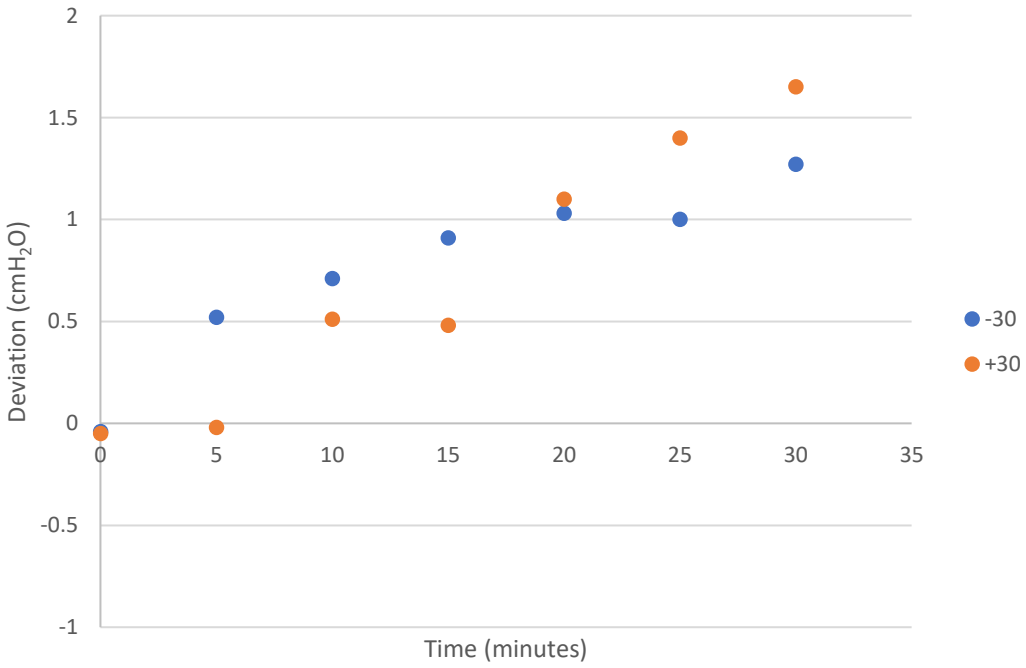

Figure 2.5 Plot showing difference between delivered and measured pressure at ±30cmH_2O over a 30-minute period using Gaeltec catheter. Deviation = delivered pressure – measured pressure.

2.3.3 Frequency response of micro-tipped transducer

The respiratory rate of a preterm infants is usually between 60-120 breaths per minute, giving a frequency of 1-2Hz. A frequency response of 10-15Hz is recommended when measuring pressure changes relating to respiratory muscle function. This must reflect the frequency response of the entire system, including catheters and connectors, not just the transducer as significant dampening of frequency response can occur(Laveneziana et al., 2019).

The frequency of the system was measured using the 'pop' test. In this test, an inflated balloon is fitted over the pressure sensor then popped, leading to an instantaneous drop in input pressure to the system. The time taken for the recorded pressure to drop from 90% to 10% of the initial pressure was recorded. The frequency response of the system (fbw) is calculated using the equation fbw = 1/(3xTr), where Tr (response time) is the time take for the pressure to change from 90% to 10% of the initial pressure in milliseconds (Figure 2.6).

This process was repeated 3 times using the Gaeltec micro-tipper pressure transducer and amplifier in series. The fastest 10-90% response time was 73 milliseconds, giving a maximum frequency response of 4.6Hz. The mean 10-90% response time was 93 milliseconds, giving a mean frequency response of 3.4Hz.

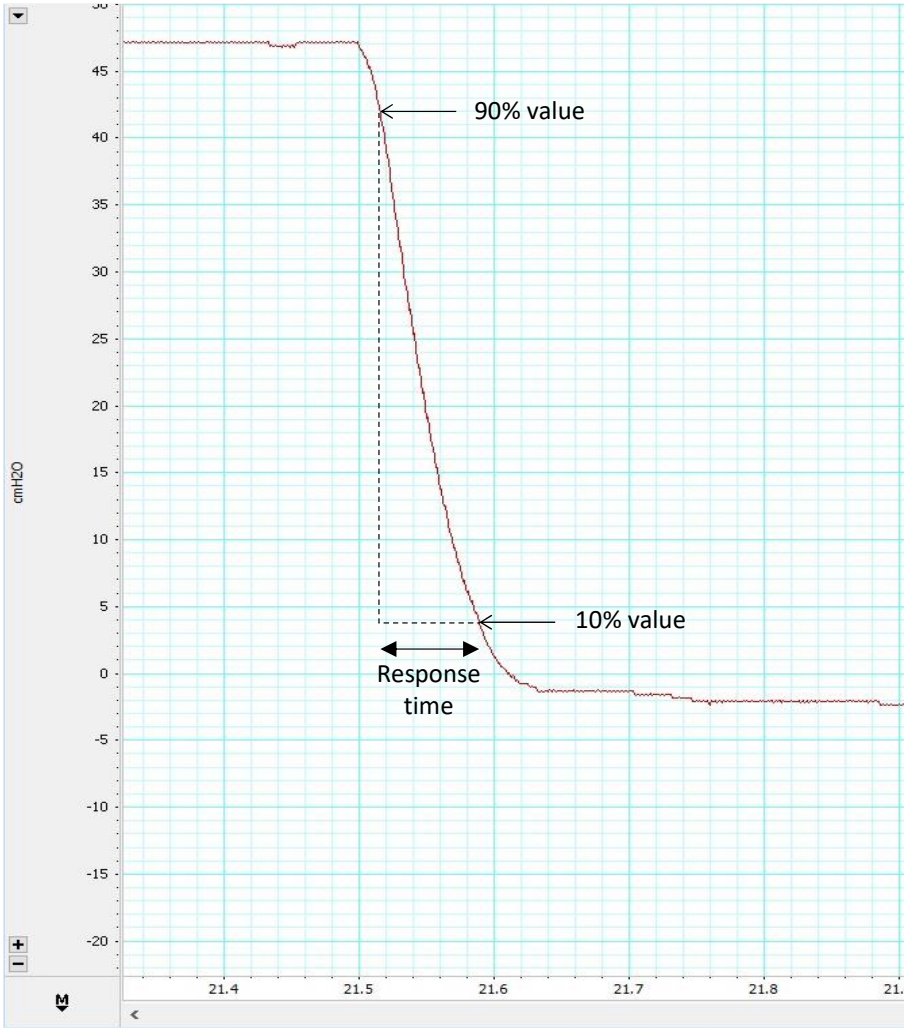

Figure 2.6 Measurement of response time during the pop test to assess frequency response.

2.3.4 Summary of micro-tipped transducer

In summary, the Gaeltec micro-tipped pressure transducer shows marked inaccuracy in measurement, with an average 5% error in pressure measurement over a relatively short, 30-minute time period, and an inadequate frequency response for this purpose. Despite this, these devices are widely used for oesophageal pressure monitoring in infants, which is concerning. This is consistent with others reporting poor agreement in oesophageal pressure changes measured with a balloon catheter and a Gaeltec micro-tipped catheter(Augusto et al., 2017), suggesting this device is not suitable for measurement of oesophageal pressure changes during tidal breathing.

2.4 Oesophageal pressure measurement using fluid-filled catheter system

Due to the inaccuracy observed using the Gaeltec micro-tipped pressure transducers, and the fact this technique requires an additional catheter to be inserted into the oesophagus, use of the infants existing feeding tube as a fluid-filled catheter system to measure oesophageal pressure was also explored.

This used the 6F, 50cm Edi-capable feeding tube (Maquet, Sweden) used for the Edi measurements. The catheter was flushed with sterile water, and the fluid filled catheter was connected to a disposable blood pressure transducer (MLT0670, ADInstruments), also flushed with sterile water before use. The BP transducer was connected to the associated amplifier (ADInstruments) via a BP Amp to MLT0670 cable (ADInstruments). The analogue output was fed into the multichannel recorder (PowerLab, ADInstruments) and displayed on the LabChart software screen.

2.4.1 Calibration of fluid filled catheter system

The fluid-filled catheter system was calibrated in the same way as the micro-tipped pressure transducer at ±30cmH_2O. Linearity of the system similarly confirmed by measuring pressure in 5cmH_2O increments from -30cmH_2O to +30cmH_2O as shown in Figure 2.7.

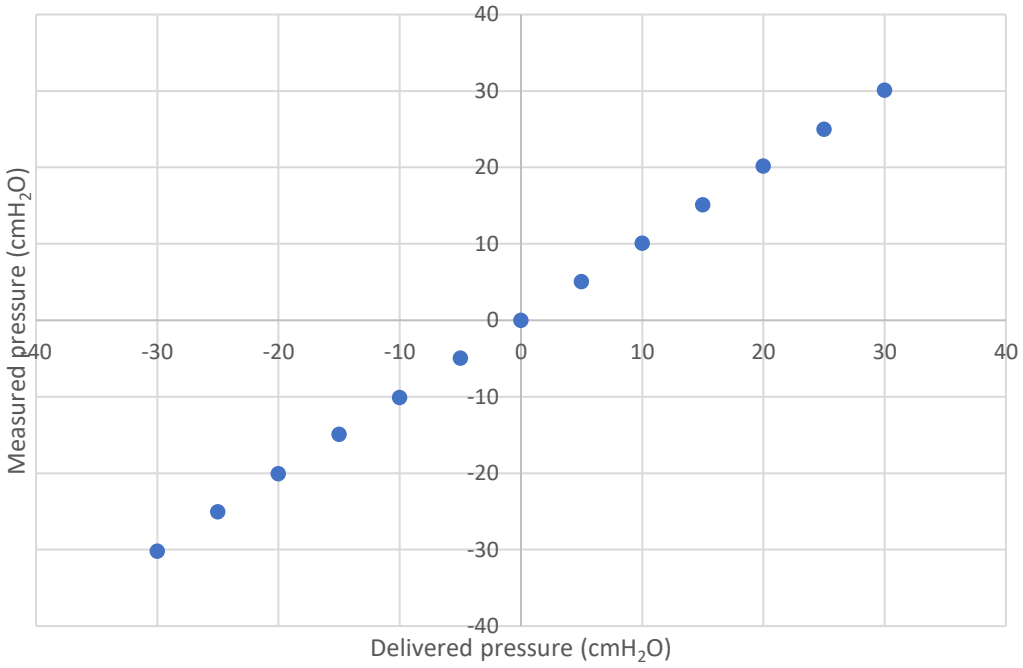

Figure 2.7 Plot showing linearity of fluid-filled catheter system.

2.4.2 Stability of fluid filled catheter system

Baseline stability of the fluid-filled catheter system was assessed over a 30-minute period. The transducer was zeroed and left open to atmospheric pressure, during which time pressure was continually recorded. This showed a change of -0.55cmH_2O over a 30-minute period.

The stability of pressure measurements at ±30cmH_2O over a 30-minute period was also assessed. As shown in Figure 2.8, the margin of error using this system was notably less than the Gaeltec catheter, with an average deviation of 0.08cmH_2O (0.27cmH_2O at +30cmH_2O and -0.19cmH_2O at -30cmH_2O) at 30-minutes.

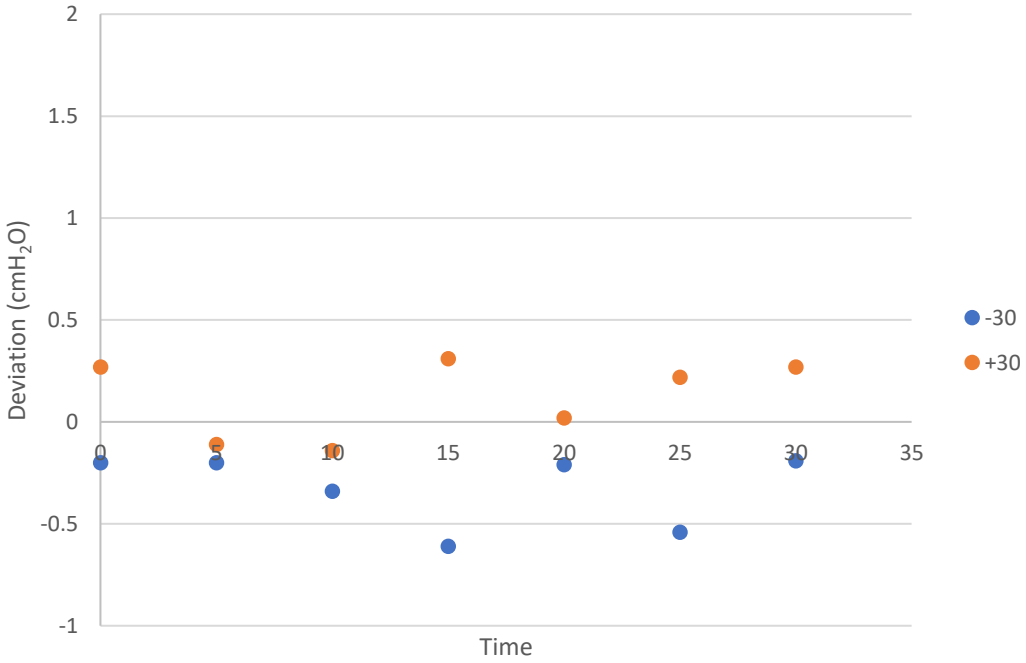

Figure 2.8 Plot showing difference between delivered and measured pressure at ±30cmH_2O over a 30-minute period using fluid filled catheter system. Deviation = delivered pressure – measured pressure.

2.4.3 Frequency response

The pop test was performed to assess the frequency response of the fluid-filled catheter system as described above. The fastest 10-90% response time of this system was 18 milliseconds, giving a maximum frequency response of 18.5Hz. The mean 10-90% response time was 23 milliseconds, giving an average frequency response of 14.5Hz.

2.5 Oesophageal pressure measurement procedure

The fluid filled catheter system was chosen for use in this study, as it shows better stability in measurement, an adequate frequency response and is more tolerable to use in preterm infants than the Gaeltec catheter. As the Gaeltec catheter is a standalone catheter, use would involve insertion of an additional catheter for each set of measurements which is potentially distressing to preterm infants. The fluid filled catheter system does involve manipulation of the gastric tube, pulling it back a few centimetres into the oesophagus for each set of measurements, but this is less disruptive and safer than insertion of an additional catheter. This technique was only suitable for infants on bolus feeds, as it involves flushing the catheter with water and it would not be acceptable to stop an infant's continuous feed for these measurements.

As this used an infant's existing feeding tube, it was not possible to calibrate system using the exact feeding tube that would be used for the measurements, as this was already in situ. Instead, an identical 6F, 50cm Edi-capable feeding tube flushed with sterile water was used and two-point calibration performed as above. The infant's feeding tube was flushed with 2ml sterile water, and the pre-calibrated BP transducer was then connected. A continuous infusion of sterile water running at 1ml/hour was applied to the feeding tube to prevent blockage. The feeding tube was then pulled back until the characteristic oesophageal waveform, with a negative deflection during inspiration was observed (Figure 2.9) and the tube re-secured in this position.

2.5.1 Oesophageal pressure parameters measured

The oesophageal pressure (Poes) recording was analysed on a breath-by-breath basis using LabChart 8 software. The following parameters (illustrated in Figure 2.9) were measured:

- ΔPoes: The change in Poes from the start of inspiration to the end of inspiration.
- PTP/breath: Pressure time product per breath, measured as the area under the Poes signal between the onset and end of inspiration.
- Respiratory rate: Number of cycles during recording period.
- PTP/min: Pressure time product per minute, calculated by multiplying the PTP/breath by the respiratory rate.

Ideally the beginning and end of inspiration are detected using a flow meter, however this involves placing a mask on the infant's face which alters normal breathing, and is unreliable when an infant is on high flow(Fleming et al., 1982). As a result, inspiration was measured from the start of the downward deflection in the Poes trace, to the maximal trough of the Poes trace.

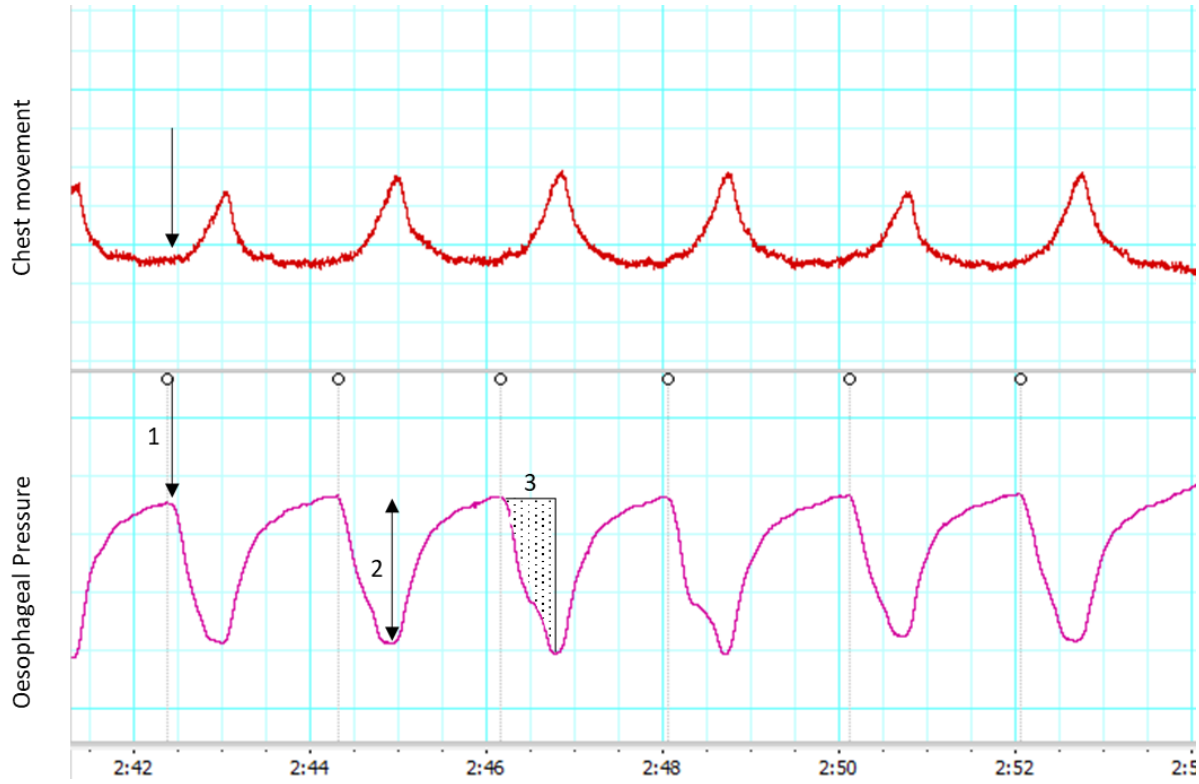

Figure 2.9 Oesophageal pressure trace. Representative recording of chest wall motion using respiratory inductance plethysmography (top) and oesophageal pressure (bottom) showing: 1: The characteristic downward deflection in Poes at the start of inspiration. 2: ΔPoes measured as the change in Poes from the start of inspiration to the end of inspiration. 3: The pressure time product per breath measured as the inspiratory time integral of Poes.

2.6 Respiratory inductance plethysmography

Uncalibrated respiratory inductance plethysmography (RIP, Respitrace 200, Nims) was used to monitor chest and abdominal excursion during recording periods. Two soft, elasticated bands containing inductance coils were placed around the rib cage, under the axillae, and around the abdomen at the level of umbilicus. Paediatric sized bands were used in all cases, and bands were adjusted to fit snugly around the infant.

The Respitrace system was connected directly to a multichannel recorder (PowerLab, ADInstruments) and the analogue voltage output signal continuously displayed on the associated software recording screen (PowerChart, ADInstruments). The output voltage from the RIP is proportional to the change in band inductance, which is in turn proportional to the change in cross-sectional area of the underlying chest or abdomen. As infants in the study were receiving high flow, it was not possible to measure tidal volume, and hence calibrate this system. However, the uncalibrated system was used to identify periods of normal breathing, exclude periods of artefact and confirm the beginning and end of inspiration.

2.7 Pulse oximetry

Heart rate and saturations were continuously monitored throughout the recording period. A disposable neonatal sensor (LNOP Neo, Masimo, USA) was applied to the infant's wrist or foot, and connected to a pulse oximeter (Radical, Masimo, USA). The pulse oximeter was connected directly to the multichannel recorder (PowerLab, ADInstruments) and the analogue output displayed on the associated software recording screen (PowerChart, ADInstruments).

2.8 Lung function tests

Lung function tests were performed in the Children's Outpatient Department at the Great North Children's Hospital, Newcastle upon Tyne. All tests were supervised by Ruth Levey, paediatric respiratory physiologist.

2.8.1 Spirometry

Spirometry was performed using the Jaeger MasterScreen Pulmonary Function Testing system according to American Thoracic Society (ATS) and European Respiratory Society (ERS) technical standards(Graham et al., 2019). All measurements were performed with the child seated, and a nose clip used to occlude the nostrils. FEV_1, FVC and other expiratory flow rates were measured using a standard FVC manoeuvre. This consists of maximal inspiration, a 'blast' of expiration followed by complete expiration, then inspiration at maximal flow back to maximal lung volume. A minimum of three manoeuvres were performed, but up to eight were permitted to meet ATS/ERS acceptability, usability, and repeatability criteria(Graham et al., 2019). These measurements were repeated following administration of 400 micrograms of salbutamol via a metered dose inhaler and spacer to assess for bronchodilator responsiveness.

2.8.2 Lung volumes

Lung volumes were measured by body plethysmography using the Jaeger MasterScreen Body plethysmograph according to ATS/ERS technical standards(Wanger et al., 2005). All measurements were performed with the child seated in the plethysmograph with the door closed, and a nose-clip was worn to occlude the nostrils. An FRC manoeuvre was performed during which the child breathed quietly via a mouthpiece until a stable end-expiratory volume was achieved, then a shutter was closed at end-expiration for 2-3 seconds and the child asked to pant gently for 3-5 breaths to measure intrathoracic gas volume at FRC. Following this, the shutter was opened, and the child performed an expiratory reserve manoeuvre, followed by a slow inspiratory vital capacity manoeuvre (Figure 2.10). This manoeuvre was repeated until at least three FRC_{pleth} values that agree within 5% were obtained.

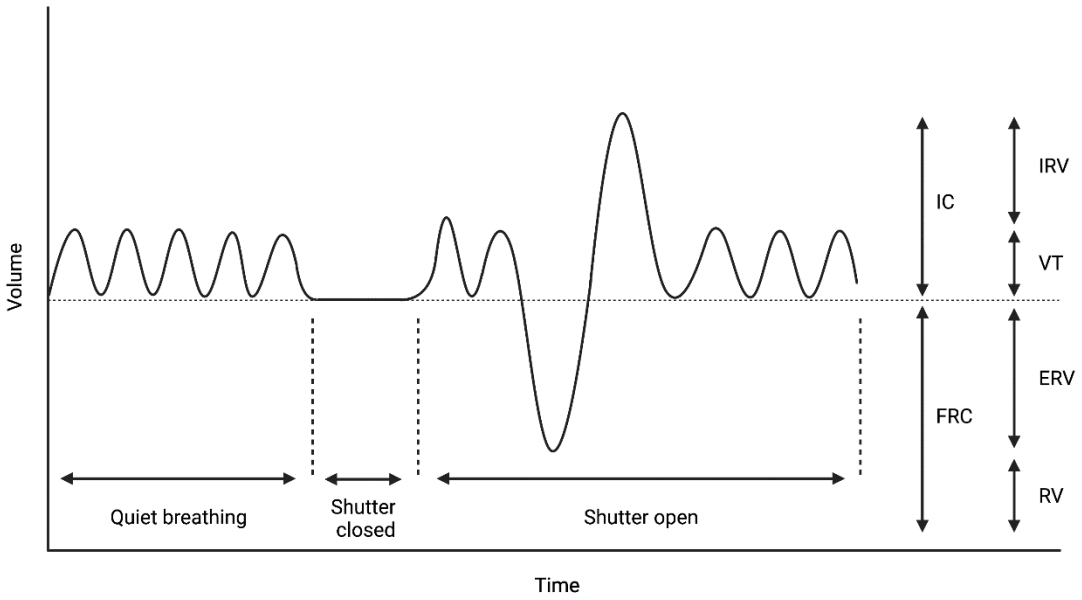

Figure 2.10 Lung volume measurement during body plethysmography. IC: Inspiratory capacity. FRC: Functional residual capacity. IRV: Inspiratory reserve volume. VT: Tidal volume. ERV: Expiratory reserve volume. RV: Residual volume. Modified from Wanger et al 2005.

2.8.3 Gas transfer

Gas transfer testing was performed using the Jaeger MasterScreen Pulmonary Function Testing system according to ERS/ATS standards for single-breath carbon monoxide uptake in the lung(Graham et al., 2017). Measurements were made in the seated position with the child wearing a nose clip. After a period of normal breathing, the child was asked to exhale to residual volume then inhale rapidly to total lung capacity, during which the test gas was inhaled. This breath was held for 10±2 seconds followed by a rapid expiration. Standard ERS/ATS acceptability and reproducibility criteria were similarly used.

2.8.4 Fraction of exhaled nitric oxide

Fraction of exhaled nitric oxide was measuring using a handheld point of care testing device (NIOX Vero, Circassia, Sweden) according to manufacturer's instructions.

2.9 Optoelectronic plethysmography

2.9.1 Principles of optoelectronic plethysmography

Optoelectronic plethysmography (OEP) is a motion analysis system (BTS Bioengineering, Italy), which tracks changes in thoracoabdominal volume during breathing by modelling the thoracoabdominal surface. The system uses a series of 89 reflective markers which are placed in specific positions on the subject's chest, back and abdomen as demonstrated in Figure 2.11.

A series of 8 cameras (Smart System, BTS Bioengineering, Italy) positioned around the subject are used to continually track the position of each marker (Figure 2.12). The cameras emit an infrared signal, which is reflected by the markers and captured by the cameras at a frequency of 60Hz. The dedicated OEP software calculates the 2-dimensional (2D) coordinates of each marker in each camera, then integrates the signal provided by at least 2 cameras to calculate the 3-dimensional (3D) coordinates of each marker using stereophotogrammetry. In this process, the combination of at least two, 2D images obtained from different cameras at the same instant of time is used to calculate the 3D coordinates of a point. Markers not visible in two cameras can be manually reconstructed from adjacent markers if required.

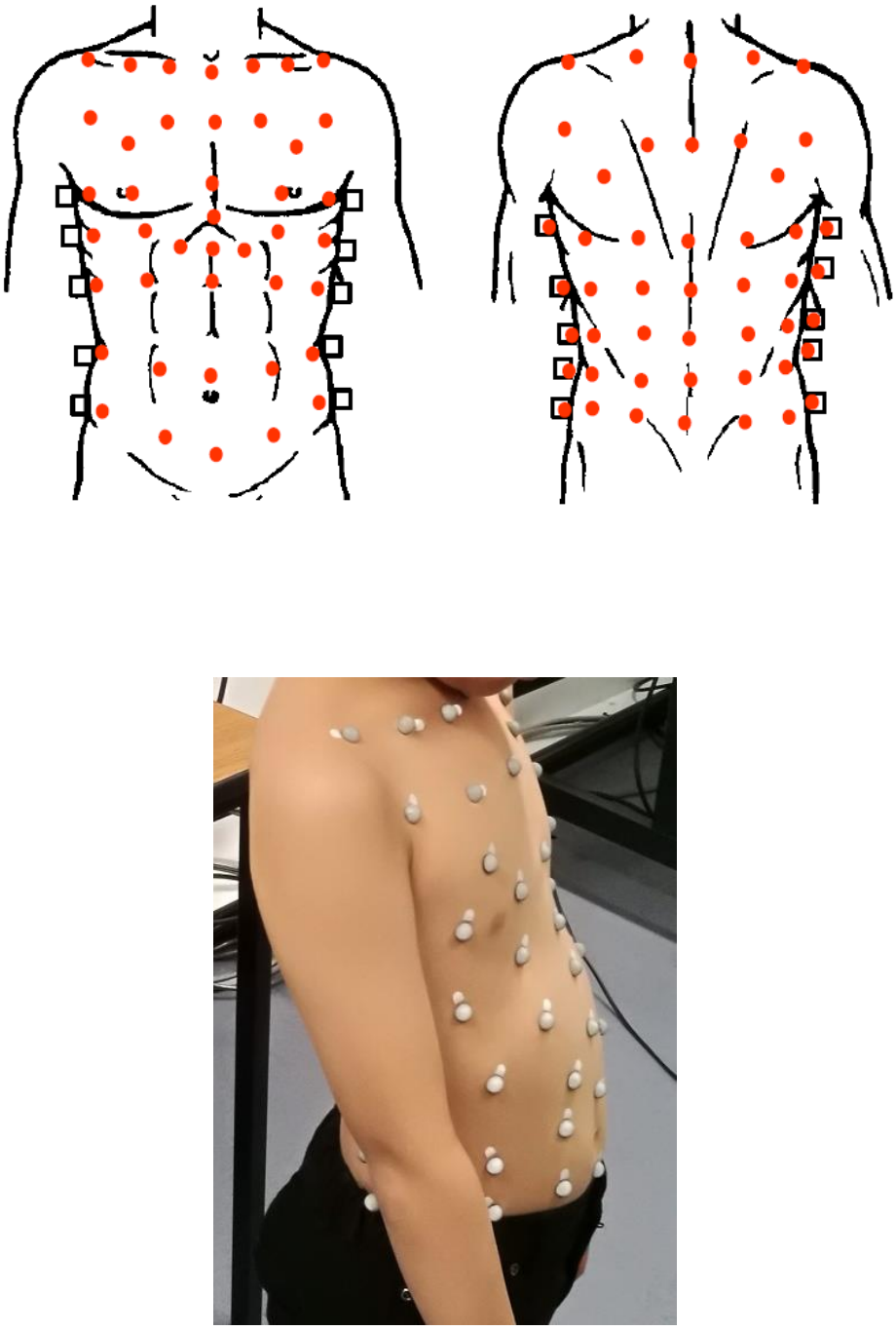

Figure 2.11 Optoelectronic plethysmography marker position. Top panel shows schematic representation of marker position (red dots) on chest, back and abdomen(BTS Bioengineering, 2011). Lower panel shows markers applied to the torso of a 10-year-old boy participating in the study.

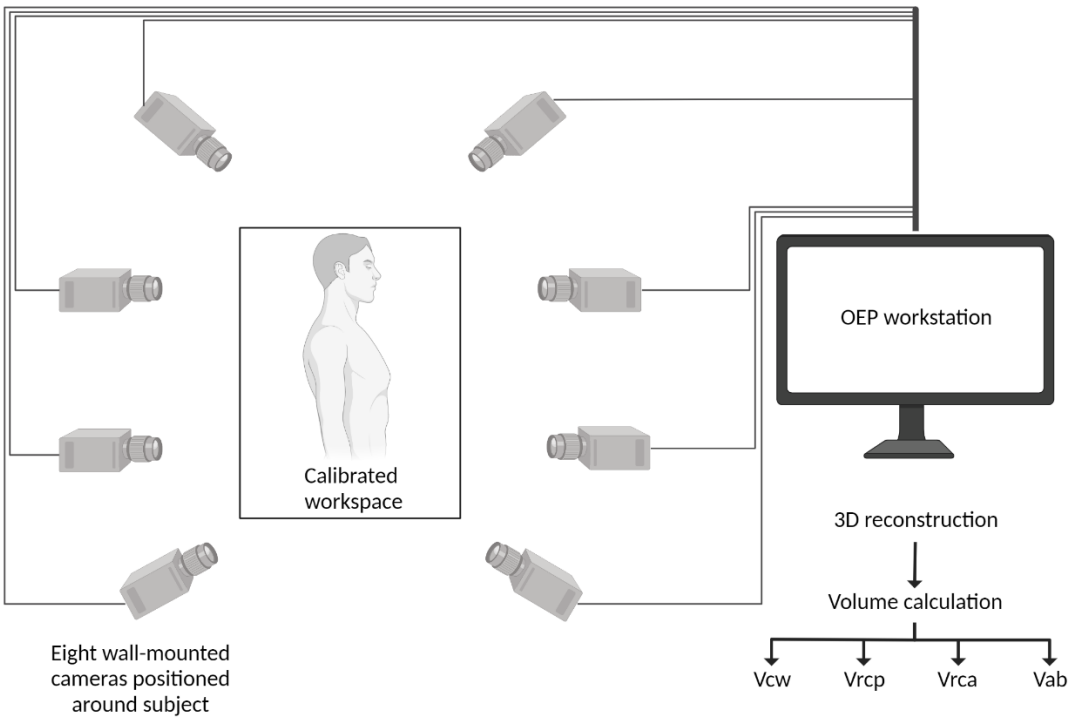

Figure 2.12 Schematic representation of the optoelectronic plethysmography (OEP) setup. A series of 8 cameras positioned around the subject continually track the position of the applied reflective markers. The signals are processed, and a 3-dimensional (3D) model reconstructed. Volumes are calculated for the total chest wall (Vcw), pulmonary rib cage (Vrcp), abdominal rib cage (Vrca) and abdominal (Vab) compartments. Modified from Massaroni et al 2017.

A geometrical model is then applied to create a 3D image of the thoracoabdominal wall (Figure 2.13). Each series of three markers forms a triangle which represents the closed surface of the thoracoabdominal wall. The internal volume of each shape is calculated using Gauss's theorem, in which the surface integral is converted to the volume integral, and the total volume of the thoracoabdominal wall calculated as the sum of the volume of each triangle.

The OEP model is divided into three compartments:

- Pulmonary rib cage (Rcp): Above the level of the xiphisternum
- Abdominal rib care (Rca): Between the level of the xiphisternum and costal margin
- Abdomen (Ab): Below the level of the costal margin

In reporting volumes, the pulmonary and abdominal rib cage compartments are combined and reported as the total rib cage volume. As rib cage expansion also influences abdominal volume, the total volume change measured in all three compartments is referred to as the chest wall (CW) volume(Aliverti et al., 2002). The output of the OEP system is a plot showing these compartmental volumes and the total chest wall volume on a breath-by-breath basis (Figure 2.14). This allows measurement of total and compartmental volume changes, breathing timing and chest wall kinematics including degree of thoracoabdominal synchrony.

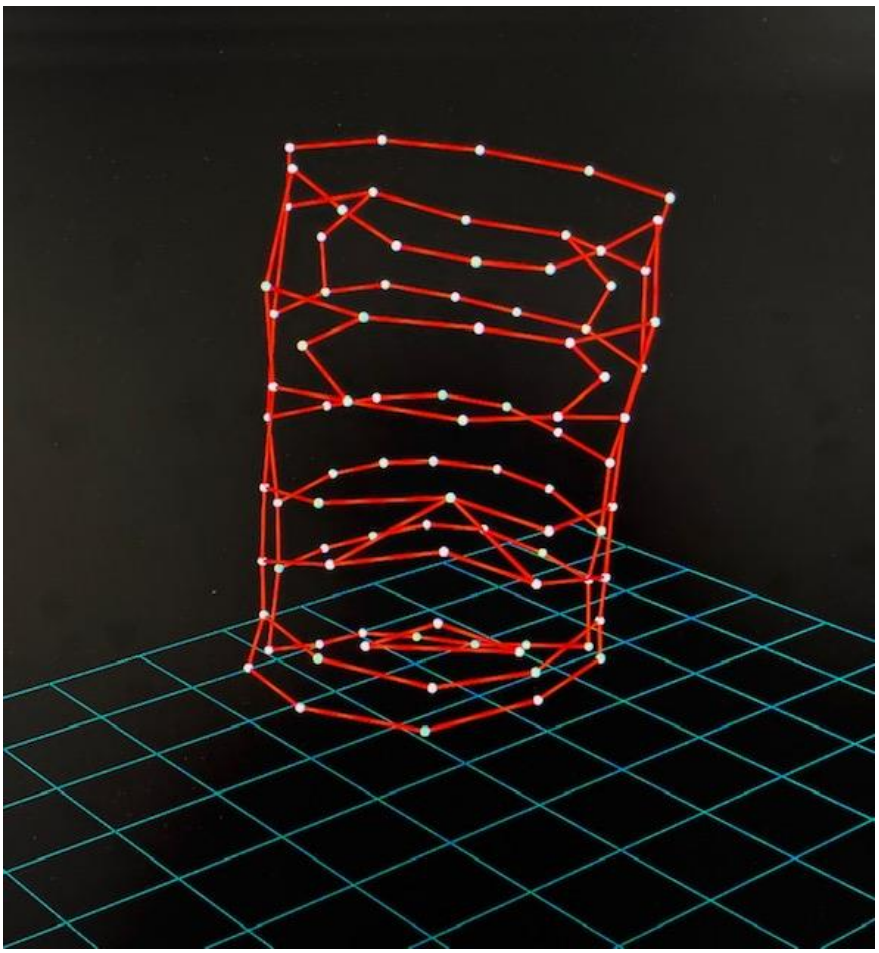

Figure 2.13 Reconstructed 3-dimensional model of the thoracoabdominal wall in a child during exercise created using optoelectronic plethysmography.

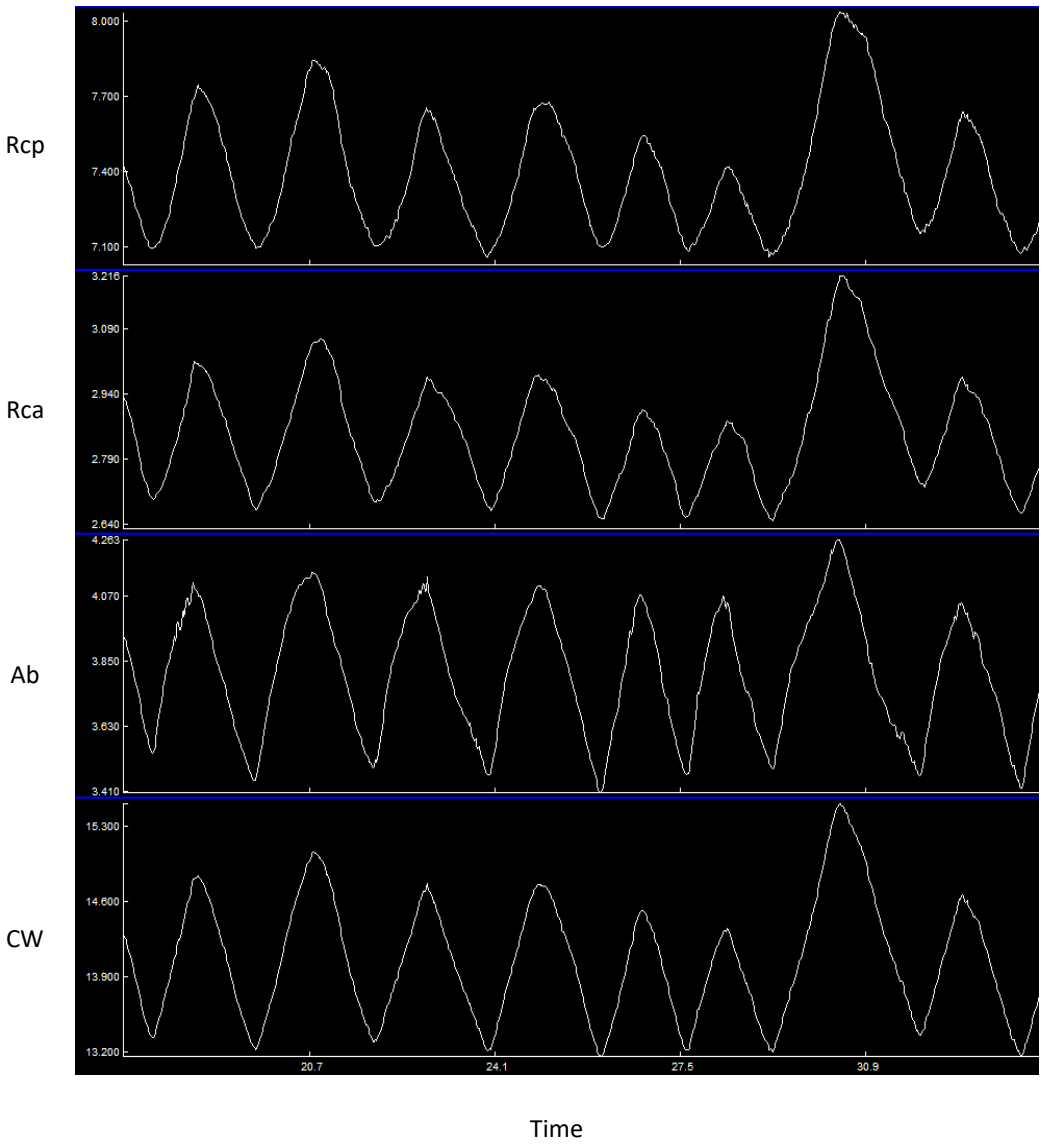

Figure 2.14 Optoelectronic plethysmography output showing breath-by-breath volume change of the pulmonary rib cage (Rcp), abdominal rib cage (Rca), abdomen (Ab) and total chest wall volume (CW).

2.9.2 Validity of OEP

The accuracy of the OEP system has been assessed in several ways. Using a simulated model the OEP system has been shown to detect linear changes in marker position as small as 30µm and measure volume changes with <6% error in the range 0-2.78L(Bastianini et al., 2012; Massaroni et al., 2016). The tidal volumes anticipated during exercise in children fall within these limits, showing accuracy within an appropriate range(Welsh et al., 2010; Prenzel et al., 2020).

As OEP measures the total volume of the chest wall, this may include changes in blood volume in the thorax and abdomen in addition to changes in lung volume. This is particularly relevant during exercise when the high variation in pressure occurs in the respiratory system, and blood is redistributed to the extremities. A number of studies have compared tidal volumes and inspiratory capacity measured using OEP with those measured using a spirometer or pneumotachograph at rest and during exercise. A strong linear relationship has been reported between measurement techniques, with r^2 values >0.9, indicating high correlation between changes in volume measured using OEP and these reference techniques, suggesting OEP does accurately measure lung volume changes(Aliverti et al., 2004; Vogiatzis et al., 2005; Layton et al., 2013).

2.9.3 Optimisation of OEP system

In this study we used the OEP system in the Department of Sport, Exercise and Rehabilitation at Northumbria University, Newcastle upon Tyne. Prior to commencing study recruitment, a series of pilot tests were undertaken in healthy, volunteer children to optimise the system for paediatric use. The results of the pilot tests are summarised in Table 2.1.

There are no published exercise test reference data for healthy children using optoelectronic plethysmography, therefore data from two similar healthy cohorts using standard cardiopulmonary exercise testing are displayed in Table 2.2 for comparison. Average baseline values for respiratory rate, tidal volume and minute ventilation are comparable between the pilot cohort and healthy controls reported by Fawke and MacLean using standard exercise tests, however at peak exercise changes in respiratory rate and hence minute ventilation appear lower using OEP(Fawke et al., 2010; Maclean et al., 2016). This may reflect differences in the measurement techniques, as using a facemask or mouthpiece and nose clip, as required during standard cardiopulmonary exercise testing, likely alters normal breathing patterns due to increased resistance and discomfort. Alternatively, differences in study population or exercise protocol may contribute to this.

Test	Age (y)	Sex	Height (cm)	Weight (kg)	Minute vent (L/kg/min)		Respiratory rate (bpm)		Tidal volume (ml/kg)		EEVcw (L)		
					Rest	Max	Rest	Max	Rest	Max	Rest	Max	Change
1[a]	8	M	123		-	-	-	-	-	-	-	-	
2	10	M	132	26.1	0.2	0.87	24	39	9	22.5	7.58	7.42	-0.16
3	10	M	148	39	0.27	0.6	21	25	13.4	24	10.74	10.47	-0.27
4	13	F	172	59.8	0.15	0.66	21	32	7	20	13.76	13.62	-0.14
5	11	F	149	41.2	0.23	0.5	23	33	9.9	15.3	10.61	10.51	-0.10
6	13	F	163	48.8	0.38	0.86	27	30	14.1	29.1	12.46	12.64	+0.18
7	16	F	176	55.3	0.19	1.03	20	36	9.9	28.6	15.04	14.36	-0.68
8	10	M	132	26.1	0.25	0.94	30	38	8.4	24.9	7.54	7.59	+0.05
Mean[b]	**11.9**		**153.1**	**42.3**	**0.24**	**0.78**	**23**	**33**	**10.2**	**23.5**	**11.1**	**10.9**	**-0.16**

Table 2.1 Results of pilot tests using optoelectronic plethysmography (OEP) to assess the ventilatory response to exercise in children. Minute vent: Minute ventilation. EEVcw: End-expiratory volume of the chest wall. Y: Years. Bpm: Breaths per minute. [a]Participant too short to cycle comfortably on cycle ergometer therefore no useable data obtained. [b]Excluding test 1.

Study	Number	Age (y)	Minute vent (L/kg/min)		Respiratory rate (bpm)		Tidal volume (ml/kg)	
			Rest	Max	Rest	Max	Rest	Max
Welsh (2009)	38	11.0 (0.5)	0.2 (0.04)	1.42 (0.31)	16.7 (4.0)	50.9 (11.0)	12.2 (3.7)	28.3 (5.1)
MacLean (2016)	62	11.6 (1.9)	0.25 (0.09)	1.4 (0.38)	20.6 (5.2)	47.5 (12.4)	13.4 (5.1)	29.5 (6.5)

Table 2.2 Exercise data reported in healthy control subjects using standard cardiopulmonary exercise testing. Data from Welsh *et al* reported as median (IQR) and MacLean *et al* as mean (SD). Minute vent: Minute ventilation. Bpm: Breaths per minute. Y: Years.

As a result of these pilot tests, a number of modifications were undertaken to improve the quality of data obtained, namely:

- Minimum height requirement: The first participant was too short to cycle comfortably on the ergometer (height 127cm) and the second borderline height (132cm) therefore a minimum height limit of 135cm was introduced for the study and children >10 years of age recruited (rather than >8 years as initially planned).

- Zoomed in cameras: The system was previously used for OEP studies in adults, therefore the cameras were zoomed in and angled to focus on a smaller area and increase the resolution of the images.

- Addition of arm supports: Arm supports, for the participant to hold whilst cycling, were positioned lateral to the cycle ergometer to ensure their arms did not obscure the view of the lateral markers during exercise.

- Ensuring cadence maintained during cycling: It was observed that as workload increased, there was a tendency for participants to slow their cycling cadence to overcome the increased resistance therefore peak exercise was not clearly observed. To prevent this, a member of the study team continually observed cadence, and provided verbal encouragement to the participant to maintain the cadence at >50 revolutions per minute. The test was stopped as soon as the child was unable to maintain this rate, indicating they had reached their maximal workload. This was implemented in pilot tests 6-8, and a higher peak minute ventilation was obtained during these tests suggesting this was successful.

2.9.4 Study OEP measurement protocol

All study OEP measurements were performed using the OEP system (BTS Bioengineering, Italy) in the Department of Sport, Exercise and Rehabilitation at Northumbria University, Newcastle upon Tyne. The system was calibrated according to manufacturer's instructions prior to each use.

A series of 89 reflective markers were applied to the chest, back and abdomen of participants in the standard configuration (Figure 2.11). Boys removed their top, so markers were applied directly to the skin, whilst girls wore a tight-fitting sports bra or crop top, and markers were applied either to the skin or clothing as required. All measurements were made with the child sitting on the cycle ergometer, holding the arm supports laterally. During the study, movement of the markers was tracked by 8 cameras positioned around the participant (4 positioned in front of the child and 4 behind). Position of the cameras was not changed between participants and all cameras sampled at a frequency of 60Hz.

Three minutes of quiet breathing were recorded as a baseline before starting the exercise test. During this time, three inspiratory capacity manoeuvres were performed. The exercise test was performed on a cycle ergometer (Ergoselect 200, Ergoline, Germany). Three minutes of unloaded cycling were performed as a warm-up to allow the child to become accustomed to the environment and equipment.

Following this, a ramped exercise test using a modified Godfrey protocol was performed (Table 2.3). Cycling cadence was maintained at 50-60 revolutions per minute throughout the test, and the work load stratified so the subject would be anticipated to reach peak exercise within 8-10 minutes of the protocol commencing(Rowland, 1993).

Height (cm)	Initial load (W)	Increment (W)	Stage duration (min)
<120cm	10	10	1
120-150cm	15	15	1
>150cm	20	20	1

Table 2.3 Godfrey cycle ergometer protocol.

The test was terminated at the point of voluntary exhaustion when the child was unable to continue or maintain an adequate cadence despite verbal encouragement. Heart rate and saturations were monitored throughout using a pulse oximeter (Nonin Onyx Vantage 9590, USA).

2.9.5 OEP parameters measured

OEP recordings were made for 3-minutes of quiet breathing, the final 1-minute of unloaded cycling, then for alternate 30-second blocks up to the point of maximal exercise. Data were stored on the OEP workstation and analysed using the dedicated OEP analysis software (Smart Tracker, BTS Bioengineering, Italy). All artefact free breaths in each recording were included in the analysis.

The following parameters were measured using OEP at baseline, and incrementally to peak exercise:

- Tidal volume, respiratory rate, and minute ventilation.
- End-inspiratory and expiratory volume of the chest wall: Total volume representing the combined volume of the pulmonary rib cage, abdominal rib cage and abdominal compartments.
- End-inspiratory and expiratory volume of the rib cage: Combined volume of the pulmonary and abdominal rib cage compartments.
- End-inspiratory and expiratory volume of the abdomen.

Heart rate and oxygen saturations were recorded at baseline and every 2 minutes during exercise. In addition, total exercise time and maximal workload were recorded at the end of the test.

Chapter 3. Longitudinal cohort study of changes in diaphragm electrical activity with weaning nasal high flow in preterm infants

3.1 Introduction

As discussed previously, nasal high flow therapy is a widely used mode of respiratory support for neonates, particularly as a weaning modality in preterm infants. Retrospective studies have associated increasing use of high flow with a longer duration of respiratory support and increased rates of bronchopulmonary dysplasia in preterm infants(Taha et al., 2016; Heath Jeffery et al., 2017; Sand et al., 2022). Due to the retrospective, observational nature of these studies, it is unclear whether this reflects differences in infant characteristics, respiratory support provided or weaning strategy, as a tendency to wean high flow less aggressively than CPAP due to its improved tolerance has been observed. There is little objective evidence to guide weaning of high flow, and marked variation in practice is evident, highlighting weaning as a key area for future study(Farley et al., 2015; Shetty, Sundaresan, et al., 2016).

In practice, weaning high flow is largely a trial-and-error process based on clinical assessment including oxygen requirement and a subjective assessment of work of breathing. Diaphragm electrical activity (Edi) is an objective measure of respiratory effort and correlates with work of breathing, therefore may be a useful tool to guide weaning(Essouri et al., 2019). Edi measurement is safe and feasible in preterm infants, and high flow has been shown to reduce Edi compared to no support(Stein et al., 2013; Oda et al., 2019). Edi increased when weaning preterm infants from CPAP, with the greatest increase in those failing the weaning attempt, suggesting this may be a useful parameter to guide weaning of support(Kraaijenga et al., 2017). Little is known about the changes in Edi that occur with weaning high flow and whether this could be used to prospectively guide weaning in an objective, personalised manner.

3.2 Hypothesis

This study investigated the hypothesis that maximum diaphragm electrical activity will increase when weaning nasal high flow therapy in preterm infants.

3.3 Aims

The specific aims of this study were to:

- Develop a weaning protocol for high flow on the neonatal unit and assess the success of this weaning protocol.
- Describe the changes in diaphragm electrical activity that occur when weaning nasal high flow support in preterm infants.
- Compare changes in Edi during successful and unsuccessful weaning steps.
- Compare change in Edi with change in oesophageal pressure swing when weaning high flow.

3.4 Development of a high flow weaning protocol

The first step in designing this study was to develop a high flow weaning protocol. This needed to facilitate proactive weaning, but also be acceptable to the clinicians responsible for infants in the study to ensure adequate compliance. Development of the weaning protocol involved consideration of published international consensus statements, a retrospective review of current practice, and a national survey of high flow practice.

3.4.1 Published consensus statements

No prospective, randomised trials have assessed high flow weaning strategies, however two international consensus statements on use of high flow in neonates have been published, which include recommendations regarding weaning(Farley et al., 2015; Roehr et al., 2016; Yoder et al., 2017). These statements are based on expert opinion, rather than objective trial evidence therefore are subjective and should be interpreted with caution, but they were considered when developing the weaning protocol to ensure practice was not significantly out with international practice and broaden its generalisability. Weaning was generally recommended in 1L/min steps, every 24 hours when the fraction of inspired oxygen (FiO_2) is <0.3, although slower weaning was recommended in extremely low birthweight infants and those with BPD.

3.4.2 Retrospective study of current high flow practice

A retrospective study of high flow weaning practice on the neonatal intensive care unit at the Royal Victoria Infirmary, Newcastle upon Tyne was performed to assess current practice. All infants admitted over a one-year period from 1st January to 31st December 2018 who received high flow support during their admission were identified using BadgerNet, the national neonatal electronic patient record system. In total, 109 infants were identified: 8 infants received the majority of their neonatal care in a different unit and 5 infants had major anomalies not typical of standard neonatal practice therefore were excluded. The medical notes of a further 9 infants were unavailable for review, therefore 87 infants were included.

Medical and nursing records were retrospectively reviewed, and information gathered using a data collection form including infant demographics, previous respiratory management, high flow use and weaning. Successful weaning was defined as remaining at a lower flow rate (flow rate reduction steps) or off respiratory support (discontinuation steps) for ≥72 hours. This was chosen as a clinically important time point as infants who remain stable off respiratory support for 72 hours are generally felt to be safe to transfer from a neonatal intensive care or high-dependency unit to a local special care baby unit or postnatal ward.

The 87 infants studied received 135 episodes of high flow; 114 weaned to air or low flow oxygen, 17 required escalation of support to CPAP or invasive ventilation, and a further 2 remained on long-term respiratory support (2 infants were transferred to a different hospital on high flow therefore outcome unknown).

Median gestational age at birth was 28.3 weeks (IQR 27.1-30.3) and median corrected gestational age when commencing high flow 30.9 weeks (IQR 29.6-34.3). High flow was most frequently used to wean from CPAP in infants with evolving or established BPD (Table 3.1). Median starting flow rate was 5L/min (IQR 4-6). In total, 522 weaning steps consisting of 408 flow rate reductions and 114 discontinuation steps were included in the study.

Overall, 441/522 (85.5%) of weaning steps in this cohort were successful. Most weaning steps occurred when FiO_2 <0.30, however the overall success rate was the same for all weaning steps with FiO_2 ≤0.3 and with FiO_2 ≤0.35 (374/432; 86.6% v 407/470; 86.6%). Success of weaning did not appear to differ according to capillary carbon dioxide (CO_2) level

in this cohort, however this likely reflects heterogeneity in the study population, as many preterm infants have a chronically elevated but compensated pCO_2.

Duration of high flow therapy was influenced by gestational age and use of postnatal steroids (Table 3.1). Infants born at <28 weeks gestation received high flow for significantly longer than infants born at 28-31^{+6} weeks gestation (median duration 20 days v 7.5 days; p=0.003). Similarly, infants receiving postnatal steroids received high flow for significantly longer those who did not receive steroids (median duration 22 days v 8 days; p<0.001).

	Number (%)	
Indication for High Flow		
Primary support	10/135 (7.4%)	
Post-extubation	6/135 (4.4%)	
Wean from/alternative to CPAP	119/135 (88.1%)	
Starting Flow Rate		
≤3 L/min	10/135 (7.4%)	
4 L/min	48/135 (35.6%)	
5 L/min	39/135 (28.9%)	
6 L/min	34/135 (25.2%)	
≥7 L/min	4/135 (3.0%)	
Duration of High Flow (days)		
Gestational age: <28 weeks 28^{+0}-31^{+6} weeks ≥32 weeks	 20 (14-31) 7.5 (3.25-19.75) 2 (1-3)	
Infant received postnatal steroid: Yes No	 22 (15-43) 8 (2-19)	
FiO_2 when Weaning		
	Successful	**Unsuccessful**
0.21 – 0.25	279/312 (89.4%)	33/312 (10.6%)
0.26 – 0.30	95/120 (79.2%)	25/120 (20.8%)
0.31 – 0.35	33/38 (86.8%)	5/38 (13.2%)
0.36 – 0.40	30/46 (65.2%)	16/46 (34.8%)
>0.40	4/6 (66.7%)	2/6 (33.3%)
pCO_2 when Weaning		
<5.0 kPa	55/62 (88.7%)	7/62 (11.3%)
5.0 – 6.9 kPa	156/183 (85.3%)	27/183 (14.8%)
7.0 – 8.9 kPa	59/73 (80.8%)	14/73 (19.2%)
≥ 9.0 kPa	5/6 (83.3%)	1/6 (16.7%)
Flow Rate when Discontinuing		
≤2 L/min	74/94 (78.7%)	20/94 (21.3%)
3 L/min	9/12 (75%)	3/12 (25%)
4 L/min	6/7 (85.7%)	1/7 (14.3%)
5 L/min	1/1 (100%)	NA

Table 3.1 Current use of high flow and weaning practice at the Royal Victoria Infirmary. CPAP: Continuous positive airway pressure. FiO_2: Fraction of inspired oxygen. pCO_2: Partial pressure of carbon dioxide on capillary blood gas (measurements were included if taken within the 24hours prior to weaning). kPa: Kilopascals.

3.4.3 National survey of high flow practice

The final data considered when designing the study weaning protocol was a national survey of high flow practice in preterm infants in the United Kingdom (UK). This was part of a larger survey exploring use of high flow in extremely preterm infants (Appendix C) but included questions regarding weaning practice to ensure the study protocol was in line with national practice, and not simply based on single-centre data.

An online survey was sent to the lead consultant and nurse in each neonatal unit in the UK, via the 13 neonatal network leads. The survey was open from 1st June-1st September 2020 and each network lead distributed the survey link twice. Responses were obtained from all 13 neonatal networks. In total, 114 individuals (58 consultant neonatologists/paediatricians and 56 senior nurses) from 94 different UK neonatal units responded.

Results of the survey relating to high flow weaning practice are summarized in Table 3.2. Most respondents (65/108; 60.2%) report weaning high flow in 1L/min steps, with lowest flow rate 2L/min (67/108; 62%). Oxygen requirement and clinical examination were commonly considered when weaning high flow, however other factors such as blood gases and time since previous wean were less frequently considered. Consistent with our audit data, the majority of respondents report weaning high flow when FiO_2 was <0.3 (78/108; 72.2%) and wean less frequently in the most preterm infants.

	Number (%)
Total individuals responded	114
Individual units responded	94
Uses high flow	89/94 (94.7%)
Subsequent data displayed includes all respondents from units using nasal high flow (n=108)	
Highest flow rate used	
≤6 L/min	28/108 (25.9%)
7 L/min	6/108 (5.6%)
8 L/min	70/108 (64.8%)
>8 L/min	4/108 (3.7%)
Lowest flow rate used	
2 L/min	67/108 (62%)
3 L/min	27/108 (25%)
4 L/min	11/108 (10.2%)
≥5 L/min	3/108 (2.8%)
Flow rate change when weaning	
0.5 L/min	33/108 (30.6%)
1 L/min	65/108 (60.2%)
Other	10/108 (9.3%)
Factors considered when weaning	
Oxygen requirement	103/108 (95.4%)
Clinical examination	101/108 (93.5%)
Blood gas	76/108 (70.4%)
Time since last weaned	59/108 (54.6)
Other	6/108 (5.6%)
Oxygen threshold for weaning	
≤0.25	21/108 (19.4%)
≤0.3	57/108 (52.8%)
≤0.35	9/108 (8.3%)
>0.35	18/108 (16.7%)
Not known	3/108 (2.8%)
Frequency of weaning: Infant ≤28 weeks	
Daily	15/108 (13.9%)
Every 2 days	22/108 (20.4%)
Every 3+ days	7/108 (6.5%)
No set time	45/108 (41.7%)
Not known/would not use high flow	19/108 (17.6%)
Frequency of weaning: Infant 28-32 weeks	
Daily	36/108 (33.3%)
Every 2 days	21/108 (19.4%)
Every 3+ days	2/108 (1.9%)
No set time	40/108 (37%)
Not known/would not use high flow	9/108 (8.3%)
Frequency of weaning: Infant ≥32 weeks	
Daily	51/108 (47.2%)
Every 2 days	7/108 (6.5%)
Every 3+ days	0/108 (0%)
No set time	49/108 (45.4%)
Not known/would not use high flow	1/108 (0.9%)

Table 3.2 National survey of high flow weaning practice in the United Kingdom. All data displayed number (%).

3.4.4 High flow weaning protocol

The final devised weaning protocol is shown in Figure 3.1. Weaning was indicated when FiO_2 was ≤0.35 as this was the most discriminatory threshold identified. Although the national survey and consensus statements more commonly recommended weaning when FiO_2 was ≤0.3, no difference in success was evident when a threshold of ≤0.35 was used in our retrospective cohort study, therefore this was used in the study protocol. A specific pCO_2 was not defined due to the chronic hypercapnia and variation in 'normal' CO_2 that occurs in preterm infants, however a compensated pH and absence of significant tachypnoea or apnoea requiring intervention were specified to reflect stability.

Flow rate reductions of 1L/min were specified in the protocol in line with current unit and national practice. Although some individuals wean in 0.5L/min steps, physiological studies have shown that the change in positive end expiratory pressure with weaning is minimal (average 0.6cmH_2O per 1L/min flow rate change), therefore this is unlikely to have a clinically relevant effect(Liew et al., 2020). Weaning to a minimum flow rate of 2L/min was specified as, although some advocate discontinuing from higher flow rates, it is evident from physiological studies that even this relatively low flow rate does provide a degree of positive pressure support in preterm infants, and this is in line with current unit and national practice.

Timing of flow rate reductions was stratified according to gestational age and use of steroids, as these factors were associated with duration of support required. A range of timings were specified to accommodate the heterogeneity of the infants involved; the upper limit was calculated by dividing the median duration of high flow support for each group by median number of weaning steps required. The lower gestational age bracket in the weaning protocol was initially <28 weeks in line with the retrospective study and survey data, however following implementation this was lowered to <27 weeks as it became apparent that the occasional 27-week gestation infant may be able to be weaned daily. Predefined criteria to assess tolerance of change, and an escalation plan in case of an unsuccessful wean were included.

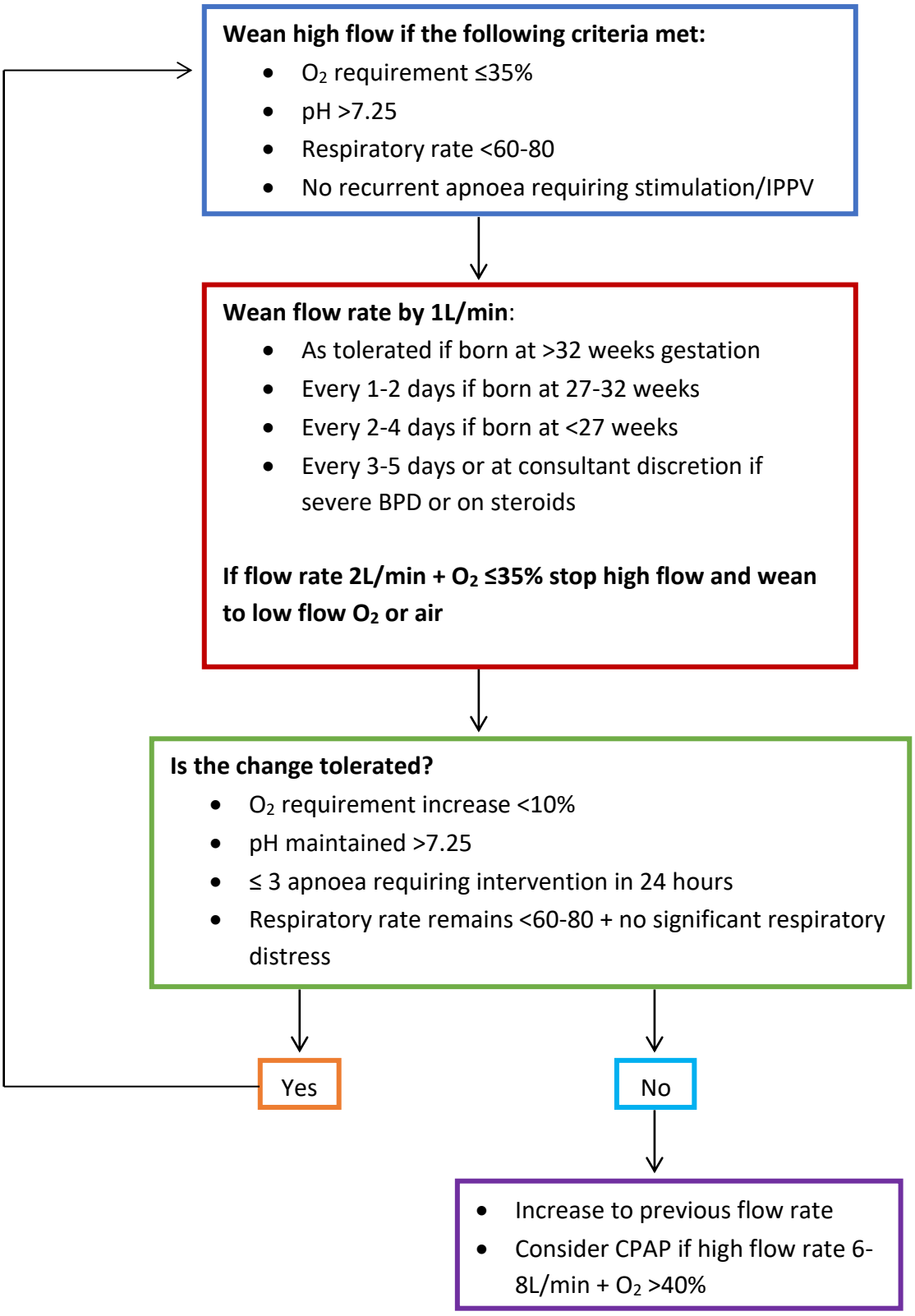

Figure 3.1 High flow study weaning protocol. O_2: Oxygen. IPPV: Intermittent positive pressure ventilation. BPD: Bronchopulmonary dysplasia. CPAP: Continuous positive airway pressure.

3.5 Study protocol

3.5.1 Ethical approval

This study was approved by the Newcastle and North Tyneside Research Ethics Committee (reference 19/NE/0317).

3.5.2 Participant identification and recruitment

This was a prospective, observational cohort study performed on the neonatal intensive care unit at the Royal Victoria Infirmary, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne from August 2020 to September 2021. Preterm infants born at <32 weeks gestation, receiving high flow as part of their routine clinical care were recruited. Exclusion criteria included major congenital, cardiac or neuromuscular abnormalities, or conditions that preclude passage of a gastric tube e.g. oesophageal atresia.

High flow therapy was commenced at a time and flow rate decided by the responsible senior clinician. Parents of eligible infants were approached prior to, or as soon as possible after the infant commenced high flow, and informed written parental consent was obtained prior to participation in the study.

3.5.3 Edi measurement protocol

High flow was delivered using a Fabien Therapy Evolution device (Accutronic) with appropriately sized nasal prongs selected to occlude less than half of the nostril as per the manufacturer's instructions. Weaning steps included both flow rate reductions (i.e. decreasing flow rate by 1L/min), and discontinuation steps (cessation of high flow from 2L/min to room air or low flow nasal cannula oxygen as required). Weaning steps were classified as successful if the infant remained at the lower rate or off high flow (or weaned further) for ≥72 hours and unsuccessful if increasing the flow rate or restarting high flow was required within 72 hours.

Following recruitment to the study, high flow was weaned according to the pre-specified study protocol (Figure 3.1). The infant's normal gastric feeding tube was replaced with an Edi-capable feeding tube (6F Edi catheter, Maquet, Sweden) prior to the first weaning step. This was done at a time acceptable to the family and nursing staff, and timed with a routine

tube change wherever possible. A series of measurements were made at 4 set timepoints: immediately before, immediately after, 4-hours after and 24-hours after each weaning step (Figure 3.2).

During each measurement period, heart rate and saturations were continually recorded using a pulse oximeter (Massimo Radical), and uncalibrated respiratory inductance plethysmography was used to monitor chest and abdominal excursion (Nims Respitrace 200). Diaphragm electrical activity was measured using the Edi-capable feeding tube, containing miniaturised electrodes at the level of the diaphragm (6F Edi catheter, Maquet, Sweden). The catheter was connected to a Servo-n ventilator (Maquet, Sweden) and optimal position of the catheter confirmed using the catheter positioning screen prior to use. The analogue Edi signal was transferred directly to a multichannel recorder (PowerLab, ADInstruments) via a digital to analogue convertor with a sampling frequency of 20Hz.

All measurements were made for a continuous 10-minute period with the infant asleep or quietly awake. Each series of measurements was made with the infant in either a prone or supine position, and for infants receiving bolus feeds, measurements were performed at least 1 hour after a feed. Mouth position was not controlled as the aim was to record normal breathing, representative of the infant's general condition.

A capillary blood gas was taken 4 hours after each weaning step to measure pCO_2. A pre-wean capillary gas was not routinely taken, but the most recent CO_2 was recorded if it was within the preceding 24 hours. Demographic and clinical data were obtained from an infant's medical records.

3.5.4 Oesophageal pressure measurement

It was originally planned that oesophageal pressure would be measured in all infants at 3 weaning steps (6 to 5L/min; 4 to 3L/min and discontinuation from 2L/min), however due to the difficulties with catheter stability and tolerance discussed earlier in this thesis (chapter 2), oesophageal pressure measurement was limited to a small subset of infants as an additional exploratory variable.

Oesophageal pressure was measured in 9 infants using their existing Edi-capable feeding tube as a fluid-filled catheter. Following the 10-minute, pre-wean Edi measurement period

the catheter was flushed with sterile water and connected to a pressure transducer (BP transducer, ADInstruments), linked via an amplifier to the multichannel recorder (PowerLab, ADInstruments). The tube was pulled back so the tip was positioned in the lower oesophagus, the position of which was confirmed by visualisation of the characteristic oesophageal pressure trace with a downward deflection during inspiration. To ensure patency of the catheter, a continuous infusion of sterile water was connected, running at 1ml/hour.

Oesophageal pressure was recorded for a 5-minute period immediately before and after the weaning step. During this time, RIP, heart rate and saturations were also continuously recorded. Following this, the tube was advanced to its previous length, back to a gastric position, and the Edi protocol resumed as above. The study protocol is outlined in Figure 3.2

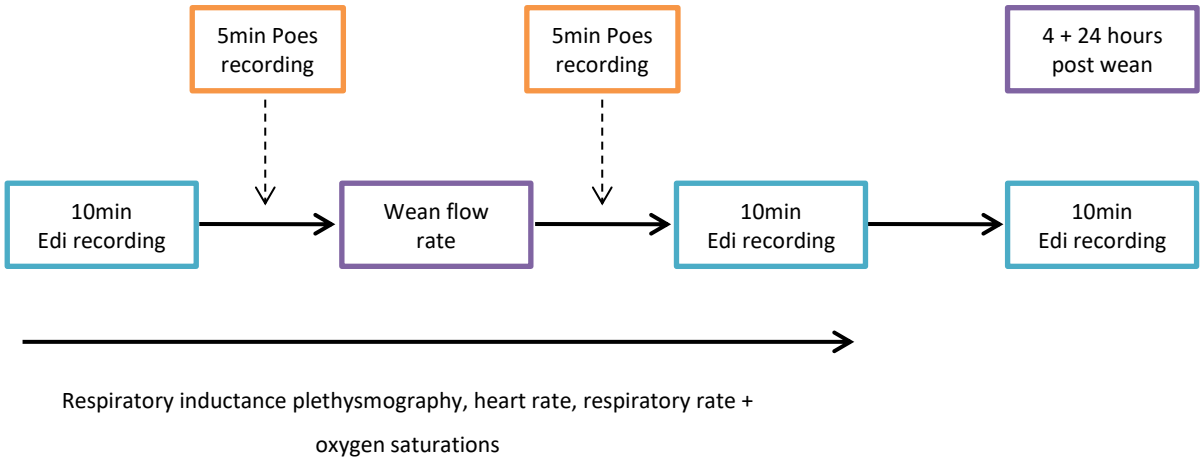

Figure 3.2 High flow weaning study measurement protocol. Edi: Electrical activity of the diaphragm. Poes: Oesophageal pressure. Dashed lines reflect additional measurements made in a subset of infants.

3.5.5 Data storage and analysis

Edi or oesophageal pressure, respiratory inductance plethysmography, heart rate and saturation data were simultaneously recorded and stored in a multichannel recorder (PowerLab, ADInstruments).

For Edi recordings, all artefact free breaths during each 10-minute recording included in the analysis. Periods of movement artefact, central apnoea and sigh breaths were excluded, but

all other breaths were included to take into account the high physiological variability in infant breathing. For each breath, the maximal Edi during inspiration (Edi max), the minimum Edi during expiration (Edi min), amplitude of the Edi signal (Edi delta = Edi max – Edi min), and area under the Edi curve (Edi a.u.c.) were measured. The average change in these parameters from baseline (pre-wean) was calculated for each timepoint. Neural respiratory rate was calculated from the Edi recordings, and the number of central respiratory pauses, defined as Edi amplitude <1microvolt for >5seconds, in each 10-minute period were recorded(Beck et al., 2011).

For oesophageal pressure recordings, a representative sample of 30 artefact-free breaths were analysed. For each breath the change in oesophageal pressure during inspiration (ΔPoes) and the pressure time product (PTP/breath) were measured. Respiratory rate was calculated using the oesophageal pressure cycle time, and the PTPoes/min calculated by multiplying PTPoes/breath by the respiratory rate.

All analysis was performed using ADInstruments LabChart 8 software.

3.5.6 Statistics

Data are summarised as frequencies and percentages for categorical variables, or median and interquartile ranges (25^{th}-75^{th} percentile) for continuous, non-parametric variables. Changes in physiological parameters from baseline with weaning were analysed using the Wilcoxon-signed rank test with sequential Bonferroni correction, and comparison between groups were made using the Mann-Whitney U test. The Pearson correlation coefficient was calculated to explore the correlation between variables. A p-value <0.05 was considered significant. Statistical analysis was performed using SPSS v27 and GraphPad Prism v9.0.

Using published preterm Edi data, a sample size of 40 infants was estimated to allow detection of a 25% increase in Edi max with 90% power and significance level 0.05(Stein et al., 2013).

3.6 Results

3.6.1 Infant demographics

During the study period, 61 potentially eligible infants were identified; 15 were not approached and 6 declined to participate (Figure 3.3). Although no minimum level of high flow was specified for recruitment, 4 infants were not approached as they rapidly required only low levels of support therefore a period of weaning was not required. Similarly, no minimum weight was specified, but two extremely growth restricted infants (<700g) were not approached as felt to be too small for the equipment. In total, 40 eligible preterm infants were recruited.

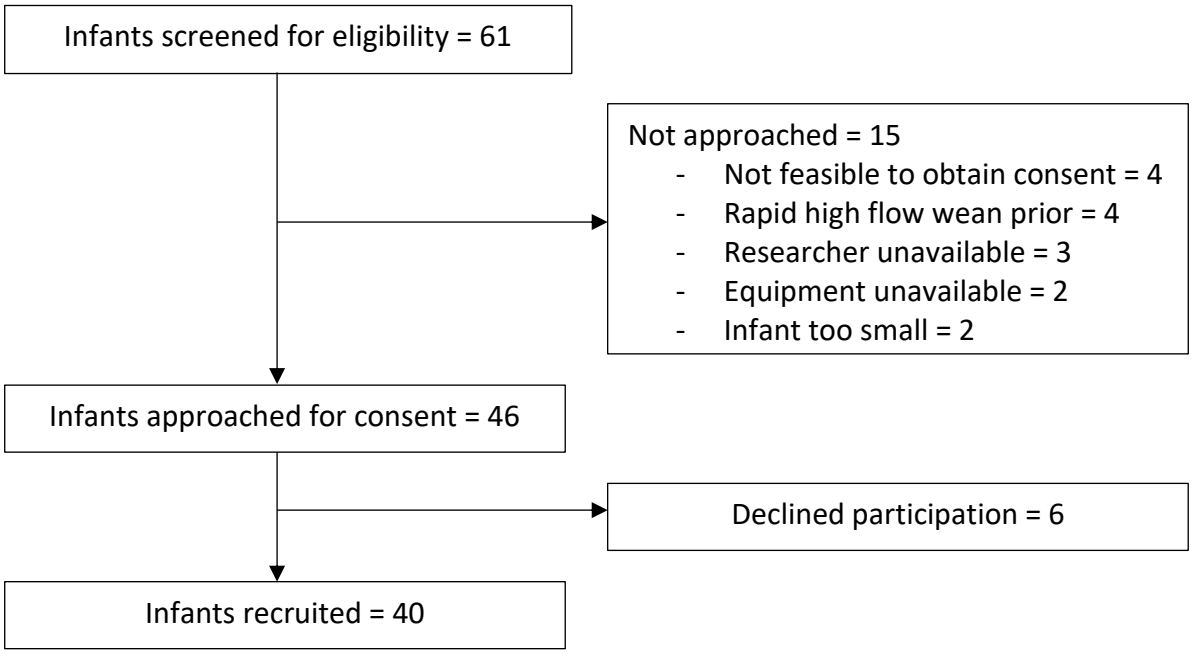

Figure 3.3 High flow study participant identification and recruitment.

Demographic details of infants recruited are in Table 3.3. Median gestational age at birth was 26.4 weeks (25.0-27.3) and birth weight 0.81kg (0.69-1.01). Most infants received invasive ventilation and CPAP prior to high flow (92.5% and 97.5% respectively). High frequency oscillatory ventilation and inhaled nitric oxide were used in around 1 in 3 infants; these are used as rescue therapies for severe respiratory failure in our unit therefore reflect severe respiratory disease. Postnatal steroids were used in 22/40 infants (55%).

At the point of commencing high flow, median CGA was 31.2 weeks (29.5-32.7) and weight 1.28kg (1.11-1.59). Starting flow rate was 6L/min (5-6) equivalent to 4.3L/kg/min (3.2-5.4). Median duration of high flow therapy during the study period was 15 days (11-21). Thirty-three (82.5%) infants had moderate/severe BPD, defined as need for oxygen and/or positive pressure support at 36 weeks CGA, and 30/40 (80%) required home oxygen. All infants survived to discharge.

	Number (%) or median (IQR)
Demographics and Background	
Gestation (weeks)	26.4 (25.0-27.3)
Birth weight (g)	0.81 (0.69-1.01)
Male	23/40 (57.5%)
Caesarean-section delivery	23/40 (57.5%)
Maternal antenatal steroids	
None	4/40 (10%)
1 dose	17/40 (42.5%)
≥2 doses	19/40 (47.5%)
Invasive ventilation	
Received	37/40 (92.5%)
Age first received (days)	0 (0-0)
Ventilator days	17 (3-27.5)
Received HFOV	12/40 (30%)
Received iNO	13/40 (32.5%)
CPAP	
Received	39/40 (97.5%)
Age first received (days)	10 (2-22.5)
CPAP days	18 (6.5-28.5)
Received postnatal steroids	22/40 (55%)
Received diuretics	11/40 (27.5%)
PDA medical therapy	12/40 (30%)
PDA ligation	4/40 (10%)
IVH grade ≥2	6/40 (15%)
Treatment for ROP	9/40 (22.5%)
High Flow Therapy	
Age commenced high flow (days)	35 (14-55.3)
CGA commenced high flow (weeks)	31.2 (29.5-32.7)
Weight at starting high flow (kg)	1.28 (1.11-1.59)
Starting flow rate (L/min)	6 (5-6)
Weight-adjusted starting flow rate (L/min/kg)	4.3 (3.2-5.4)
Study high flow days	15 (11-21)
Total high flow days	18 (11-29.5)
Weight at discontinuation (kg)	1.8 (1.3-2.1)
Weight-adjusted flow rate at discontinuation (L/min/kg)	0.9 (0.7-1.1)
Respiratory Outcomes	
Moderate/severe BPD at 36 weeks CGA	33/40 (82.5%)
Respiratory support at 36 weeks CGA	
None	7/40 (17.5%)
Low flow	19/40 (47.5%)
High flow	11/40 (27.5%)
CPAP	3/40 (7.5%)
Home oxygen	32/40 (80%)

Table 3.3 Infant characteristics and high flow parameters. HFOV: High frequency oscillatory ventilation. iNO: Inhaled nitric oxide. CPAP: Continuous positive airway pressure. PDA: Patent ductus arteriosus. IVH: Intraventricular haemorrhage. ROP: Retinopathy of prematurity. CGA: Corrected gestational age.

3.6.2 Study measurements

Measurements were made for 162 weaning steps; data from 6 steps were excluded due to technical issues therefore 156 weaning steps were included in the analysis. This included 117 flow rate reductions and 39 discontinuation steps. Data were available immediately pre- and post-wean for all 156 steps, at 4 hours for 142 and at 24 hours for 131 steps. Missing data points were due to researcher unavailability (26/39), removal of the Edi-capable gastric tube prior to data collection (9/39), or a further change in flow rate before the measurement was due (4/39). Median number of breaths included per 10-minute recording was 306 (236-420).

3.6.3 Weaning protocol success

Weaning occurred as per protocol in 132/156 (85%) steps; of those that occurred outside the protocol 13/24 (54%) occurred ahead of recommended time and 11/24 (46%) occurred later than the protocol recommended at the discretion of the responsible clinician. Overall, 142/156 (91%) of weaning steps were successful i.e. infant remained at the lower flow rate of off high flow for ≥72 hours.

The unsuccessful weaning steps were 9 flow rate reductions and 5 discontinuation steps. Reasons for unsuccessful weaning were increased apnoea/desaturation in 9/14 (64%), increased respiratory distress in 3/14 (21%) and increased FiO_2 in 2/14 (14%). Two infants required escalation of their respiratory support to CPAP during the study period due to a deterioration associated with sepsis.

3.6.4 Change in Edi with flow rate reduction and discontinuation steps

Considering all weaning steps together, a statistically significant increase in Edi max, Edi delta and Edi a.u.c. were evident immediately and at 24-hours post wean, whilst a significant increase in Edi min was evident only at 24-hours post wean (Table 3.4). However, when considering the flow rate reduction and discontinuation steps separately, these differences exclusively occurred in the discontinuation steps (Table 3.5, Table 3.6 and Figure 3.4 to Figure 3.7).

In the combined flow rate reduction steps, no significant change in any Edi parameter was evident (Table 3.5). Data for individual flow rate reduction steps are displayed in Table 3.7. A statistically significant increase in Edi delta was evident at 24 hours post-wean from 3 to 2 L/min, but no other significant differences were identified.

In contrast, following discontinuation of high flow Edi max, Edi delta and Edi a.u.c. increased significantly (Table 3.6). Immediately following discontinuation of high flow, Edi max increased significantly from a median of 10.89µV (IQR 7.3-14.05) at baseline to 13.13µV (IQR 11.1-16.1; $p<0.001$) post-discontinuation (Figure 3.4). At 4-hours post discontinuation, Edi max was not significantly different to baseline (median 10.49µV [IQR 7.75-15.85]; $p=0.1$), however a significant increase was again evident at 24 hours post discontinuation (median 13.56µV [IQR 9.89-17.0]; $p<0.001$).

Similarly, Edi delta showed a statistically significant increase from a baseline of 8.17µV (IQR 5.93-11.02) to 9.42µV (IQR 8.06-13.95; $p<0.001$) immediately post-discontinuation, and 9.76µV (IQR 7.83-14.94; $p<0.001$) at 24-hours post-discontinuation of high flow (Figure 3.6). Edi min did not change significantly at any time point following discontinuation of high flow (Figure 3.5).

As the positive distending pressure delivered by high flow is related to infant weight, the correlation between change in Edi and change in weight adjusted flow rate when discontinuing high flow was assessed. No correlation between change in Edi max, Edi min, Edi delta or Edi area under curve and change in weight-adjusted flow rate (measured in L/min per kg) was evident (Figure 3.8 - Figure 3.11)

	Pre-Wean	Immediately post-wean	4 hours post-wean	24 hours post-wean
All Steps Combined (n=156)				
Number included	156	156	142	131
Edi Max (μV)	8.91 (6.05-12.91)	10.40 (6.05-12.91)*	8.95 (6.30-13.03)	9.54 (7.03-14.30)*
Edi Min (μV)	1.18 (0.72-2.16)	1.39 (0.72-2.27)	1.19 (0.71-1.97)	1.47 (0.89-2.77)*
Edi Delta (μV)	7.29 (4.67-10.82)	7.78 (4.96-11.36)*	6.83 (4.97 (11.17)	7.38 (5.35-10.87)*
Edi area under curve (μV)	4.65 (2.94-6.32)	4.91 (3.22-7.20)*	4.38 (2.90-6.43)	4.79 (3.22-6.50)*
Heart rate	155.7 (147.3-162.5)	156.6 (148.1-162.6)	154.6 (145.3-161.2)	156.8 (148.8-164.2)
Respiratory rate	59.8 (49.7-70.9)	61.5 (50.3-69.0)	61.4 (49.6-70.0)	63.4 (52.7-73.6)*
Central apnoea >5sec	1 (0-3)	1 (0-3)	1 (0-4)	1 (0-3)

Table 3.4 Diaphragm electrical activity (Edi) pre and post all weaning (flow rate reduction and discontinuation) steps combined. μV: Microvolts. All data number or median (IQR). Wilcoxon signed ranks test with sequential Bonferroni correction used to compare change from baseline (pre-wean): *Significantly different to pre-wean at timepoint ($p<0.05$).

	Pre-Wean	Immediately post-wean	4 hours post-wean	24 hours post-wean
Flow Rate Reduction Steps (n=117)				
Number included	117	117	105	97
Edi Max (μV)	8.57 (5.62-11.92)	8.65 (5.36-12.43)	8.22 (5.83-12.69)	8.73 (6.27-12.31)
Edi Min (μV)	1.13 (0.70-1.87)	1.10 (0.71-1.93)	1.10 (0.70-1.87)	1.19 (0.79-2.40)
Edi Delta (μV)	7.0 (4.35-10.23)	6.70 (4.48-10.78)	6.53 (4.73-10.04)	6.76 (4.91-9.90)
Edi area under curve (μV)	4.35 (2.83-6.08)	4.37 (2.82-6.34)	4.16 (2.80-5.75)	4.38 (3.04-5.94)
Heart rate	154.3 (147.4-162.7)	156.2 (146.7-161.2)	155.2 (147.3-160.5)	156.8 (149.4-164.2)
Respiratory rate	58.9 (48.5-69.8)	61.5 (48.9-68.8)	59.7 (49.7-68.3)	61.8 (52.4-72.4)*
Central apnoea >5sec	2 (0-4)	2 (0-4)	2 (0-5)	1 (0-3.5)

Table 3.5 Diaphragm electrical activity (Edi) pre and post flow rate reduction steps. μV: Microvolts. All data number or median (IQR). Wilcoxon signed ranks test with sequential Bonferroni correction used to compare change from baseline (pre-wean): *Significantly different to pre-wean at timepoint ($p<0.05$).

	Pre-Wean	Immediately post-wean	4 hours post-wean	24 hours post-wean
Discontinuation Steps (n=39)				
Number included	39	39	37	34
Edi Max (μV)	10.89 (7.30-14.05)	13.13 (11.10-16.10)*	10.49 (7.75-15.85)	13.56 (9.89-17.0)*
Edi Min (μV)	1.87 (0.89-2.64)	2.18 (1.08-3.80)	1.59 (0.91-2.69)	2.21 (1.14-3.76)
Edi Delta (μV)	8.17 (5.93-11.02)	9.42 (8.06-13.95)*	8.26 (5.36-13.51)	9.76 (7.83-14.94)*
Edi area under curve (μV)	5.16 (3.41-7.0)	7.14 (4.89-8.59)*	5.27 (3.33-7.87)	5.80 (4.96-8.38)*
Heart rate	157 (144.3-161.4)	158.4 (152.8-166.5)	152.2 (143.5-164.0)	156.7 (147.4-165.1)
Respiratory rate	62.6 (54.3-76.7)	62.5 (52.6-69.1)	66.1 (49.6-71.6)	68.5 (53.6-74.5)
Central apnoea >5sec	1 (0-2)	0 (0-1)	0 (0-2)	0 (0-1)

Table 3.6 Diaphragm electrical activity (Edi) pre and post discontinuation steps. μV: Microvolts. All data number or median (IQR). Wilcoxon signed ranks test with sequential Bonferroni correction used to compare change from baseline (pre-wean): *Significantly different to pre-wean at timepoint ($p<0.05$).

	Pre-Wean	Immediately post wean	4 hours post-wean	24 hours post-wean
Wean 6 to 5 L/min (n=14)				
Edi Max (μV)	7.25 (4.96-9.85)	6.36 (4.76-11.40)	8.22 (6.45-12.0)	7.95 (5.84-11.14)
Edi Min (μV)	0.91 (0.59-1.13)	0.84 (0.57-1.43)	0.81 (0.60-3.23)	1.29 (0.90-2.22)
Edi Delta (μV)	6.26 (3.66-8.66)	5.32 (3.38-9.25)	6.60 (4.67-10.21)	6.38 (4.43-8.90)
Edi a.u.c. (μV)	3.60 (2.82-5.32)	3.03 (2.65-6.04)	5.0 (2.79-6.35)	4.0 (3.09-5.54)
Wean 5 to 4 L/min (n=27)				
Edi Max (μV)	8.27 (5.03-11.09)	8.38 (5.09-11.44)	7.31 (5.42-10.68)	8.12 (5.40-12.03)
Edi Min (μV)	0.89 (0.53-1.87)	0.81 (0.6-1.67)	0.90 (0.69-1.58)	1.0 (0.68-1.48)
Edi Delta (μV)	6.17 (4.0-9.7)	6.81 (4.29-10.85)	6.43 (4.39-9.36)	5.88 (4.51-10.23)
Edi a.u.c. (μV)	4.33 (2.55-6.03)	4.66 (2.7-6.44)	3.99 (2.68-5.26)	4.36 (2.72-6.06)
Wean 4 to 3 L/min (n=38)				
Edi Max (μV)	10.08 (6.05-15.36)	8.51 (6.35-14.06)	8.95 (6.55-12.62)	8.52 (6.33-11.27)
Edi Min (μV)	1.42 (0.80-2.24)	1.2 (0.83-2.10)	1.28 (0.73-1.85)	1.19 (0.71-2.40)
Edi Delta (μV)	8.21 (4.67-12.23)	6.73 (4.75-11.06)	6.83 (5.08-9.19)	6.70 (5.05-9.08)
Edi a.u.c. (μV)	4.99 (2.87-7.16)	4.40 (3.12-7.27)	4.73 (2.90-5.47)	4.31 (2.90-5.96)
Wean 3 to 2 L/min (n=38)				
Edi Max (μV)	8.34 (5.71-12.58)	8.92 (5.97-12.26)	8.28 (6.11-13.04)	10.23 (7.2-14.28)
Edi Min (μV)	1.18 (0.68-1.89)	1.46 (0.71-2.26)	1.10 (0.69-1.88)	1.87 (0.99-3.32)
Edi Delta (μV)	6.17 (4.51-11.38)	6.85 (4.85-11.30)	6.03 (4.59-11.54)	7.39 (5.44-10.87)*
Edi a.u.c. (μV)	3.98 (2.71-5.94)	4.34 (3.07-5.89)	3.92 (2.72-5.75)	4.79 (3.34-6.50)

Table 3.7 Diaphragm electrical activity (Edi) values with individual flow rate reduction steps. A.u.c: Area under curve. μV: Microvolts. All data median (IQR). Wilcoxon signed ranks test with sequential Bonferroni correction: *Significantly different to pre-wean at timepoint ($p<0.05$).

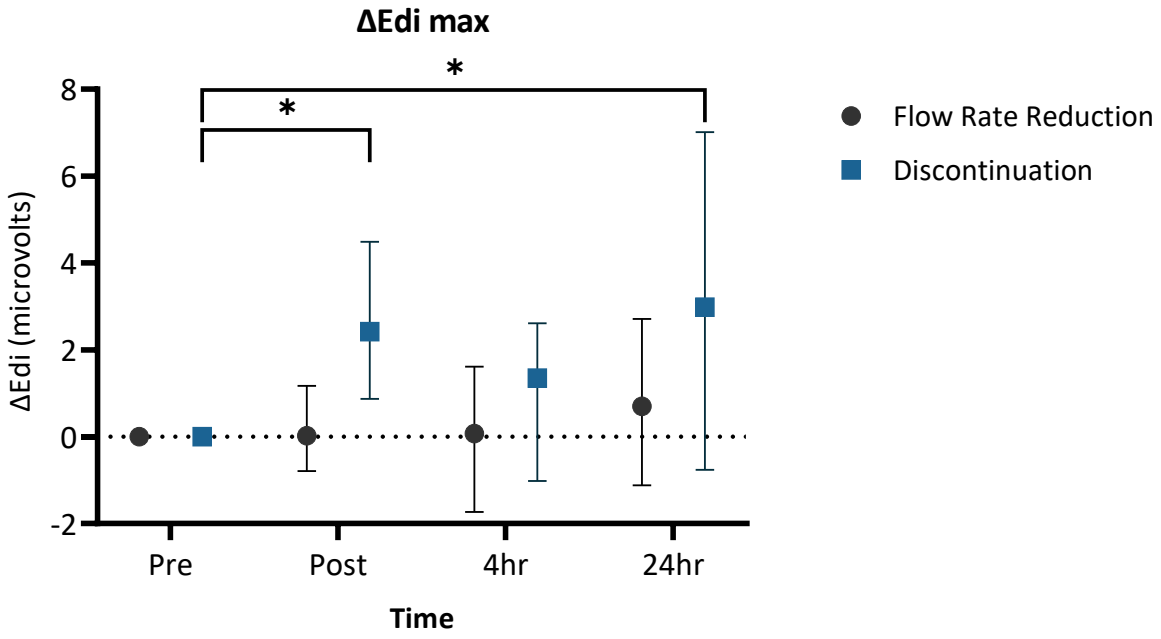

Figure 3.4 Change in maximum diaphragm electrical activity (Edi max) with flow rate reduction and discontinuation steps. Data presented as median (IQR). *Significantly different to pre-wean values ($p<0.05$)

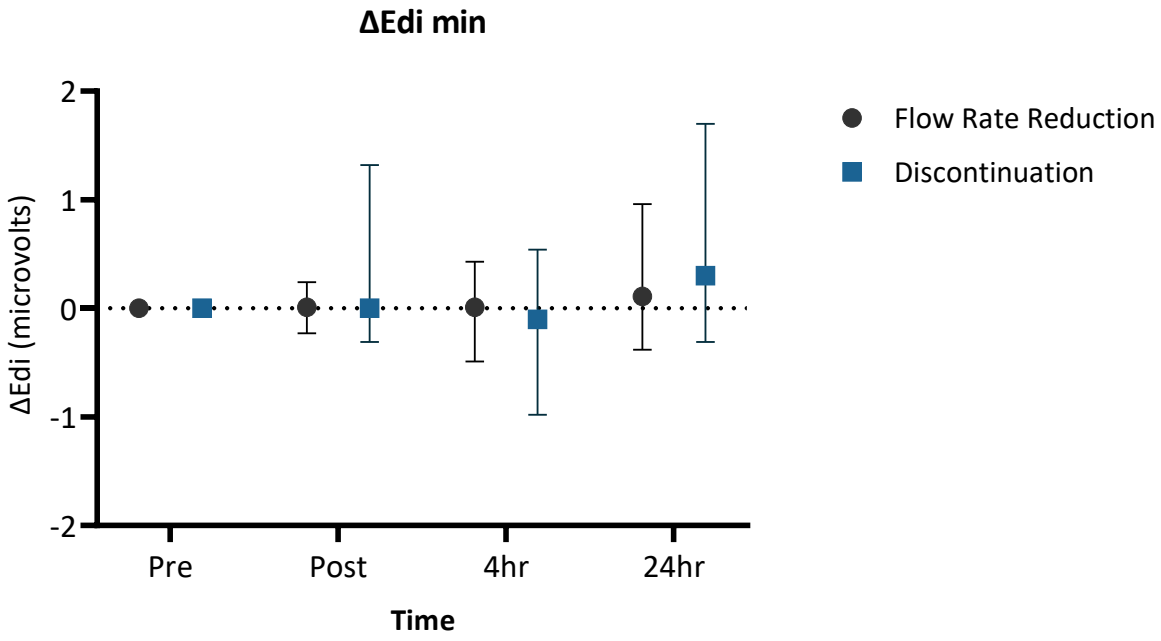

Figure 3.5 Change in minimum diaphragm electrical activity (Edi min) with flow rate reduction and discontinuation steps. Data presented as median (IQR). *Significantly different to pre-wean values ($p<0.05$)

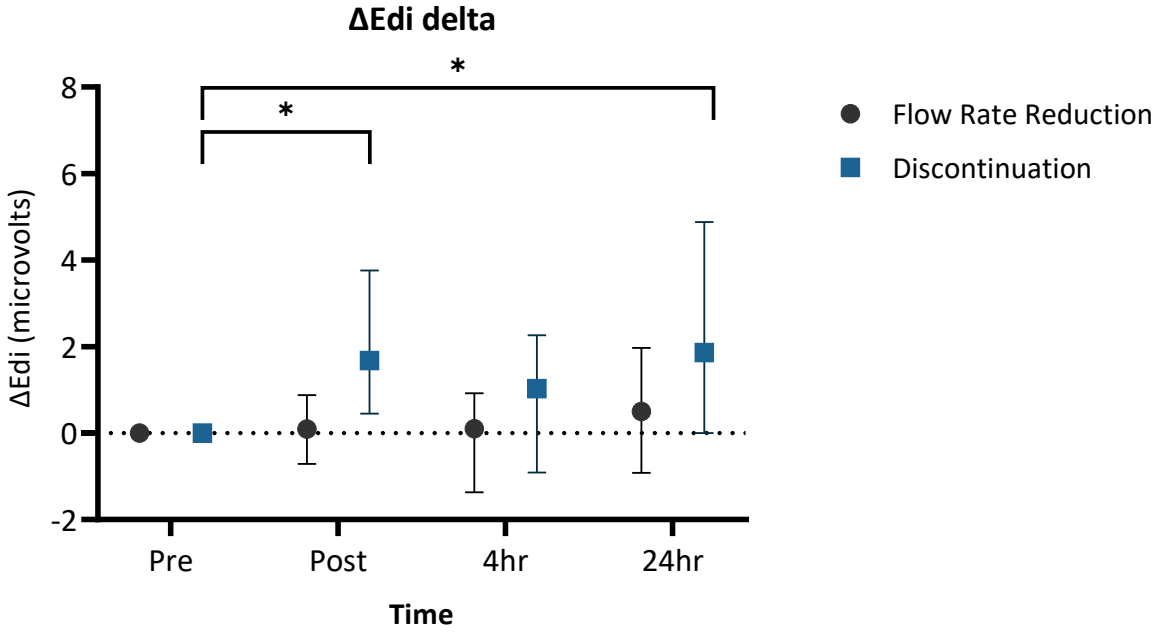

Figure 3.6 Change in diaphragm electrical activity delta (Edi delta) with flow rate reduction and discontinuation steps. Data presented as median (IQR). *Significantly different to pre-wean values ($p<0.05$)

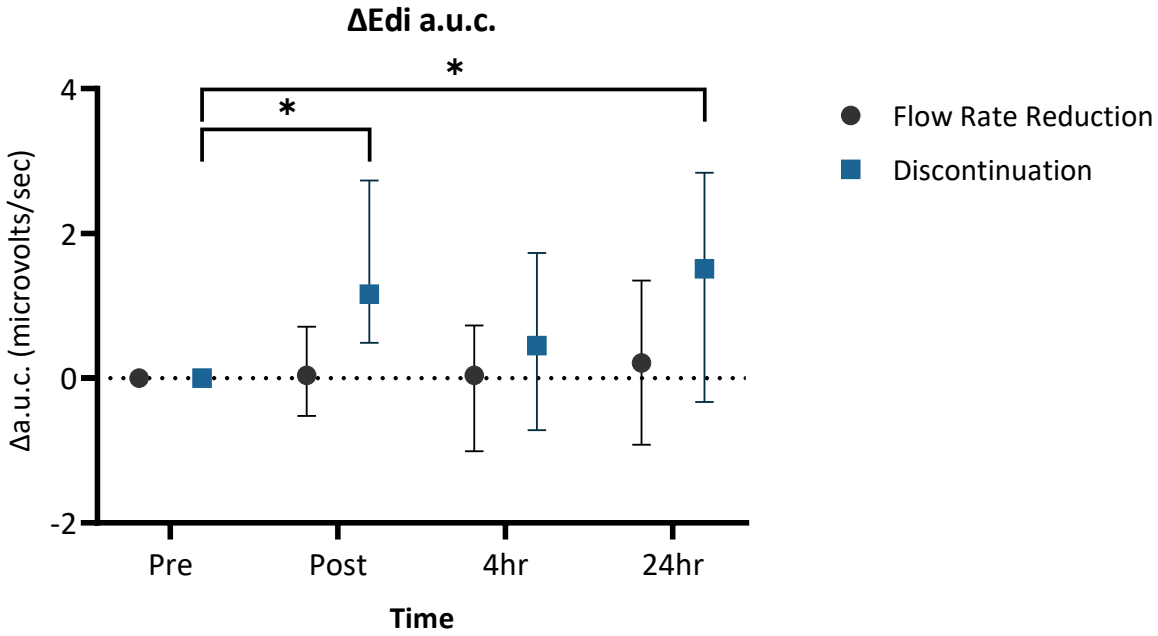

Figure 3.7 Change in diaphragm electrical activity area under the curve (Edi a.u.c.) with flow rate reduction and discontinuation steps. Data presented as median (IQR). *Significantly different to pre-wean values ($p<0.05$)

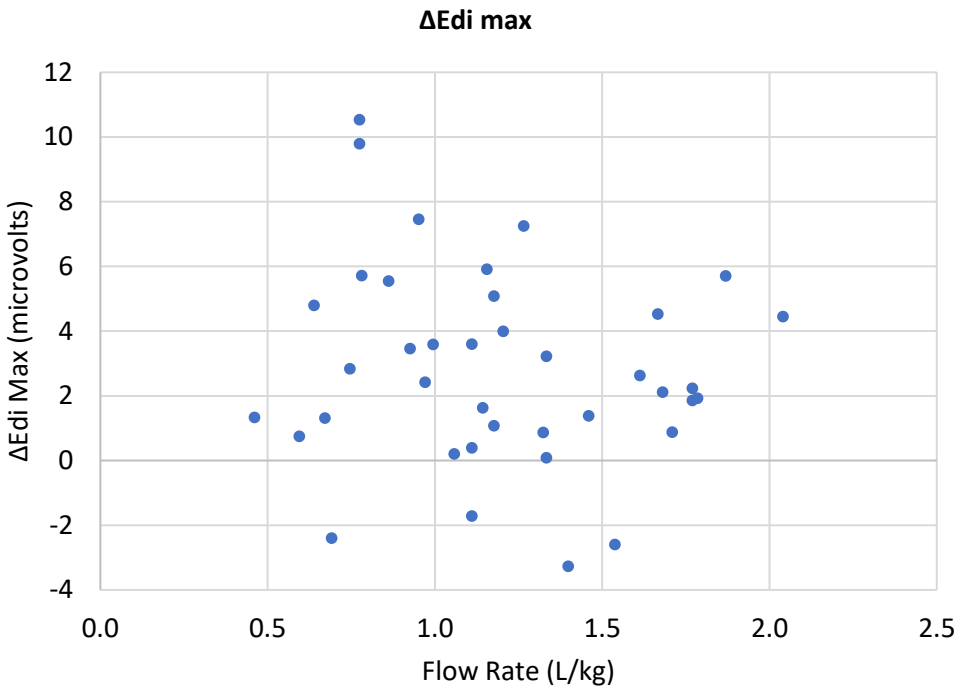

Figure 3.8 Scatterplot of weight adjusted flow rate and change maximum diaphragm electrical activity (Edi max) when discontinuing high flow. Pearson correlation coefficient -0.138 (p=0.40)

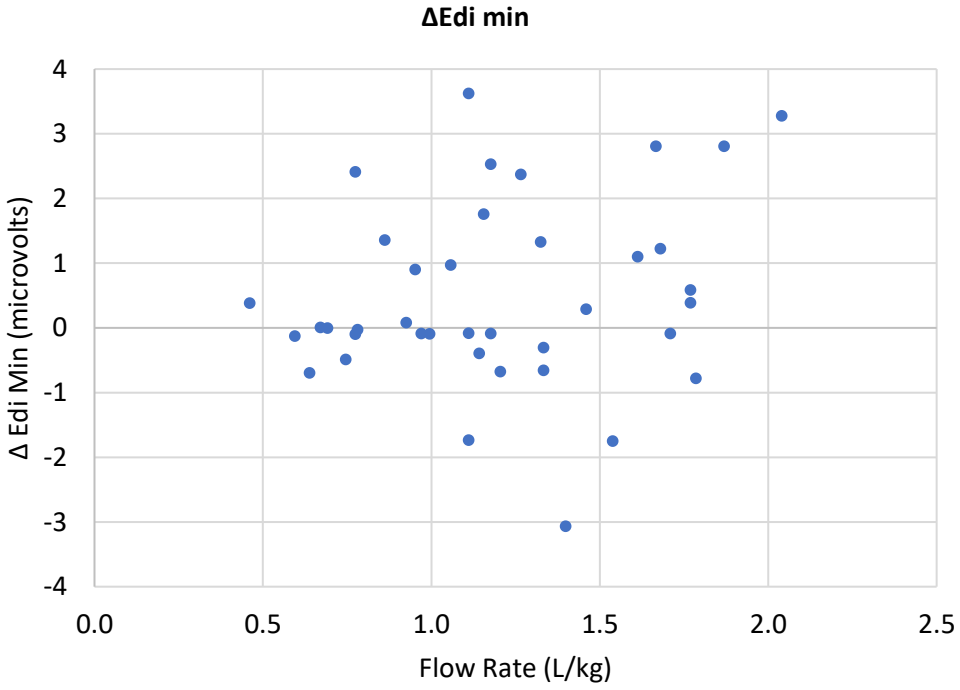

Figure 3.9 Scatterplot of weight adjusted flow rate and change in minimum diaphragm electrical activity (Edi min) when discontinuing high flow. Pearson correlation coefficient 0.206 (p=0.21)

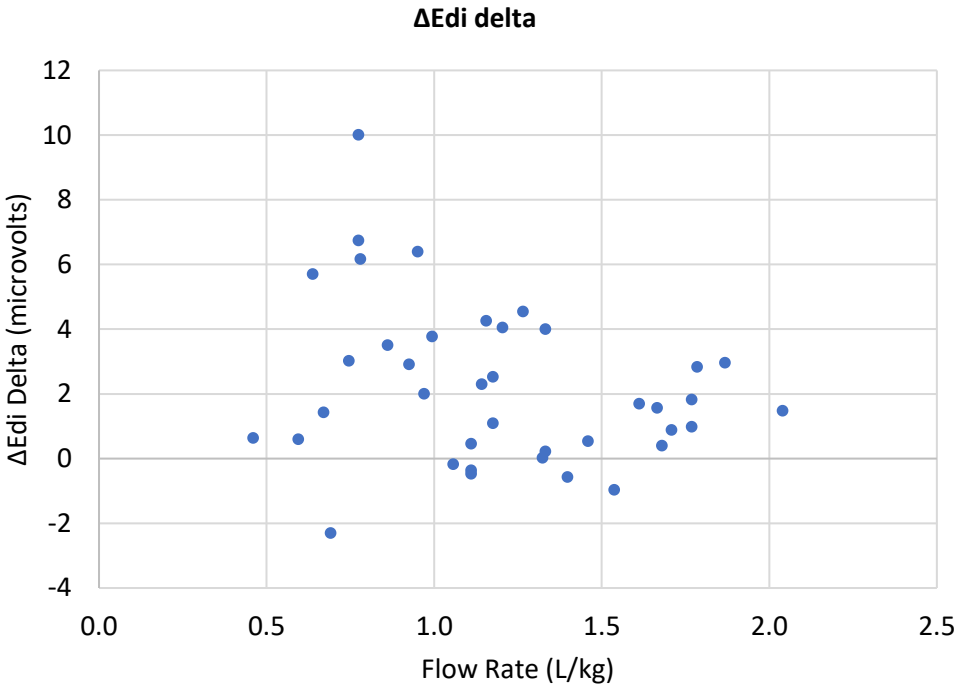

Figure 3.10 Scatterplot of weight adjusted flow rate and change diaphragm electrical activity delta (Edi delta) when discontinuing high flow. Pearson correlation coefficient -0.269 (p=0.1)

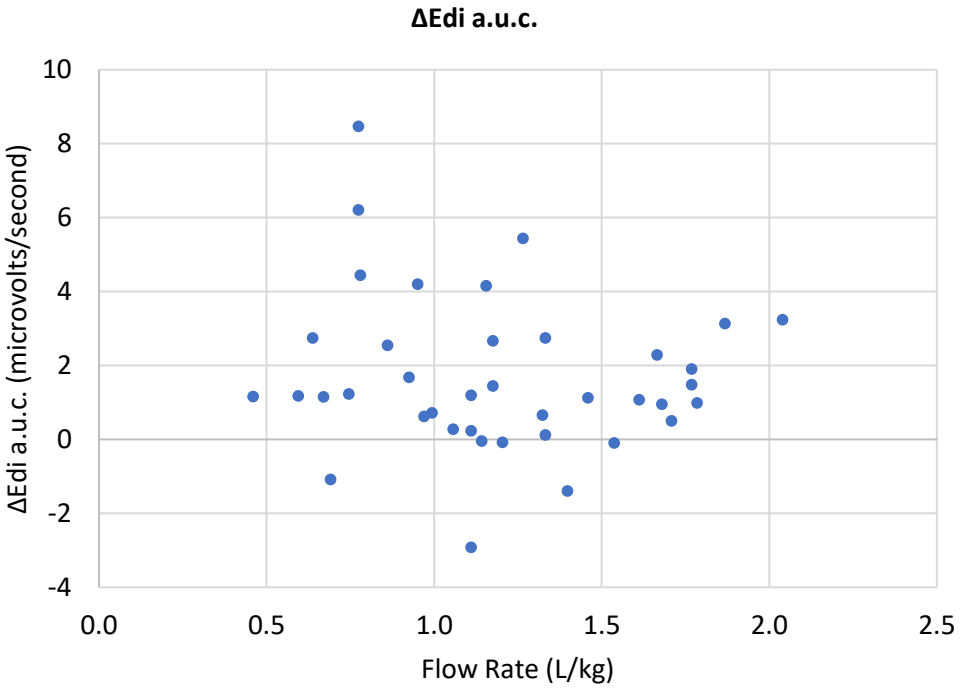

Figure 3.11 Scatterplot of weight adjusted flow rate and change diaphragm electrical activity area under the curve (Edi a.u.c.) when discontinuing high flow. Pearson correlation coefficient -0.122 (p=0.46)

3.6.5 Change in clinical parameters

There was no significant change in median FiO_2 from baseline (0.26 [IQR 0.22-0.28]) to 4-hours or 24-hours post weaning (median 0.28 [IQR 0.22-0.30; p=0.28] and 0.26 [IQR 0.22-0.30; p=0.54] respectively). Capillary pCO_2 did not change from baseline to 4-hours post weaning (median 6.6kPa [IQR 6.0-7.3] v 6.7kPa [IQR 6.1-7.3]; p=0.17).

A statistically significant increase in respiratory rate was observed 24-hours post flow rate reduction, from median 58.9 (IQR 48.5-69.8) to 61.8 (IQR 52.4-72.4) breaths per minute (p=0.005), however it is unlikely this is of clinical significance. No other significant changes in clinical parameters (heart rate, respiratory rate or frequency of central apnoea >5 seconds) were observed with flow rate reduction or discontinuation of high flow (Table 3.4 to Table 3.6).

3.6.6 Successful versus unsuccessful weaning

No significant difference in any Edi or clinical parameters were observed between successful and unsuccessful weaning steps (Table 3.8 and Figure 3.12 to Figure 3.15).

Although median Edi values did not differ between successful and unsuccessful weaning steps, a significant increase in Edi max, Edi delta and Edi a.u.c. were demonstrated immediately and at 24-hours post successful weaning steps (Figure 3.12 to Figure 3.15). This longitudinal trend was also evident in unsuccessful weaning steps, although the differences were not statistically significant in this group, likely reflecting the small number of unsuccessful steps.

All Weaning Steps Successful v Unsuccessful								
	Successful (n=142)	**Unsuccessful** (n=14)	**Successful** (n=142)	**Unsuccessful** (n=14)	**Successful** (n=128)	**Unsuccessful** (n=14)	**Successful** (n=120)	**Unsuccessful** (n=11)
Edi Max (µV)	8.86 (6.03-12.94)	10.91 (5.97-12.76)	10.40 (6.15-13.89)[a]	10.15 (7.35-13.23)	8.73 (6.27-12.82)	12.65 (7.32-15.23)	9.40 (6.88-14.47)[c]	11.10 (8.37-13.50)
Edi Min (µV)	1.18 (0.72-2.16)	1.25 (0.75-1.76)	1.46 (0.72-2.35)	1.25 (0.63-1.89)	1.19 (0.70-1.95)	1.39 (0.90-3.87)	1.47 (0.89-2.73)	1.38 (0.70-2.83)
Edi Delta (µV)	7.10 (4.66-10.65)	8.89 (4.30-11.02)	7.78 (4.94-11.39)[a]	8.45 (5.90-11.79)	6.70 (4.96-10.56)	8.41 (6.17-12.16)	7.38 (5.30-11.01)[c]	8.82 (5.44-10.85)
Heart rate	155 (146.4-162.1)	158.7 (154.0-165.0)	156.6 (147.6-162.1)	161.0 (150.5-165.0)	154.2 (144.2-160.6)	157.5 (153.5-163.6)*	156.8 (148.3-164.3)	159.6 (152.7-165.9)
Respiratory rate	59.8 (49.1-70.6)	60.3 (54.0-74.1)	61.6 (50.6-69.0)	53.5 (45.9-67.8)	61.4 (49.4-69.9)	61.3 (51.2-75.5)	63.0 (52.4-73.4)	65.6 (59.2-78.2)[c]
Central pause >5sec	1 (0-3)	1 (0-4.5)	1 (0-3.3)	0.5 (0-3.5)	1 (0-4)	1.5 (0-3.3)	1 (0-3)	1 (0-2)

Table 3.8 Comparison of diaphragm electrical activity (Edi) and clinical parameters in successful and unsuccessful weaning steps.

All data median (IQR). Mann-Whitney U test used to compare successful and unsuccessful categories: *Successful significantly different to unsuccessful ($p<0.05$). Wilcoxon signed ranks test with sequential Bonferroni correction used to compare change from baseline (pre-wean values): [a] Post wean significantly different to pre-wean ($p<0.05$); [b] 4hr significantly different to pre-wean ($p<0.05$); [c] 24hr significantly different to pre-wean ($p<0.05$).

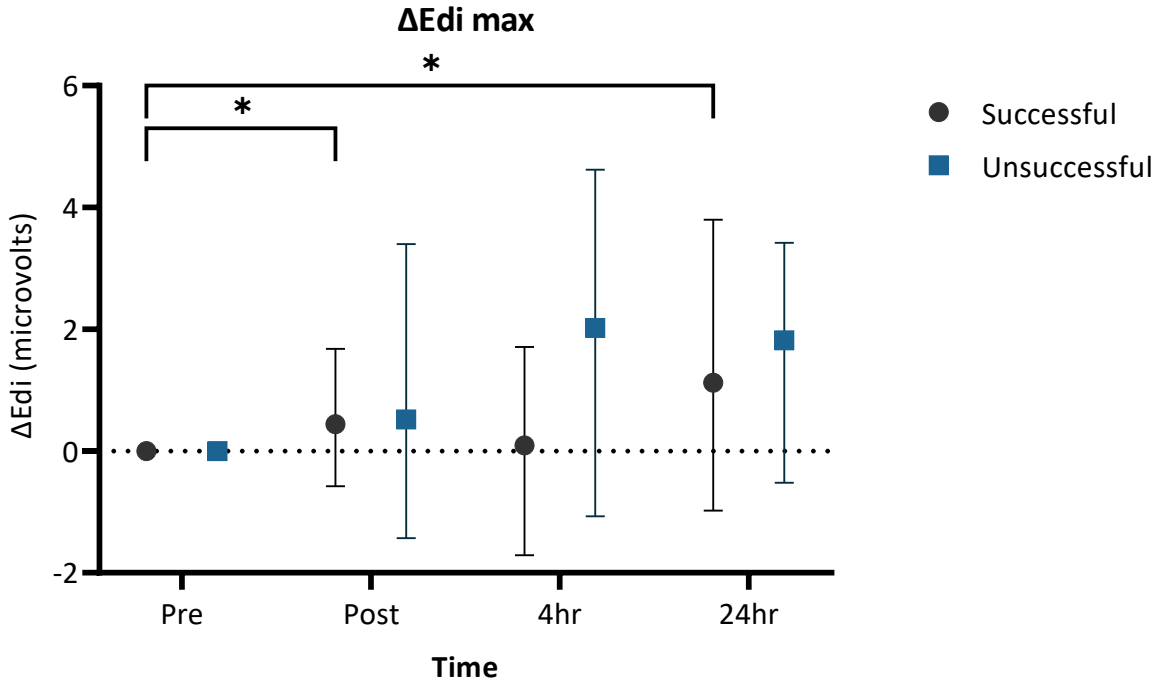

Figure 3.12 Change in maximum diaphragm electrical activity (Edi max) with successful and unsuccessful weaning steps. Data presented as median (IQR). * Significantly different to pre-wean values ($p<0.05$).

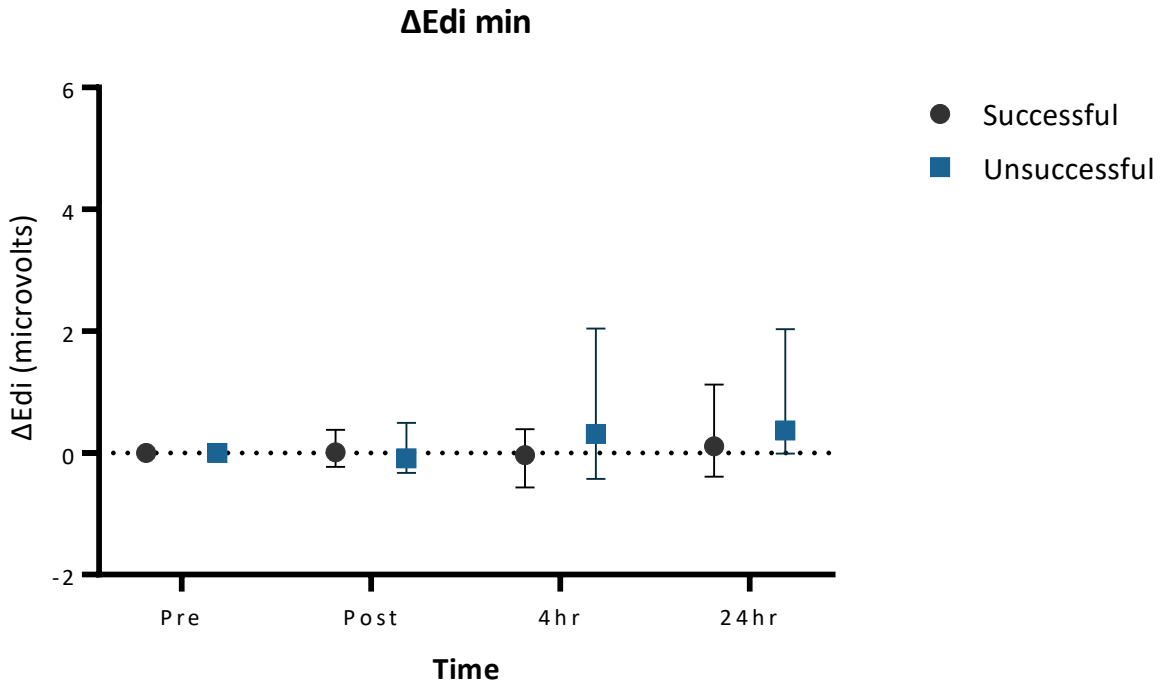

Figure 3.13 Change in minimum diaphragm electrical activity (Edi min) with successful and unsuccessful weaning steps. Data presented as median (IQR). * Significantly different to pre-wean values ($p<0.05$).

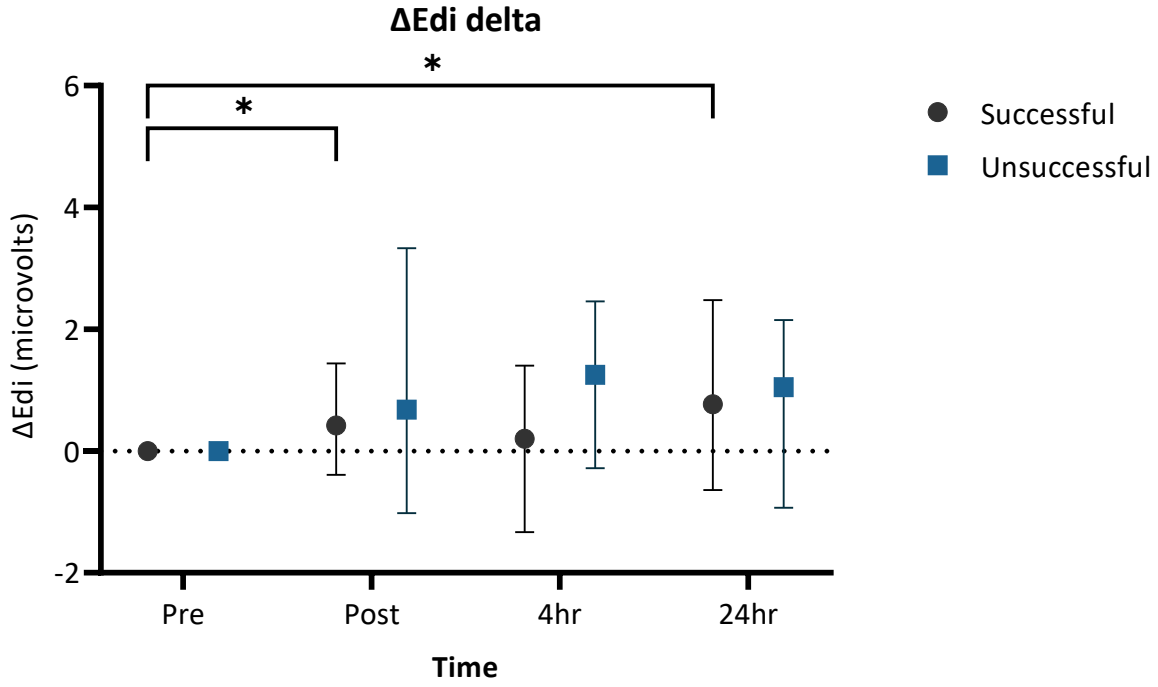

Figure 3.14 Change in diaphragm electrical activity delta (Edi delta) with successful and unsuccessful weaning steps. Data presented as median (IQR). * Significantly different to pre-wean values ($p<0.05$).

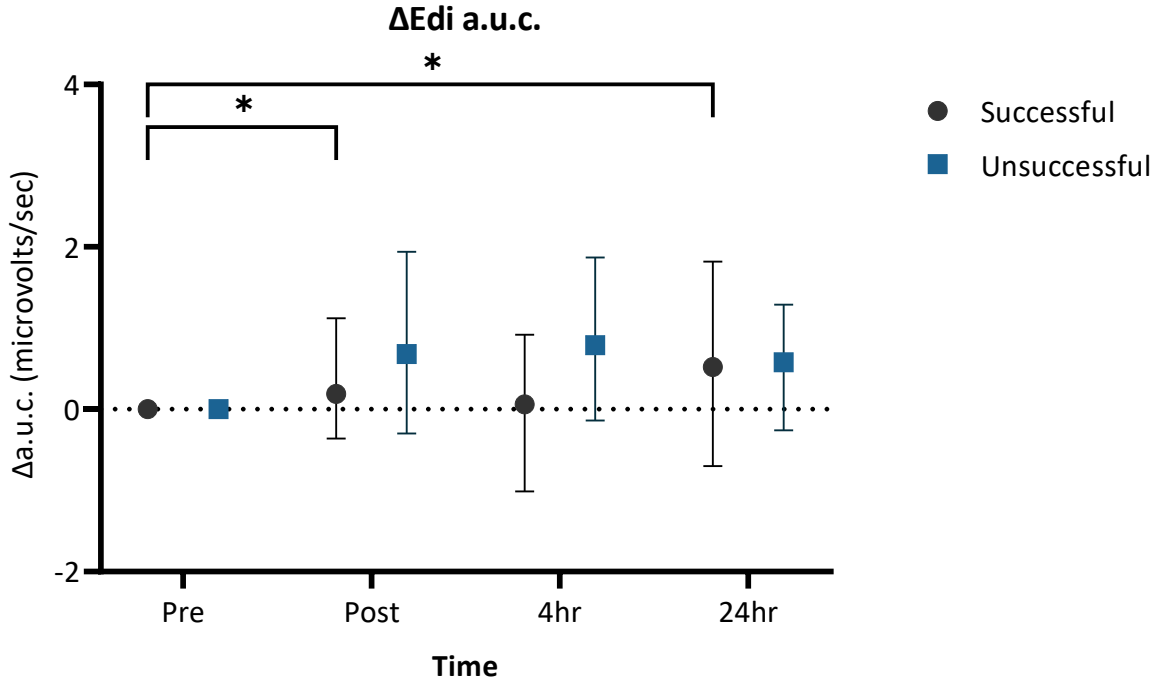

Figure 3.15 Change in diaphragm electrical activity area under the curve (Edi a.u.c.) with successful and unsuccessful weaning steps. Data presented as median (IQR). * Significantly different to pre-wean values ($p<0.05$).

3.6.7 Oesophageal pressure measurements

Oesophageal pressure measurements were undertaken in a convenience sample of 9 infants from May to September 2021. Only infants receiving bolus feeds were included to avoid discontinuing milk in infants receiving a continuous feed. Seventeen recordings were made, but 3 were excluded due to poor data quality. In total, 14 recordings, consisting of 7 flow rate reductions (4 to 3L/min) and 7 discontinuation steps were included.

3.6.8 Change in oesophageal pressure with weaning

Considering all weaning steps together, the amplitude of the oesophageal pressure swing (ΔPoes) did not change significantly with weaning high flow. However, when considering the discontinuation and weaning steps separately, a statistically significant increase in median ΔPoes from -17.2cmH_2O (IQR -20.8 to -15.2) to -20.3cmH_2O (IQR -23.7 to -19.2; p=0.04) was observed in the flow rate reduction steps but not the discontinuation steps.

No significant difference in pressure time product per breath (PTPoes/breath) or respiratory rate was observed when weaning high flow, however a significant increase in pressure time product per minute (PTP/min) from median 170.2 (IQR 114.5-213.8) to 222.4 (IQR 167.8-262.8; p=0.04) was observed when all weaning steps were combined. This was not statistically significant in either the flow rate reduction or discontinuation steps alone, although number of steps was small (Table 3.9).

3.6.9 Correlation between Edi and oesophageal pressure swings

There was no correlation between median ΔPoes and median Edi max in this cohort (Figure 3.16). Similarly, there was no correlation between percentage change in median ΔPoes and Edi max with weaning (Figure 3.17). However, respiratory rates measured during the oesophageal pressure recordings and the Edi recordings correlated strongly (Figure 3.18).

	Pre-Wean	Post-Wean
All steps (n=14)		
ΔPoes (cmH_2O)	-17.4 (-20.8 - -15.2)	-19.6 (-23.7 - -14.1)
PTPoes/breath (cmH_2O/s)	3.4 (1.6-4.3)	3.1 (1.8-5.4)
Respiratory rate	65.3 (45.8-68.4)	65.7 (46.0-79.3)
PTPoes/min ($cmH_2O/s/min$)	170.2 (114.5-213.8)	222.4 (167.8-262.8)*
Flow rate reduction steps (n=7)		
ΔPoes (cmH_2O)	-17.2 (-20.8 - -15.5)	-20.3 (-23.7 - -19.2)*
PTPoes/breath (cmH_2O/s)	3.3 (2.5-5.0)	3.4 (2.8-5.6)
Respiratory rate	65.4 (45.1-68.3)	66.6 (41.1-76.8)
PTPoes/min ($cmH_2O/s/min$)	166.4 (152.2-224.9)	230.2 (170.0-258.9)
Discontinuation steps (n=7)		
ΔPoes (cmH_2O)	-17.5 (-20.9 - -8.0)	-14.3 (-25.9 - -11.5)
PTPoes/breath (cmH_2O/s)	3.5 (1.4-4.1)	1.83 (1.7-5.4)
Respiratory rate	65.2 (49.0-68.9)	65.1 (56.0-101.3)
PTPoes/min ($cmH_2O/s/min$)	174.1 (96.5-210.1)	185.2 (112.7-293.4)

Table 3.9 Change in oesophageal pressure with weaning high flow. Poes: Oesophageal pressure. PTPoes: Oesophageal pressure time product. Wilcoxon signed ranks test used to compare change from baseline (pre-wean values): *Post wean significantly different to pre-wean ($p<0.05$).

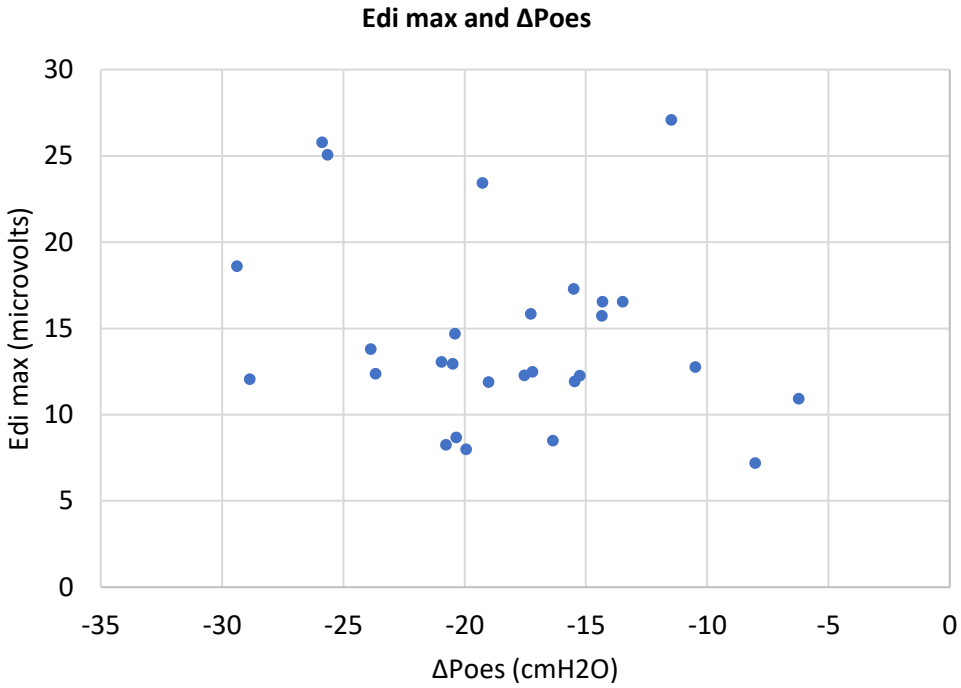

Figure 3.16 Scatterplot showing lack of correlation between maximum diaphragm electrical activity delta (Edi max) and oesophageal pressure swing (ΔPoes) with weaning high flow. Pearson correlation coefficient -0.29 (p=0.14).

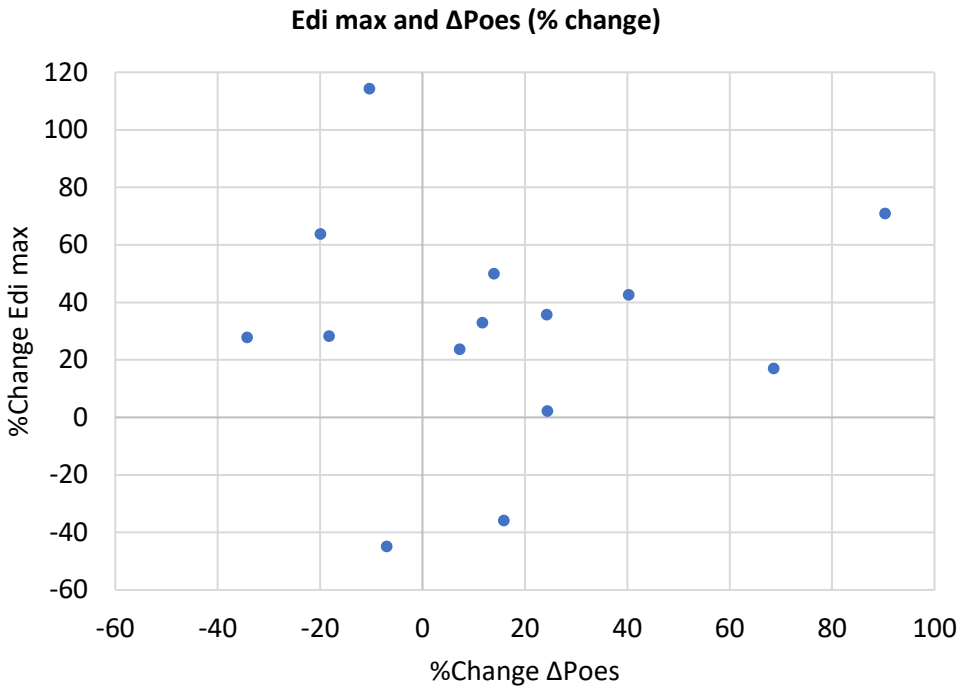

Figure 3.17 Scatterplot showing lack of correlation between percentage change in maximum diaphragm electrical activity (Edi max) and oesophageal pressure swing (ΔPoes). Pearson correlation coefficient 0.05 (p=0.86)

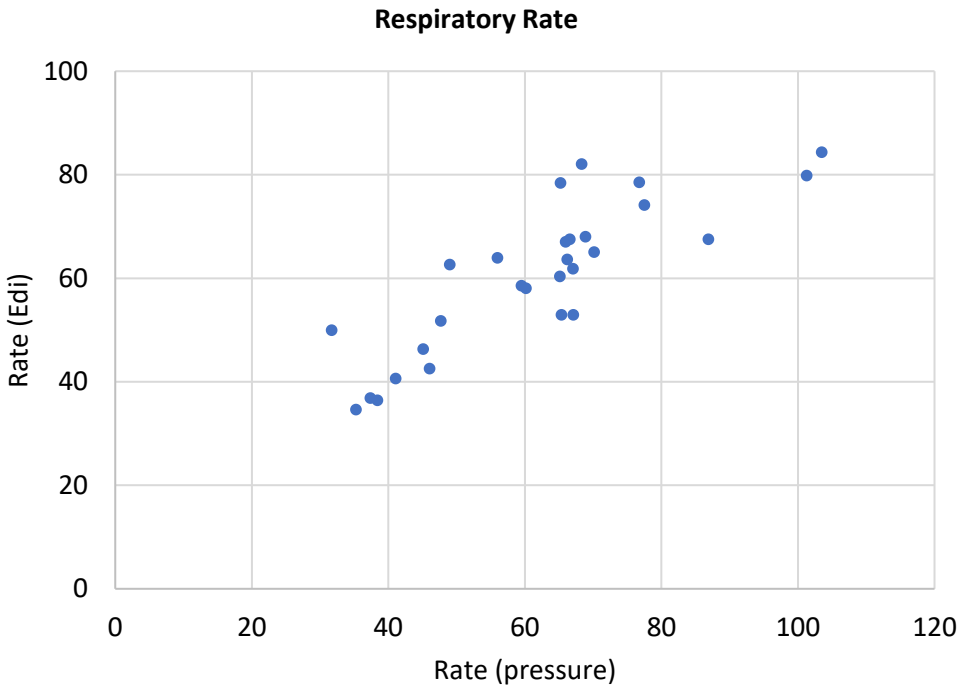

Figure 3.18 Scatter plot showing correlation between respiratory rates measured using electrical activity of the diaphragm (Edi) and oesophageal pressure. Pearson correlation coefficient 0.84 (p<0.001)

3.7 Discussion

This study was designed to explore in detail the physiological changes that occur when weaning high flow support in preterm infants. No significant change in the primary outcome of Edi max was observed with flow rate reduction steps, but a significant increase in Edi max was evident following discontinuation of high flow.

A number of studies have explored the physiological effects of high flow, particularly on delivered airway pressures. Although this is linearly related to flow rate, it is highly variable and influenced by infant factors such as weight and mouth position. Furthermore, the mechanism of high flow is multifactorial therefore assessing the impact of flow rate changes directly on objective measures of breathing effort such as Edi is more clinically useful.

3.7.1 Protocolisation of weaning high flow in preterm infants.

The first step in this study was to develop a weaning protocol as a framework for the measurement protocol. There is little published evidence to guide weaning of high flow, therefore we designed this protocol based on a retrospective study of our own unit practice, international consensus statements and a national survey of practice in the United Kingdom(Farley et al., 2015; Roehr et al., 2016; Yoder et al., 2017).

Compliance with the study protocol was high (85%), suggesting it is acceptable to clinicians and a useful framework for clinical practice. Weaning was highly successful, with over 90% of weaning steps occurring successfully. Protocolisation of high flow weaning in paediatric intensive care and infants with bronchiolitis has been shown to be effective and associated with increased success, suggesting a consistent, structured approach is helpful in clinical practice(Petrillo-Albarano et al., 2014; Garcia-Jacques et al., 2017).

The high success rate of this protocol raises the question of whether weaning could have occurred more quickly. Weaning respiratory support in this vulnerable group of infants is a complex decision, not just dependent on respiratory status. The priority for preterm infants at this stage of their neonatal care is a period of stability to allow growth and development. As a result, there is often reluctance to wean support at the same time as changing other aspects of care e.g. increasing feed volumes or weaning steroids. High flow is well tolerated by infants, and popular with parents and nursing staff as it is easy to use, minimally invasive

and comfortable therefore less of a burden than CPAP(Shetty, Sundaresan, et al., 2016; Naples & Harigopal, 2022). A recent retrospective study of trends in non-invasive respiratory support use in the United Kingdom using data from over 56,000 infants in the National Neonatal Research Database showed that from 2010-2017 use of high flow increased significantly, and exposure to high flow was associated with a longer duration of respiratory support and increased odds of BPD(Sand et al., 2022). Whilst confounding factors, namely differences in infant characteristics and indications for high flow use, mean a causal relationship cannot be inferred from this retrospective data it is plausible that the favourable characteristics of high flow mean it is weaned less aggressively than CPAP resulting in a longer period of respiratory support. Alternatively, the highly variable and unregulated distending pressure provided by high flow may cause barotrauma and atelectotrauma, resulting in a greater degree of lung injury(Wilkinson et al., 2008; Liew et al., 2020). Smaller observational studies have similarly shown prolonged respiratory support and increased BPD since introduction of high flow(Taha et al., 2016; Heath Jeffery et al., 2017).

Ultimately, weaning support in this group of infants requires a balance between progression off support and stability for growth and maturation. The high success rate and minimal change in both Edi and clinical parameters associated with weaning using this protocol suggests it is a safe and effective protocol for clinical use. A faster wean with more rigorous weaning criteria may be possible, and is a potential area for future study.

3.7.2 Edi does not change with reductions in high flow rate in preterm infants

No significant change in any Edi parameters were observed during the combined flow rate reduction steps in this study, with the only significant change an increase in Edi delta when weaning from 3 to 2L/min. This is consistent with the findings of both Hough *et al* and Jeffreys *et al* who reported similar levels of diaphragm activity measured by transcutaneous electromyography (EMG) in preterm infants at flow rates of 4, 6 and 8L/min(Hough et al., 2020; Jeffreys et al., 2019).

The distending pressure delivered by high flow is highly variable and unpredictable, both between and within individuals, and is influenced not only by flow rate, but also by infant weight, mouth position and the degree of leak at the nostril(Wilkinson et al., 2008; Liew et al., 2020). This inconsistent, variable support may account for the lack of change in Edi when

weaning. Notably, there was wide variation in baseline Edi values in the study population; whilst variation in severity of lung disease likely contributes, the impact of variation in the adequacy of high flow support is unclear and requires further study.

The Edi technique we used in this study measures activity of the crural diaphragm and correlates with work of breathing measured using oesophageal manometry, however it does not take into account the activity of other parts of the diaphragm or the intercostal muscles(Essouri et al., 2019). In preterm infants, it is generally believed that the diaphragm is responsible for most of the work of breathing, although the intercostal muscles do contribute to some extent(Lopes et al., 1981). Intercostal muscle activity precedes diaphragm activation during inspiration and contributes to maintenance of functional residual capacity, with infants able to recruit their intercostal muscles more resistant to diaphragm fatigue and apnoea with associated clinical deterioration(Hutten et al., 2008). It is possible that changes in intercostal muscle activity, not measured in this study compensate for changes in flow rate, however Hough et al measured changes in intercostal muscle activity using transcutaneous EMG in preterm infants, and showed no significant difference between activity at flow rates of 2, 4, 6 and 8L/min suggesting that this is not the case(Hough et al., 2020).

As discussed above, stability is essential in weaning preterm infants from respiratory support and the lack of significant change in Edi supports use of our weaning protocol as an effective way to achieve this. This also adds weight to the physiological data supporting weaning in 1L/min steps rather than 0.5L/min, as this will have no clinically relevant effect.

On sub-analysis of individual flow rate reduction steps, a significant increase in Edi delta was observed at 24 hours post flow rate reduction from 3 to 2 L/min only. Whilst this may be a chance finding, it is possible that this reflects a critical level of support in some infants, below which the physiological effects of high flow are reduced.

3.7.3 Edi increases when discontinuing high flow in preterm infants

In contrast to the flow rate reduction steps, a significant increase in Edi max, Edi delta and Edi a.u.c. was observed in the 24-hours following discontinuation of high flow. This increase was significant immediately post-discontinuation and at 24-hours, suggesting that high flow at 2L/min does unload diaphragmatic work of breathing to some extent.

Although these differences are statistically significant, the clinical significance of these changes in Edi need consideration. Stein *et al* studied normal ranges of Edi in preterm infants, and reported a mean Edi max 10.8 ± 3.7μV with no change in Edi max or min with increasing postnatal age(Stein et al., 2013). Following discontinuation of high flow in this study, median Edi increased from 10.89 (7.30-14.05) to 13.56 (9.89-17.0) at 24 hours, reflecting a median increase of 38.3% (-4.6-59.2%) from baseline. Although wide variation in the change in Edi was apparent, the upper quartile for Edi peak was >15μV at all timepoints following discontinuation of high flow, suggesting clinically significant increased work of breathing in a number of infants. Some centres advocate discontinuing high flow from higher flow rates (e.g. 4L/min), and given the minimal change in Edi parameters with flow rate reduction steps it is unclear whether this would have a greater effect, but is an area for future study.

Interestingly, Edi min, which reflects the tonic diaphragm activity required to maintain functional residual capacity and prevent atelectasis was not altered by discontinuing high flow support. Edi min is altered by positive end expiratory pressure, and has been shown to increase when discontinuing 3cmH_2O CPAP in preterm infants(Emeriaud et al., 2006; Kraaijenga et al., 2017). The lack of change in this cohort likely reflects the low and variable distending pressure delivered by high flow at 2L/min, and suggests the impact of high flow on inspiratory work of breathing may be predominantly due to other mechanisms such as overcoming nasopharyngeal resistance(Liew et al., 2020).

As the distending pressure generated by high flow is related to infant weight, an exploratory analysis assessing the correlation between changes Edi parameters and weight-adjusted flow rate when discontinuing high flow was performed. No correlation was observed in any Edi parameter in this cohort. Whilst this may reflect lack of effect, confounding by indication may contribute. In this cohort, high flow was used as a weaning modality to step down from CPAP in the recovery phase, therefore infants receiving high flow later in their neonatal course at a higher weight are likely have more severe lung disease, therefore intrinsically higher Edi.

3.7.4 Edi does not differ between successful and unsuccessful weaning steps

No difference in any Edi or clinical parameters was observed between successful and unsuccessful weaning steps in this study. However, the number of unsuccessful weaning steps was small, limiting our ability to draw firm conclusions regarding this. Kraaijenga *et al* reported a greater increase in Edi delta over the first 180 minutes in infants unsuccessfully weaned from CPAP compared to those successfully weaned, whilst De Waal *et al* showed no difference in infants unsuccessfully transitioning from CPAP to high flow. Both of these studies were similarly limited by a small number of unsuccessful weaning steps therefore the association between change in Edi and success of weaning remains unclear.

Although no difference in absolute Edi values between successful and unsuccessful weaning steps was evident, the successful group showed a longitudinal increase in Edi max and Edi delta from baseline; this trend was also observed in the unsuccessful group, but the changes did not reach statistical significance. This is very likely due to the small number of unsuccessful weaning steps meaning this is underpowered to assess this change, however in infants failing extubation attempts a smaller increase in Edi max and Edi delta has been reported, suggesting that inability to increase work of breathing with increased demand may contribute to failure in some cases(Iyer et al., 2017). Ultimately, further work is required to explore the association of change in Edi with weaning success, and explore the predictive value of Edi to prospectively guide weaning.

3.7.5 Oesophageal pressure measurement is not suitable for clinical use in preterm infants

Oesophageal pressure measurement is generally regarded as the gold-standard technique for assessment of respiratory muscle effort; however, it is invasive, complex and time-consuming therefore not suitable for daily clinical practice. Finding a suitable catheter to measure this in preterm infants was difficult, as specific balloon catheters are too big and the Gaeltec microtip catheter shows significant baseline drift therefore is unreliable. These techniques both require insertion of an additional oesophageal catheter which is distressing for the infant, and potentially increases risk of complications such as oesophageal perforation in the smallest infants.

In this study, the infant's existing feeding tube was used as a fluid filled catheter, connected to a pressure transducer to measure oesophageal pressure changes. This method was chosen as it is less invasive, not requiring insertion of a new catheter, but still involved manipulating and re-fixing the tube which disturbs the infant and alters normal breathing. Recordings are highly sensitive to movement artefact, peristalsis, and small changes in tube position, therefore very limited artefact free data can be obtained from a 5- or 10-minute recording.

Oesophageal pressure was measured during a small number of weaning steps in this study. An increase in oesophageal pressure swing was observed only during flow rate reduction steps, and an increase in PTP/min evident when all steps were combined. The small number of steps included in this part of the study, and practical difficulties described above mean these results should be interpreted with caution, and it not possible to draw any clear conclusions from this.

In contrast, the Edi measurement technique is essentially non-invasive as it uses an infant's existing feeding tube and requires no manipulation. This procedure was extremely well tolerated, and large amounts of artefact-free data can be obtained (median >300 breaths per 10-minute recording). As a result, this technique is much better suited to clinical use, therefore was the focus of this study.

A linear relationship between the amplitude of the Edi signal and oesophageal pressure swings is well described in the literature, although the slope of this relationship varies between individuals(Fauroux et al., 2003; Bellani et al., 2013; Essouri et al., 2019). While most of this work has been done in adults, Essouri et al simultaneously measured oesophageal pressure and Edi in sixteen children with a median age of 4 months, and found a strong linear correlation between maximal Edi and maximal swing in oesophageal pressure both during positive pressure ventilation and following extubation(Essouri et al., 2019). No correlation between median Edi max and ΔPoes was observed in this study, however it was not possible to measure these parameters simultaneously due to limitations of the equipment available for preterm infants, therefore median values for sequential recording periods are compared. The strong correlation in respiratory rate measured during the Edi and Poes recordings, suggest breathing pattern was similar between the two periods, but as the relationship between Edi and Poes differs between individuals, and there is high inter-

and intra-individual variation in both these parameters, the lack of correlation between averaged values in this small sample is not surprising.

Ultimately, it is clear that oesophageal pressure-based techniques are not suitable for clinical use, or an accessible research tool in preterm infants. The Edi technique is much better suited to clinical use as it is minimally invasive, easy to use and, in combination with the Servo ventilator, can be used as a real-time, objective marker of respiratory muscle effort.

3.7.6 Strengths and limitations of high flow weaning study

A major strength of this study is the detailed, longitudinal assessment and large number of infants that were included, providing comprehensive data regarding the changes in Edi that occur with weaning high flow. The study procedure was well tolerated by the infants, and parents, nursing and medical staff were all supportive and engaged with the study so recruitment was successful and compliance with the study protocol high.

Recordings were made in 10-minute blocks at 4 timepoints, longitudinally over 24 hours after each weaning step. We initially planned to include 2 additional timepoints (2-hours and 6-hours post wean), but after recruiting the first participants it was quickly evident this was too much of a burden on the infant and family as, although well tolerated, was very time consuming and would interfere with other aspects of their care. This protocol was designed to achieve a balance between ensuring adequate, informative data was obtained, whilst not disrupting the infant's care or family experience. As infant breathing is highly variable, all artefact free breaths during a 10-minute period were included in the analysis, resulting in an average of >1000 per weaning step; a much more representative approach than selecting short periods for analysis.

As discussed above, Edi measurement using this technique does not take into account the contribution of the intercostal muscles, which may have a relevant contribute to breathing effort. This technique was chosen as it is minimally invasive, well tolerated, and suitable for everyday clinical use unlike oesophageal pressure-based techniques to assess work of breathing, or transcutaneous EMG to assess intercostal muscle activity.

Infants in the study were a heterogeneous group with a range of gestational and postnatal ages, and varying severity of lung disease. Each infant acted as their own control when

assessing changes in Edi and clinical parameters, to accommodate changes in baseline characteristics, however it is possible that the effect varied between subgroups. Many infants in this study had significant lung disease, with moderate or severe BPD, but all were in the stable weaning phase, therefore these findings may be different in the early phase of respiratory distress syndrome or other acute illness.

3.8 Conclusions

In conclusion, in this chapter I have described the development of a successful protocol for weaning high flow in preterm infants and the physiological changes in breathing that occur during weaning. Oesophageal pressure measurement was not feasible for assessment of respiratory muscle effort in preterm infants in this study, but diaphragm electrical activity was well-suited to this.

No significant change in respiratory effort measured using the primary outcome of Edi max was evident with flow rate reduction steps, but a significant increase in Edi max was evident with discontinuation of high flow. This data supports use of our weaning protocol in clinical practice, and provides further insight into the physiological effects of high flow in preterm infants. In this study, no difference in Edi was observed between successful and unsuccessful weaning steps, however the number of unsuccessful steps was small and further work is required to explore this relationship further.

Chapter 4. National surveillance study of life-threatening bronchopulmonary dysplasia in preterm infants

4.1 Introduction

BPD is traditionally classified according to respiratory support and/or oxygen requirement at 36 weeks corrected gestation, but it is increasingly apparent that the predictive value and clinical utility of this definition is limited(Jobe & Bancalari, 2001). This definition categorises infants who are generally well but have an ongoing oxygen requirement they will outgrow with time, together with a smaller group of infants with life-threatening lung disease who die or require extensive support during a prolonged admission to survive. Need for positive pressure respiratory support near term is more closely associated with longer-term morbidity and mortality, so may be a more useful approach to risk-stratification and classification of BPD(Jensen et al., 2019; Isayama et al., 2017).

Although extensively studied as a broad group, there has been little research focus on infants with the most severe BPD, including infants requiring positive pressure respiratory support near term. There is strikingly little evidence to guide the management of severe, established BPD, and in an individual neonatal unit cases are rare. As a result, clinicians have limited experience with such infants making counselling and management decisions difficult. Ultimately, increasing our knowledge of the antecedent exposures, current treatment, and outcomes of infants with the most severe BPD will facilitate management decisions, counselling, and identification of further research priorities.

4.2 Hypothesis

This study explored the hypothesis that preterm infants requiring positive pressure respiratory support or pulmonary vasodilatory therapy at, or beyond, 38 weeks corrected gestation are a distinct subgroup with higher morbidity and mortality than other infants with BPD.

4.3 Aims

The specific aims of this study were to:

- Identify the minimum incidence of life-threatening BPD in preterm infants in the UK and Ireland during the study period.
- Describe the baseline characteristics, antecedent exposures and neonatal care received by affected infants.
- Explore the short-term outcomes of affected infants up to 1-year of age.

4.4 Study Protocol

4.4.1 Case definition

Life-threatening BPD was defined in infants born at <32 weeks gestation requiring positive pressure respiratory support and/or pulmonary vasodilator therapy at, or beyond, 38 weeks corrected gestational age without intercurrent illness to explain this need. Positive pressure support included invasive mechanical ventilation, continuous positive airway pressure/bilevel positive airway pressure (CPAP/BiPAP), and nasal high flow at a rate ≥2L/min.

This novel definition was chosen to include infants with the most severe lung disease, and include a feasible number of infants to study in this manner. This was estimated using local audit data and Regional Maternity Service Office data of respiratory deaths after 38 weeks corrected gestational age. Locally, there were 2-4 cases of severe BPD and 1 late respiratory death in approximately 200 admissions <32 weeks gestation per year, giving a rate of 1-2%(Northern Regional Maternity Survey Office., 2010). Estimating 10,000 births <32 weeks gestation nationally per year, this would give 100-200 cases of life-threatening BPD during the study period which is appropriate for the BPSU rare diseases methodology(UK Office for National Statistics, 2020). Assessment at 36 weeks was considered, in line with current BPD definitions, but this would give a much larger number of cases, not suitable for a BPSU study, and include infants with milder disease which were not the focus of the study.

4.4.2 British Paediatric Surveillance Unit methodology

The British Paediatric Surveillance Unit (BPSU) is a national centre for rare disease surveillance. Each month, all substantive paediatricians (i.e. consultants and associate specialists) in the UK and Ireland are asked to report whether they have seen a case of the conditions currently under surveillance. In order to track compliance with reporting,

clinicians are also asked to positively report if they have not seen any cases. Initially this was performed using postcards (the 'orange card' system) but this is now an electronic reporting system distributed by email. At any time, 6-8 conditions are typically under surveillance. Any case notifications received by the BPSU are sent to the research team, who subsequently send data collection questionnaire to the reporting clinician (Figure 4.1).

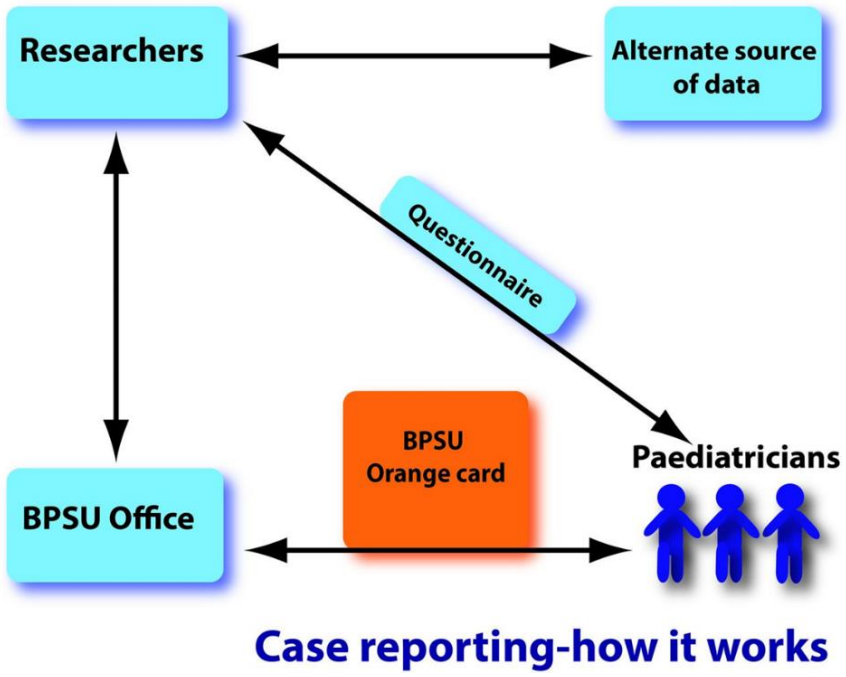

Figure 4.1 British Paediatric Surveillance Unit (BPSU) reporting methodology. Reproduced with permission (Lynn & Reading, 2020).

4.4.3 Data collection

This study was performed using the standard BPSU methodology described above. Surveillance was undertaken for a 13-month period from 1st July 2017 to 31st July 2018. A 13-month period is standard for BPSU studies, to allow time for an adequate number of cases to be reported. Following case notification, reporting clinicians were then sent a series of three questionnaires collecting study data up to one year of age:

- Questionnaire 1: This was sent at the point of case notification and covered infant demographics, pregnancy and delivery details, and early neonatal care including use of surfactant.
- Questionnaire 2: This was sent at 8-weeks post term corrected age and collected data on care in the neonatal unit, including respiratory support received, medication

use, infection data, and outcomes at the point of discharge from the neonatal unit or death.

- Questionnaire 3: This was sent at 1-year of age and collected data following discharge from the neonatal unit. This included additional periods of respiratory support, major morbidities and an assessment of neurodevelopmental status. A formal neurodevelopmental assessment was not performed, but clinicians reported the presence or absence of major or minor neurodevelopmental concerns.

Data collection questionnaires were sent and returned by post. Clinicians completed these forms for their own cases, using data from the infants' medical records. In cases where an infant was transferred to another hospital or department before discharge home, the third questionnaire was completed by the receiving clinician responsible for follow-up. Up to three reminders were sent for each non-returned questionnaire by email and by post.

4.4.4 Statistics

Descriptive statistics using frequencies, measures of central tendency and dispersion were used in this study. As data were not normally distributed, the median and interquartile range (25^{th}-75^{th} centile) were the preferred method of reporting distributions. Continuous, non-parametric variables were compared using the Mann-Whitney U test, and categorical variables using the Chi-squared or Fisher's exact test according to sample size. A p-value of <0.05 was considered significant.

Binomial logistic regression analysis was used to evaluate predictors of outcome. All models included gestational age, birth weight and sex, plus variables with $p<0.1$ on univariate analysis that did not show multicollinearity. All statistical analysis was performed using IBM SPSS v26.

4.4.5 Ethical Approval

This study was approved by the North-East Tyne and Wear South Research Ethics Committee (reference 16/NE/0343). Permission to access confidential data was obtained from the Health Research Authority via Section 251 Confidentiality Advisory Group and the Public Benefit and Privacy Panel for Health and Social Care in Scotland.

4.5 Results

4.5.1 Case reporting

During the study period, overall compliance with BPSU surveillance reporting was high, with 94.7% of reporting cards completed, either reporting a case or positively confirming they had not seen a case. In total, 329 potential case notification were received during the reporting period. In total, 90 notifications were excluded as they did not meet the case definition (n=68) or were duplicate reports (n=22). For a further 86 notifications, no data were provided despite multiple requests. These notifications were also excluded as it was not possible to confirm they met the case definition.

One hundred and fifty-three eligible cases were ultimately included. Additional data up to the point of discharge (questionnaire 2) was received for 94 cases, and data to 1-year of age (questionnaire 3) or death was provided for 77 infants (Figure 4.2). All eligible infants met the case definition by virtue of receiving respiratory support at 38 weeks CGA; none met the case definition due to need for pulmonary vasodilator therapy alone. Cases were reported from 57 different units, with individual units reporting 0-12 cases.

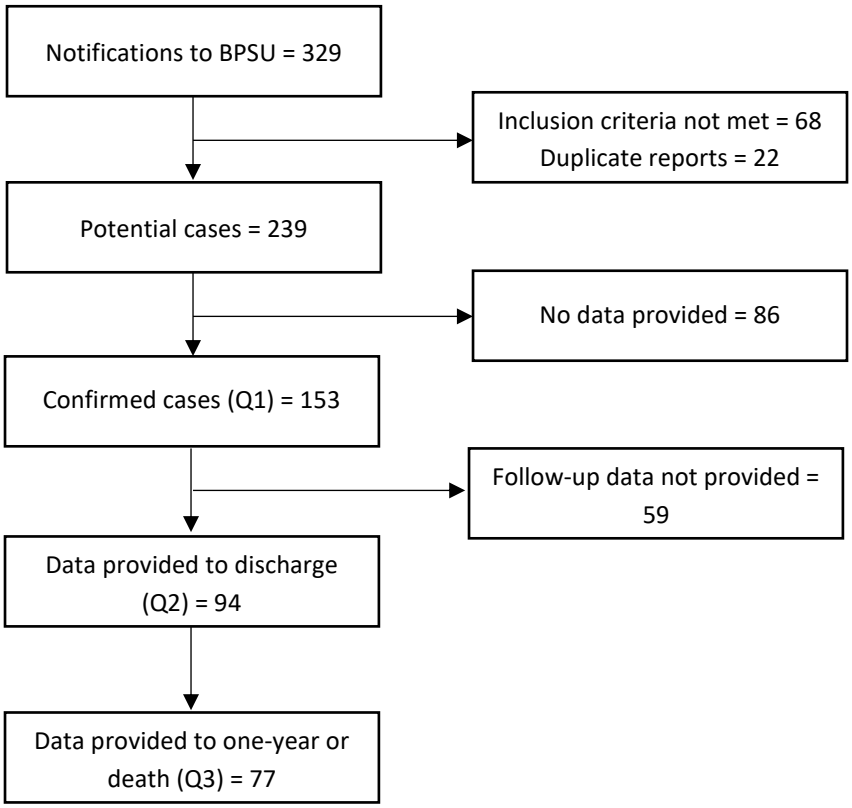

Figure 4.2 Cases reported to the British Paediatric Surveillance Unit (BPSU) and data provided up to one-year of age. Q1/Q2/Q3: Eligible questionnaire 1/2/3 returned.

4.5.2 Incidence

The minimum incidence of life-threatening BPD during the study period was calculated using 153 confirmed cases and national population estimates(UK Office for National Statistics, 2020; Public Health Scotland., 2020; Northern Ireland Statistics and Research Agency., 2020; Central Statistics Office Ireland., 2020). This gives a minimum incidence of 13.9 (95% CI: 11.8-16.3) per 1000 live-births <32 weeks gestation, or 0.17 (95% CI: 0.15-0.2) per 1000 of all live-births.

4.5.3 Demographics

Most affected infants were extremely preterm and extremely low birth weight, with a median gestational age of 26.1 weeks (IQR: 24.6-28.0) and birth weight 730g (IQR: 620-910g). However, a smaller number of more mature infants were also affected, with 7/153 (4.6%) born at 30-32 weeks gestation, and 27/153 (17.6%) with a birth weight >1000g (Table 4.1). Intrauterine growth restriction was common, with 57/153 (37.3%) infants having a birth weight <10th centile.

Significantly more affected infants were male than female (95/153 [62.1%] v 58/153 [37.9%]; $p<0.05$). Most affected infants were White British (120/153; 78.4%), consistent with the baseline UK population, of which 80.5% is White British(Gov.UK, 2020).

Demographics	Number (%) or Median (IQR)
Median gestational age at delivery (weeks)	26.1 (24.6-28)
Gestational age at delivery breakdown (weeks):	
23^{+0}-24^{+6}	50/153 (32.7%)
25^{+0}-27^{+6}	62/153 (40.5%)
28^{+0}-29^{+6}	33/153 (21.6%)
30^{+0}-32^{+0}	7/153 (4.6%)
Not known	1/153 (0.7%)
Median birth weight (grams)	730 (620-910g)
Birth weight breakdown:	
<500g	9/153 (5.9%)
500-749g	66/153 (43.1%)
750-999g	47/153 (30.7%)
≥1000g	27/153 (17.6%)
Not known	4/153 (2.6%)
Birth weight <10^{th} centile	57/153 (37.3%)
Male	95/153 (62.1%)
Female	58/153 (37.9%)
Reporting country	
England	129/153 (84.3%)
Scotland	13/153 (8.5%)
Wales	3/153 (2%)
Northern Ireland	5/153 (3.3%)
Ireland	3/153 (2%)
Ethnicity	
White British	120/153 (78.4%)
Pakistani	11/153 (7.2%)
African	7/153 (4.6%)
Indian	4/153 (2.6%)
Other	10/153 (6.5%)
Not known	1/153 (0.7%)

Table 4.1 Baseline demographics of infants with life-threatening bronchopulmonary dysplasia. Data reported as number (%) or median (IQR).

4.5.4 Antenatal and delivery details

Antenatal steroids were given in 139/153 (90.8%) cases, with one or more complete courses given in 122/153 (79.7%) cases and a further 16/153 (10.5%) receiving an incomplete course only. Delivery was via Caesarean section in 85/153 (55.6%) of cases. Prelabour and/or prolonged ruptured membranes were frequently reported (Table 4.2).

Evidence of chorioamnionitis was reported in 21/153 (13.7%) of cases, and other placental abnormalities, including evidence of ischaemia, uteroplacental insufficiency and abruption, were reported in a further 21/153 (13.7%). No significant differences in baseline demographic or delivery details were observed between infants with and without further neonatal and discharge data (Table 4.3).

	Number (%) or Median (IQR)
Received any antenatal steroid	139/153 (90.8%)
Incomplete course only	16/139 (11.5%)
One complete course	109/139 (78.4%)
Two or more complete courses	13/139 (9.4%)
Courses not known	1/139 (0.7%)
Antenatal steroid received	
Dexamethasone	66/139 (47.5%)
Betamethasone	65/139 (46.8%)
Dexamethasone and betamethasone	1/139 (0.7%)
Not known	7/139 (5.0%)
Caesarean section delivery	85/153 (55.6%)
Prelabour ruptured membranes	65/153 (42.5%)
Prolonged ruptured membranes	46/153 (30.1%)
Chorioamnionitis	21/153 (13.7%)
Other placental abnormality	21/153 (13.7%)
5-minute Apgar score	7 (5-8)
10-minute Apgar score	8 (7-9)

Table 4.2 Antenatal and delivery details of infants with life-threatening bronchopulmonary dysplasia. Data reported as number (%) or median (IQR).

	Data to Discharge Provided	Data to Discharge Not Provided	p value
Gestation (weeks)	26.3 (24.6-28.1)	25.6 (24.7-28)	0.40
Birth weight (g)	715 (601-912)	755 (630-898)	0.77
Male sex	56/94 (60%)	39/59 (66%)	0.42
Birth weight <10th centile	37/94 (39%)	20/59 (34%)	0.49
Received antenatal steroids	85/94 (90%)	53/58 (91%)	0.84
C-section delivery	54/93 (58%)	31/56 (55%)	0.75
5-minute Apgar score	7 (5-8)	6 (5-8)	0.90
10-minute Apgar score	8 (7.8-9)	8 (7-9)	0.83

Table 4.3 Demographic and delivery details of infants with and without further data showing no significant differences between groups. Data reported as number (%) or median (IQR).

4.5.5 Respiratory support

Episodes of respiratory support were considered separate if transfer to another device, or off support, was achieved for >24 hours. Detailed respiratory data was provided for 92 of 94 infants; the remaining 2 provided incomplete data on respiratory support episodes due to multiple postnatal transfers, therefore were excluded from this part of the analysis.

Invasive ventilation was received by 91/92 (98.9%) infants, whilst one infant was never ventilated. Invasive ventilation commenced on the first day of life in 85/91 (92.4%) infants, and the remaining 6 were all ventilated within the first 72 hours of life. Infants received a median 2 (IQR 1-3) episodes of invasive ventilation. The median duration of the first episode of ventilation was 19.5 days (IQR 5-35), and total duration of invasive ventilation was 29 days (IQR 17-51; range 1-239 days). Median age last receiving invasive ventilation was 50 days (IQR 22-98). High frequency oscillatory ventilation was used in 53/94 (56.4%), inhaled nitric oxide in 30/94 (31.9%), and 4/94 (4.3%) infants had a pneumothorax.

All infants receiving invasive ventilation were given surfactant; the one infant not invasively ventilated did not receive surfactant. The first dose of surfactant was given at median 11 minutes (IQR 7-23) of age, at a dose of 182mg/kg (IQR 144-211). Fifty-eight infants (58/153; 37.9%) received a single dose of surfactant, 50/153 (32.7%) received two doses and 33/153 (21.6%) received three or more (number of doses not known in 11/153; 7.2%). A second

dose of surfactant was given at median 11.6 hours of age (IQR 3.5-22.6) at a dose of 167mg/kg (IQR 130-207).

Nasal CPAP/BiPAP and high flow were both widely used, received by 96.7% and 91.3% of the study population respectively (Table 4.4). High flow was generally started later and used for a longer duration than CPAP (median 40.5 v 27 days; $p<0.05$).

Figure 4.3 shows the mode of respiratory support received at 36 weeks CGA, the traditional timepoint for BPD diagnosis, and 38 weeks CGA, the timepoint of diagnosis of life-threatening BPD. From 36 weeks to 38 weeks CGA, the proportion of infants requiring invasive ventilation did not change with 13/94 (13.8%) receiving invasive ventilation at both time points. During this time, proportion receiving CPAP for non-invasive respiratory support decreased significantly (32/94 [34%] to 20/94 [21.3%]; $p<0.05$), whilst the proportion receiving high flow increased significantly (43/94 [45.7%] to 56/94 [59.6%]; $p<0.05$).

The median duration of positive pressure support for infants discharged alive, off support was 103 days (IQR 87-134; max 258). Positive pressure support was discontinued at a median age of 41.3 weeks CGA (IQR 39.4-45.4; max 65.1). Seven infants required long term positive pressure support post-discharge, all of whom survived to one year of age.

	Invasive Ventilation	**CPAP/BiPAP**	**High Flow**
Number of infants	91/92 (98.9%)	89/92 (96.7%)	84/92 (91.3%)
Starting age (days)	0 (0-0)	20 (6-39)	49.5 (28-84)
Starting CGA (weeks)	26.4 (24.6-28.1)	29.6 (27.7-32.1)	33.6 (31.1-37.1)
Number of episodes	2 (1-3)	2 (1-3)	2 (1-3)
Total duration (days)	29 (17-51)	27 (14-45)	40.5 (22-64)
Postnatal age last received (days)	50 (22-98)	84 (49-103)	109 (89.5-143)

Table 4.4 Respiratory support received by infants with life-threatening bronchopulmonary dysplasia. Data reported as number (%) or median (IQR). CGA: corrected gestational age. CPAP: continuous positive airway pressure. BiPAP: bilevel positive airway pressure.

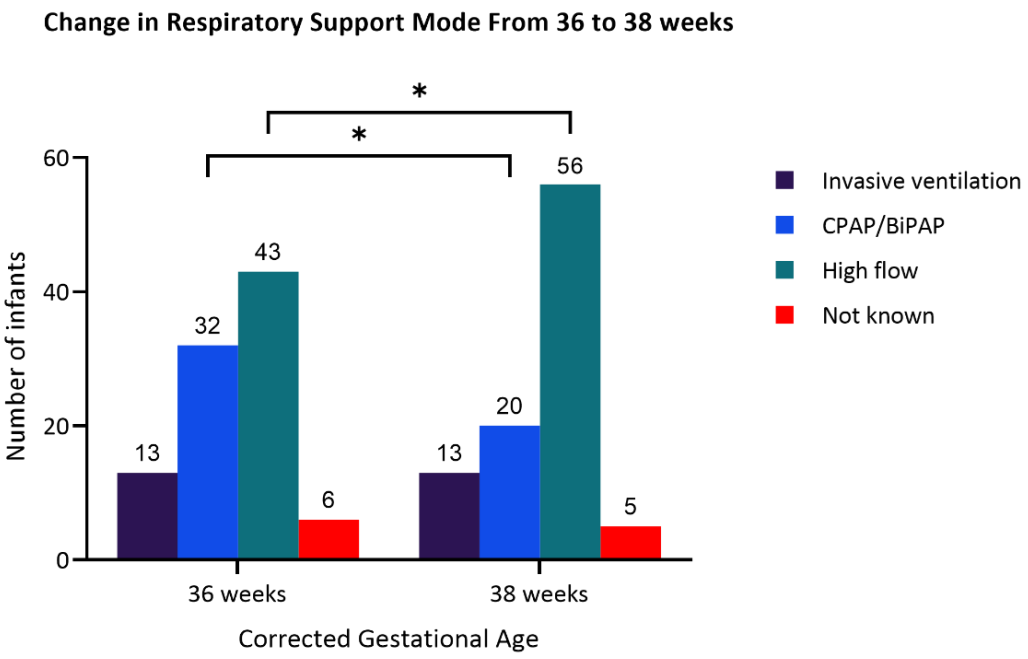

Figure 4.3 Mode of respiratory support received by infants with life-threatening bronchopulmonary dysplasia at 36 and 38 weeks corrected gestational age. CGA: Corrected gestational age. CPAP: Continuous positive airway pressure. BiPAP: Bilevel positive airway pressure. *Significant difference between 36 and 38 weeks ($p<0.05$).

4.5.6 Postnatal steroids

Postnatal steroids were used for BPD in 57/94 (60.6%) infants, starting at a median age of 26 days (IQR 14-48) or 29.7 weeks CGA (IQR 27.9-33.4; range 24.6-55.9). One infant in the study received steroid in the first 7 days of life. The first steroid received was dexamethasone in the majority of infants (52/57; 91.2%). Dexamethasone was given at a median starting dose of 135mcg/kg/day (IQR 50-150), and maximum of 150mcg/kg/day (IQR 100-200) for a median of 10 days (IQR 10-16) per course.

Courses of steroid were defined as separate if >72 hours deliberately elapsed between doses. Median number of steroid courses per infant was 1 (IQR 0-2; max 6). In total, infants in the study received 109 courses of steroid: 90 (82.6%) were dexamethasone, 10 (9.2%) prednisolone, 5 (4.6%) methylprednisolone, and 4 (3.7%) were hydrocortisone. One infant received early hydrocortisone, commencing on the first day of life. Prednisolone and methylprednisolone were generally used late in the neonatal unit course (Table 4.5).

Steroid	Number		First Course		All Courses	
	Infants	Courses	PN Age (days)	CGA (weeks)	PN Age (days)	CGA (weeks)
Dexamethasone	54	90	28 (15-48.5)	30.43 (28.1-33.8)	43 (22.0-79.0)	32.7 (28.7-38.3)
Hydrocortisone	4	4	21 (6.75-55.5)	31.14 (28.9-35.5)	21 (6.75-55.5)	31.14 (28.9-35.5)
Prednisolone	6	10	97.5 (77-147.3)	41.6 (38.0-48.4)	127.5 (86.8-162.5)	46.1 (39.1-49.9)
Methylpred	4	5	140.5 (107-170.5)	47.2 (43.6-50.1)	137 (112-169)	47.0 (44.6-49.9)

Table 4.5 Frequency and timing of postnatal steroids used in infants with life-threatening bronchopulmonary dysplasia. Data displayed as number or median (IQR). PN: Postnatal. CGA: Corrected gestational age. Methylpred: Methylprednisolone.

Two infants participated in the Mini-Dex randomised controlled trial running during the study period, therefore received Mini-Dex investigational medicinal product, which may be dexamethasone (50mcg/kg/day) or placebo(Yates et al., 2019). One of these infants also received open label dexamethasone.

In infants who received steroid, median total duration of steroid treatment was 23 days (IQR 14-44; maximum 163). Steroids were last used at a median postnatal age of 91 days (IQR 57-150), however 9 infants remained on steroid at the point of discharge.

4.5.7 Management of patent ductus arteriosus

Medical therapy for closure of a patent ductus arteriosus was used in 36/94 (38.3%) infants, starting at a median age of 7.5 days (IQR 5-14.5) or 26.3 weeks CGA (IQR 25.3-27.1). Eight infants received more than one course of treatment. Ibuprofen was the most common medication, used in 33 infants, whilst paracetamol was used in 4 infants (3 of whom also received ibuprofen). One infant in the study was reported to be in the Baby-OSCAR randomised controlled trial, therefore received either ibuprofen or placebo as the investigational medicinal product(Gupta et al., 2021).

Seventeen infants (18.1%) underwent a PDA ligation, at a median age of 43 days (IQR 37-78). Eleven of these infants had previously received medical treatment for a duct, whilst 6 infants underwent primary ligation. At the time of ligation, 9/17 (52.9%) of infants were invasively ventilated, 1/17 (5.9%) was receiving CPAP and 4/17 (23.5%) were receiving nasal high flow. Respiratory support status at the time of ligation was not known in 3 infants.

4.5.8 Management of pulmonary hypertension

Echocardiographic evidence of pulmonary hypertension was reported in 32/94 (34%) infants. Sildenafil was used in 22 infants, 20 of whom had confirmed echo evidence of pulmonary hypertension. One infant who received sildenafil did not have evidence of pulmonary hypertension, and in one infant echo findings were not known. Twelve infants with confirmed pulmonary hypertension did not receive sildenafil or other pulmonary vasodilator therapy.

Sildenafil was used at a median maximum dose of 3mg/kg/day (IQR 1.6-4.3), for a median duration of 44 days (IQR 18-132). One infant received bosentan in addition to sildenafil.

4.5.9 Infection

Culture positive sepsis occurred in 42/94 (44.7%) affected infants, with coagulase negative staphylococci the most frequently reported organisms (Table 4.6). Culture negative sepsis,

defined as ≥5 days of antibiotics without a positive culture, occurred in 49/94 (52.1%) infants. Pneumonia was diagnosed in 33/94 (35.1%) infants, with *Staphylococcus aureus* and *Klebsiella* the most commonly identified organisms. *Ureaplasma* was identified in one infant only. Median number of significant infections per infant was 2 (IQR 1-4), and age of first significant infection 7 days (IQR 1-28).

	Blood Culture/PCR Positive	**Pneumonia**
Gram Positive		
Coagulase negative staphylococcus	35	1
Enterococcus faecalis	8	1
Staphylococcus aureus	6	5
Group B streptococcus	2	-
Corynebacterium	2	-
Gram Negative		
Escherichia coli	7	2
Enterobacter	2	1
Pseudomonas	1	3
Klebsiella	1	5
Serratia	1	-
Stenotrophomonas	-	2
Proteus	-	2
Ureaplasma	-	1
Viruses		
Herpes simplex virus 2	1	-
Rhinovirus	-	3
Cytomegalovirus	-	1
Parainfluenza	-	1
Respiratory syncytial virus	-	1
Fungi		
Candida	1	-

Table 4.6 Organisms identified in culture positive sepsis episodes and/or pneumonia in infants with life-threatening bronchopulmonary dysplasia. Number of confirmed cases in study population reported. PCR: Polymerase chain reaction.

4.5.10 Other Medications

Diuretics were used in 82/94 (87.2%) infants, at a median starting age of 32 days (IQR 17-50.5). Median duration of treatment for those discontinued before discharge was 76.5 days (IQR 27-100), however 39 infants (39/94; 41.5%) remained on diuretics at the point of discharge from the neonatal unit (Table 4.7).

Inhaled steroids were used in 16/94 (17%) infants, at a median starting age of 96.5 days (IQR 59.5-126.3). Median duration of treatment was 13 days (IQR 4-49), although 5 infants remained on inhaled steroids at discharge.

Inhaled bronchodilators were used in 8/94 infants (8.5%), late in the neonatal course, starting at a median starting age of 124.5 days (IQR 120-192). Median duration of inhaled bronchodilator therapy was 8 days (IQR 5.5-24.5), and 3 infants remained on bronchodilators at the point of discharge.

Category	Infants	Starting Age (days)	Duration (days)	Continued at Discharge
PDA Closure Ibuprofen Paracetamol	36/94 (38.6%) 33/36 (91.7%) 4/36 (11.1%)	7.5 (5-14.5)	NA	NA
Postnatal corticosteroid	57/94 (60.6%)	26 (14-48)	21 (11-38)	9/94 (9.6%)
Diuretics	82/94 (87.2%)	32 (17.3-50.5)	76.5 (27-100)	39/94 (41.5%)
Inhaled steroid	16/94 (17.0%)	96.5 (59.5-126.3)	13 (4-49)	5/94 (5.3%)
Inhaled bronchodilator	8/94 (8.5%)	124.5 (120-192)	8 (5.5-24.5)	3/94 (3.2%)
Sildenafil	22/94 (23.4%)	NK	44 (18-132)	4/94 (4.3%)

Table 4.7 Medications received pre-discharge by infants with life-threatening bronchopulmonary dysplasia. Data presented as number (%) or median (IQR). PDA: Patent ductus arteriosus. NA: Not applicable. NK: Not known.

4.5.11 Outcomes

By 1 year of age, 15/94 (16%) infants died; 14 infants died before discharge from hospital and 1 infant died post-discharge. Median age of death was 159 days (IQR 105-182), or 49.6 weeks CGA (IQR 43-52.9). The reported cause of death was BPD in 11/15 (73.3%), pulmonary stenosis in 1/15 (6.7%), and not known by the reporting clinician in 3/15 (20%).

Of the 79 surviving infants, 1 (1.3%) remained an inpatient at 1 year of age. Eighteen infants were transferred to respiratory paediatrics prior to discharge, and sixteen to other destinations such as a paediatric intensive care or other paediatric wards prior to discharge. Median age of discharge home was 143 (IQR 117-185) days, or 46.6 weeks CGA (IQR 43-52.9). Key discharge details, comorbidities and outcomes are listed in Table 4.8.

At the point of discharge home, 60/79 (75.9%) infants were receiving low-flow oxygen and 8/79 (10.1%) required no respiratory support. Seven infants (7/79; 8.9%) required long-term positive pressure support at home and 5 infants had a tracheostomy, which was performed at a median age of 260 days (range 177-278).

Neurological assessment at 1 year of age was available for 60/79 surviving infants. No concerns were reported in 37/60 (61.7%), minor concerns in 10/60 (16.7%), and major concerns in 13/60 (21.7%). Following discharge, 2 infants required new invasive ventilation, 1 required CPAP and 8 required high flow during readmission in the first year of life.

Overall, death or major neurodevelopmental impairment occurred in 37% of infants (28/75), and death or major morbidity (defined as long-term ventilation, major neurodevelopmental impairment, or readmission within the first year of life) occurred in 45% (42/94) infants.

Outcomes	Number (%) or Median (IQR)
NICU destination	
Home	51/94 (54.3%)
Died	9/94 (9.6%)
Respiratory paediatrics	18/94 (19.1%)
Other (e.g. PICU, other paediatric ward)	16/94 (17.0%)
Final/1-year destination	
Discharged home	76/94 (81%)
Died	15/94 (16%)
Remained inpatient	1/94 (1.1%)
Not known	2/94 (2.1%)
Age of discharge alive	
Postnatal age (days)	143 (117-185)
Corrected gestational age (weeks)	46.6 (43-52.9)
Age of death	
Postnatal age (days)	159 (105-182)
Corrected gestational age (weeks)	49.6 (42.6-52.6)
Respiratory support at discharge	
Air	8/79 (10.1%)
Low flow oxygen	60/79 (75.9%)
LTV (ventilation, CPAP or high flow)	7/79 (8.9%)
Not known	4/79 (5.1%)
Comorbidities	
ROP requiring treatment	26/94 (27.7%)
Laser	20/94 (21.3%)
Avastin	3/94 (3.2%)
Both	3/94 (3.2%)
Periventicular leukomalacia	7/94 (7.4%)
Ventriculoperitoneal shunt inserted	5/94 (5.3%)
PEG inserted	7/94 (7.4%)
Tracheostomy	5/94 (5.3%)
Neurological assessment at 1 year	
Normal	37/60 (61.7%)
Minor concerns	10/60 (16.7%)
Major concerns	13/60 (21.7%)

Table 4.8 Discharge details and outcomes up to 1 year of age for infants with life-threatening bronchopulmonary dysplasia. Data presented as number (%) or median (IQR). NICU: Neonatal intensive care unit. PICU: Paediatric intensive care unit. LTV: Long-term ventilation. CPAP: Continuous positive airway pressure. ROP: Retinopathy of prematurity. PEG: Percutaneous endoscopic gastrostomy.

4.5.12 Univariate associations with outcomes

The association of key factors with the outcomes of death, death and/or major neurodevelopmental impairment, and death and/or long-term ventilation on univariate analysis are displayed in Table 4.9 - Table 4.11. Infants who died were significantly more likely to require invasive ventilation at or beyond 38 weeks CGA. This was also significant when retrospectively assessed at 36 weeks CGA in line with traditional BPD definitions. Infants who died were more likely to require CPAP but less likely to receive high flow past 38 weeks CGA. They received a significantly longer duration of postnatal steroid, were more likely to receive high frequency oscillation, and were more likely to have diagnosed pulmonary hypertension and receive sildenafil (Table 4.9).

The outcomes of death and/or neurodevelopmental impairment and death and/or long-term ventilation were similarly associated with significantly higher rates of invasive ventilation at 36 and 38 weeks CGA, a longer duration of postnatal steroid use, and the presence and treatment of pulmonary hypertension (Table 4.10 and Table 4.11).

	Died (n=15)	Alive (n=77)	p-value
Gestational age (weeks)	27.0 (24.1-27.7)	26.1 (24.7-28.3)	0.816
Birth weight (grams)	705 (570-869)	755 (621-930)	0.316
Birth weight <10th centile	7 (46.7%)	29 (37.7%)	0.513
Male sex	7 (46%)	48 (62%)	0.257
Received antenatal steroids	15 (100%)	68 (88.3%)	0.346
Received postnatal steroids	12 (80%)	43 (55.8%)	0.081
Age first steroid (days)	23 (7-63)	11 (0-30)	0.081
Duration postnatal steroids (days)	31 (10-53)	8 (0-27)	0.029
Maximum dose dexamethasone (mcg/kg/day)	120 (30-120)	0 (0-120)	0.032
Duration initial ventilation (days)	23 (9-43)	16 (5-34)	0.269
Duration total ventilation (days)	23 (11-42)	30 (18-54)	0.215
Any ventilation ≥36 weeks CGA	12 (80%)	24 (31.2%)	<0.001
Any ventilation ≥38 weeks CGA	12 (80%)	18 (23.4%)	<0.001
Any CPAP/BiPAP ≥38 weeks CGA	11 (73.3%)	31 (40.3%)	0.019
Any high flow ≥38 weeks CGA	8 (53.3%)	71 (92.2%)	0.001
Received inhaled nitric oxide	7 (46.7%)	23 (29.9%)	0.236
Received HFOV	12 (80%)	39 (50.6%)	0.036
Pulmonary hypertension*	12 (80%)	18/74 (24.3%)	<0.001
Received sildenafil*	10 (66.7%)	12/75 (16%)	<0.001

Table 4.9 Associations with death on univariate analysis. Data reported as number (%) or median (IQR). CPAP: Continuous positive airway pressure. BiPAP: Bilevel positive airway pressure. HFOV: High frequency oscillatory ventilation. *Reported for infants with complete data only.

	Death/NDI (n=28)	No Death/NDI (n=47)	p-value
Gestational age (weeks)	26.4 (24.6-27.4)	27.0 (25.1-28.7)	0.179
Birth weight (grams)	750 (610-892)	775 (604-1048)	0.511
Birth weight <10th centile	10 (35.7%)	22 (46.8%)	0.347
Male sex	16 (57.1%)	30 (63.8%)	0.565
Received antenatal steroids	24 (85.7%)	46 (97.9%)	0.061
Received postnatal steroids	20 (71.4%)	25 (53.2%)	0.119
Age first steroid (days)	13 (0-120)	0 (0-27.3)	0.134
Duration postnatal steroids (days)	23 (0-54)	0 (0-32)	0.030
Maximum dose dexamethasone (mcg/kg/day)	60 (0-150)	0 (0-120)	0.095
Duration initial ventilation (days)	22 (7-42)	11 (3-24)	0.069
Duration total ventilation (days)	23 (11-42)	34 (18-52)	0.108
Any ventilation ≥36 weeks CGA	17 (60.7%)	13 (27.7%)	0.005
Any ventilation ≥38 weeks CGA	15 (53.6%)	9 (19.1%)	0.002
Any CPAP/BiPAP ≥38 weeks CGA	15 (53.6%)	20 (42.6%)	0.355
Any high flow ≥38 weeks CGA	20 (71.4%)	45 (95.7%)	0.004
Received inhaled nitric oxide	12 (42.9%)	14 (29.8%)	0.25
Received HFOV	17 (60.7%)	26 (55.3%)	0.648
Pulmonary hypertension*	16 (57.1%)	10/46 (21.7%)	0.002
Received sildenafil*	11 (39.3%)	8/46 (17.4%)	0.037

Table 4.10 Associations with death/major neurodevelopmental impairment on univariate analysis. Data reported as number (%) or median (IQR). NDI: Neurodevelopmental impairment. CPAP: Continuous positive airway pressure. BiPAP: Bilevel positive airway pressure. HFOV: High frequency oscillatory ventilation. *Reported for infants with complete data only.

	Death/ LTV (n=22)	No Death/ LTV (n=70)	p-value
Gestational age (weeks)	26.8 (24.3-28.4)	26.1 (25-28.1)	0.826
Birth weight (grams)	706 (579-874)	775 (611-960)	0.385
Birth weight <10th centile	9 (40.9%)	27 (38.6%)	0.845
Male sex	11 (50%)	44 (62.9%)	0.283
Received antenatal steroids	20 (90.9%)	63 (90%)	1.0
Received postnatal steroids	17 (77.3%)	38 (54.3%)	0.055
Age first steroid (days)	18 (2-46)	10 (0-28)	0.093
Duration postnatal steroids (days)	29 (8-53)	4 (0-24)	0.009
Maximum dose dexamethasone (mcg/kg/day)	120 (0-200)	0 (0-120)	0.011
Duration initial ventilation (days)	24 (6-44)	16 (5-30)	0.213
Duration total ventilation (days)	24 (11-43)	33 (18-53)	0.145
Any ventilation ≥36 weeks CGA	15 (68.2%)	21 (30%)	0.001
Any ventilation ≥38 weeks CGA	14 (63.6%)	16 (22.9%)	<0.001
Any CPAP/BiPAP ≥38 weeks CGA	10 (45.5%)	10 (14.3%)	0.052
Any high flow ≥38 weeks CGA	14 (63.6%)	28 (40%)	0.002
Received inhaled nitric oxide	9 (40.9%)	20 (28.6%)	0.141
Received HFOV	14 (63.6%)	65 (92.9%)	0.061
Pulmonary hypertension*	13 (59.1%)	46 (65.7%)	<0.001
Received sildenafil*	14 (63.6%)	8/68 (11.8%)	<0.001

Table 4.11 Associations with death/long-term ventilation on univariate analysis. Data reported as number (%) or median (IQR). LTV: Long-term ventilation. CPAP: Continuous positive airway pressure. BiPAP: Bilevel positive airway pressure. HFOV: High frequency oscillatory ventilation. *Reported for infants with complete data only.

4.5.13 Association with outcomes on multivariate regression analysis

The association of the key outcomes of death, death and/or major neurodevelopmental impairment and death and/or long-term ventilation were further explored using binomial logistic regression analysis. Gestational age, birth weight, sex and antenatal steroid use were included in all models in addition to the factors with p-value <0.1 on univariate analysis not showing multicollinearity. All outcomes were significantly associated with need for invasive ventilation at or beyond 38 weeks corrected gestation and the presence of pulmonary hypertension on regression analysis (Table 4.12 - Table 4.14).

	Death aOR (95% CI)	**p value**
Gestational age (weeks)	1.42 (0.85-2.37)	0.183
Birth weight (g)	1.0 (0.99-1.00)	0.439
Male sex	0.40 (0.09-1.87)	0.242
Received postnatal steroids	3.42 (0.55-21.16)	0.186
Any ventilation ≥38 weeks CGA	10.95 (1.97-60.79)	0.006
Received high frequency oscillatory ventilation	2.52 (0.42-15.03)	0.309
Pulmonary hypertension	6.88 (1.47-32.28)	0.015

Table 4.12 Associations with death on multivariate analysis. Data reported as adjusted odds ratio (aOR) and 95% confidence interval (CI).

	Death/NDI aOR (95% CI)	**p value**
Gestational age (weeks)	0.96 (0.66-1.42)	0.849
Birth weight (g)	1.00 (1.0-1.0)	0.183
Male sex	0.70 (0.20-2.38)	0.562
Received antenatal steroids	0.02 (0.001-0.40)	0.010
Received postnatal steroids	4.33 (0.96-19.52)	0.057
Any ventilation ≥38 weeks CGA	5.73 (1.45-22.70)	0.013
Received high frequency oscillatory ventilation	0.47 (1.22-1.81)	0.273
Pulmonary hypertension	3.71 (1.001-13.72)	0.049

Table 4.13 Associations with death/major neurodevelopmental impairment (NDI) on multivariate analysis. Data reported as adjusted odds ratio (aOR) and 95% confidence interval (CI).

	Death/LTV aOR (95% CI)	p value
Gestational age (weeks)	1.33 (0.87-2.05)	0.188
Birth weight (g)	1.00 (1.0-1.0)	0.758
Male sex	0.40 (0.11-1.43)	0.159
Received antenatal steroids	0.71 (0.11-4.68)	0.721
Received postnatal steroids	2.91 (0.66-12.78)	0.158
Any ventilation ≥38 weeks CGA	5.95 (1.51-23.46)	0.011
Received high frequency oscillatory ventilation	1.33 (0.34-5.15)	0.681
Pulmonary hypertension	5.58 (1.61-19.40)	0.007

Table 4.14 Associations with death/long term ventilation (LTV) on multivariate analysis. Data reported as adjusted odds ratio (aOR) and 95% confidence interval (CI).

4.6 Discussion

It is evident that broad definitions of BPD do not adequately focus on the most severely affected infants who have who have distinct risks and merit separate approaches to their care. There are little data on the characteristics, management, and outcomes of infants at the most severe end of the BPD spectrum and this study describes in detail a large, novel cohort of such infants. In an individual unit cases are infrequent, making opportunities for learning limited. Collating cases at a national level in this manner provides data on an informative number of infants and demonstrates clear variation in their management between units.

4.6.1 Incidence and antenatal risk factors for life-threatening BPD

One hundred and fifty-three cases of life-threatening BPD were identified during the study period, meaning each level 3 neonatal unit in the UK and Ireland would expect to see one such infant per year. The reported minimum incidence of life-threatening BPD in this study was 13.9 per 1000 infants <32 weeks gestation. This does not include infants who died before 38 weeks gestation, and therefore is likely an underestimation of overall disease burden. Furthermore, incidence is likely to increase as the perceived limit of viability changes and increasingly immature infants are supported at birth(BAPM, 2019).

Infants in the study were generally extremely preterm and extremely low birth weight, which is to be expected as these are two of the strongest predictive factors for development

of BPD(Morrow et al., 2017). Interestingly, a small number of more mature infants were also affected, and identification of additional risk factors or antecedent events in such infants will be an important area for future study. Growth restriction was common, with 38% infants <10th centile at birth, in line with the increase in baseline risk of BPD in these infants. Rates of maternal hypertensive disorders and pre-eclampsia were not specifically surveyed, but evidence of placental insufficiency was reported in a number of infants suggesting a role for abnormal placental development in disease pathogenesis, although whether this increases risk of life-threatening BPD independently of its impact on preterm birth is unclear.

Antenatal steroid use was high, in line with the general preterm population, therefore not clearly a modifiable factor in the development of life-threatening disease(National Neonatal Audit Programme, 2020). Poorer outcomes are regularly reported for extremely preterm male infants compared to female infants, and this is a factor considered in risk assessment tools such as the NICHD BPD risk calculator(Laughon et al., 2011). Consistent with this, significantly more affected infants were male than female, supporting consideration of this factor in risk stratification for counselling and management of at-risk infants.

Chorioamnionitis was reported in 14% of infants, which is similar to other preterm cohort studies(Bell et al., 2022). Exposure to chorioamnionitis is positively associated with risk of BPD but does not appear to be strongly associated with life-threatening BPD in this cohort. A broad definition of chorioamnionitis was used, as clinicians were asked to report any suspicion of chorioamnionitis based on placental histology, appearance, or smell, however the retrospective nature of reporting may limit the availability of this data. Placental histology is often reported in maternal medical records so may not be available to clinician's reporting data from infants' records.

4.6.2 Respiratory management of infants with life-threatening BPD

By definition, infants in this study received a very prolonged period of positive pressure respiratory support. Initially this was with invasive ventilation, as over 90% of infants in the cohort were ventilated on the first day of life. Avoidance of mechanical ventilation and preferential use of CPAP as the primary mode of respiratory support has been shown to reduce rates of death and BPD in preterm infants, although some infants inevitably require invasive ventilation due to severe respiratory failure or apnoea(Subramaniam et al., 2016).

The indications for intubation and ventilation were not reported in this study, making it unclear whether a more proactive approach to non-invasive support would be possible to reduce disease in this cohort.

High-frequency oscillatory ventilation was common, used in 56% of infants, and exposure to HFOV was associated with increased risk of death on univariate analysis. This likely reflects use of HFOV as a 'rescue' therapy for severe respiratory disease rather than a causative association, but knowledge of such associations may aid risk-stratification in the future. Similarly, use of inhaled nitric oxide was significantly higher in this cohort than in the general preterm population (32% v 16.6%), indicating severe respiratory disease(Subhedar et al., 2021). Use of inhaled nitric oxide for hypoxic respiratory failure and persistent pulmonary hypertension is well-established in term and near-term infants, but remains controversial in preterm infants, with little convincing clinical evidence of benefit. There is marked variation in practice between units but overall use is increasing(Subhedar et al., 2021). Due to the high cost and unknown risks of iNO in preterm infants, further work to refine its role is required. Since iNO is generally used as a rescue therapy in severe, hypoxic respiratory failure, a randomised controlled trial would be challenging as clinicians may not have equipoise to withhold treatment. High-quality observational studies and development of consensus guidelines may help standardise use of iNO in this population.

Infants in this study were ventilated for a median of 29 (IQR 17-51) days, which is markedly longer than the general preterm population in the UK (median 10 days [IQR 3-26])(Dassios et al., 2021). Duration of invasive ventilation is strongly associated with development of BPD and has a higher predictive value than number of ventilation courses therefore a proactive approach to extubation should be undertaken even if success not guaranteed(Jensen et al., 2015). In this group, the number of courses of ventilation per infant was relatively low (median 2) despite the long cumulative duration. Whilst it is likely that this reflects severe lung disease, requiring high levels of support, it is possible that active weaning and earlier extubation may have been beneficial in some infants, and this approach is required in clinical practice.

All invasively ventilated infants received surfactant, the first dose of which was given in a timely manner at a median of 11 minutes (IQR 7-23) of age, and at recommended doses(Sweet et al., 2019). Repeat surfactant administration was more variable in frequency,

timing and dosage, reflecting the lack of a clear evidence-based approach to this. Meta-analysis of trials comparing single and multiple surfactant dosing showed greater improvement in oxygenation and ventilatory requirements, decreased risk of pneumothorax and a trend toward improved survival with repeat dosing, although the included studies are old and relevance to current practice may be limited(Soll & Özek, 2009). It is nonetheless surprising that 38% of infants received only a single dose of surfactant despite requiring prolonged ventilation, and this is potentially an area for improvement.

Invasive ventilation at or beyond 38 weeks CGA was clearly associated with adverse outcomes in this cohort, increasing risk of death 11-fold compared to infants who did not require invasive ventilation (aOR 10.95 [95% CI: 2.0-60.8]), in addition to significantly higher rates of death and/or major neurodevelopmental impairment (aOR 5.7 [95% CI: 1.5-22.7]) and death and/or long-term ventilation (aOR 5.95 [95% CI 1.5-23.5]). This is consistent with the findings of Jensen et al, who reported significantly higher rates of death, serious respiratory morbidity and neurodevelopmental impairment in infants requiring invasive support at 36 weeks CGA(Jensen et al., 2019). In the traditional NIH definition of BPD, used widely in clinical practice and as a trial outcome, these infants would be classified along with those requiring low flow oxygen or non-invasive pressure support(Jobe & Bancalari, 2001). The disease burden and outcome of such infants is clearly markedly different to those with milder disease, highlighting the limitations of such definitions, and supports the distinct classification of infants requiring invasive ventilation near/at term as an extremely high-risk subgroup.

CPAP and nasal high flow were both widely used in this cohort, received by 97% and 92% of infants respectively, although high flow was started later and used for a significantly longer duration. This pattern of use likely reflects the popularity of high flow as a weaning modality to step down from CPAP due to it increased tolerance and comfort, however the impact of increasing use of high flow on BPD rates is controversial(Shetty, Sundaresan, et al., 2016). In a large retrospective cohort study using data from the National Neonatal Research Database, Sand *et al* reported significantly increased odds of bronchopulmonary dysplasia in infants exposed to high flow support that those not receiving high flow, although a causal relationship cannot be inferred from this as indications for use, disease severity and other confounding factors were not controlled for(Sand et al., 2022). In this cohort of infants with life-threatening BPD, the risk death and/or neurodevelopmental impairment was

significantly lower in infants receiving high flow at 38 weeks than those receiving other modes of support, again likely reflecting use as a step-down therapy for weaning. This information is useful for risk stratification and counselling parents, suggestive of less severe disease and a more positive outlook for infants who receiving high flow than infants requiring invasive ventilation and/or CPAP at or beyond 38 weeks CGA.

4.6.3 Use of postnatal steroids in life-threatening BPD

Postnatal steroids, particularly dexamethasone, are one of the few, evidence-based strategies to reduce BPD in preterm infants. As a result, it is surprising that 40% of infants in this cohort did not receive any postnatal steroid. Early hydrocortisone was only used in one infant in this study, but the study period was before the publication of the 2-year outcomes of the PREMILOC study so this pattern may be changing(Baud et al., 2019). The majority of the postnatal steroid used in this group was dexamethasone. The use of postnatal dexamethasone has changed significantly in recent decades, with a clear reduction in use in the early 2000's as concern regarding increased rates of cerebral palsy associated with the use of postnatal dexamethasone emerged(Stoll et al., 2015). However, it is now clear that this risk applies to use of dexamethasone only in the first week of life, and use after this time is not associated with adverse neurodevelopmental outcomes. Dexamethasone used after 7 days of age significantly reduces the combined outcome of death or BPD (RR 0.75 [95% CI 0.67-0.84]), without increasing the risk of cerebral palsy (RR 1.17 [95% CI 0.84-1.61])(Doyle et al., 2021b). Despite this, some clinicians are still reluctant to use postnatal steroids resulting in marked variation in practice. At an individual level, infants have the most potential to benefit from postnatal steroids when their risk of BPD is highest(Doyle et al., 2014). Optimisation of risk assessment tools to apply in the first weeks of life may help clinicians identify the infants most likely to benefit from steroids, and prevent high-risk infants missing the opportunity receive steroids in a timely manner.

Despite clear evidence of benefit, the optimal timing, dosing, and regimen of dexamethasone remains unclear. Infants in this study received steroid at a median age of 26 days, with most infants receiving a regimen in line with the DART study(Doyle et al., 2006). This used a 10-day tapering course of dexamethasone with a cumulative dose of 0.89mg/kg, although the evidence for this is limited. The DART study recruited a total of 70 infants and showed a significant improvement in the primary outcome of extubation with

dexamethasone, but this study was not aimed at reducing BPD. A recent network meta-analysis of postnatal steroid regimens suggests moderately early initiated (8-14 days), medium cumulative (2-4mg/kg) dose dexamethasone is most likely to reduce BPD therefore earlier use in the second week of life at a higher dose and/or longer duration may be beneficial(Ramaswamy et al., 2021).

There has been significant research focus on use of postnatal steroids to prevent BPD, but there is little evidence to guide the use of steroids in the later management of established BPD and marked variation in practice was evident in this study. The first steroid used in the majority of infants was dexamethasone, whilst prednisolone and methylprednisolone were used less frequently and much later during admission, at a median CGA of >40 weeks. Retrospective studies have associated prednisolone use with reduced respiratory support and oxygen requirement in infants with established BPD, however no prospective studies have compared steroid regimens or assessed the impact of late steroid use in established BPD on longer-term clinical outcomes(Bhandari et al., 2008; Linafelter et al., 2019). Strategies to manage established, severe BPD should be differentiated from strategies to prevent BPD and are a key area for future study.

4.6.4 Management of PDA in infants with life-threatening BPD

The role of the PDA in development of BPD, and the potential benefit of PDA closure, is controversial. In this cohort, 38% of infants received medical therapy in the form of ibuprofen and/or paracetamol to close a PDA. Screening rates and response to treatment were not surveyed, so is it not known what proportion of infants had a spontaneously closing duct, an untreated, open duct, or a persistent duct despite treatment.

A retrospective cohort study of preterm infants in England and Wales using data from the National Neonatal Research Database, showed that between 2010 and 2017, 35% (6,384/18,181) of infants born at <32 weeks gestation received medication or surgery for treatment of a PDA. Rates of treatment in this cohort were higher (overall 42/94; 45%), however differences in the baseline demographics of included infants make comparison difficult. Medical treatment was commenced at a median age of 7.5 days, suggesting most clinicians use a selective approach to treatment of the duct, although the clinical and

echocardiographic criteria used to assess haemodynamic significance were not surveyed and potentially a source of variation in practice.

PDA ligation was performed in a smaller number of infants (17/94; 18%), with marked variation in the timing of surgery and respiratory status evident. It is notable that 4/17 (23.5%) of infants undergoing PDA ligation were on high flow support. Whilst PDA ligation has been associated with reduced duration of invasive ventilation, there is little evidence to support a role for ligation in infants receiving non-invasive support, particularly high flow(Lehenbauer et al., 2018). There are significant risks associated with PDA ligation including pneumothorax, laryngeal nerve injury, post-ligation cardiac syndrome and increased rates of necrotising enterocolitis and intraventricular haemorrhage, therefore careful risk assessment and patient selection is required(Härkin et al., 2018).

4.6.5 Pulmonary hypertension in life-threatening BPD

Abnormalities in pulmonary vascular structure and function are increasingly recognised as a key component of BPD, and a subset of infants develop clinical pulmonary hypertension. In this cohort, 34% of infants had documented echocardiographic evidence of pulmonary hypertension, although rates of screening were not surveyed therefore this may be an underestimation. Furthermore, specific diagnostic criteria were not defined, which may lead to variation in reporting, however this rate is comparable to a recent meta-analysis reporting pulmonary hypertension in 39% (95% CI 29-49%) of infants with severe BPD(Arjaans et al., 2018).

Presence of pulmonary hypertension in this cohort was one of the strongest predictors of death, major neurodevelopmental impairment and/or need for long-term ventilation, highlighting this as a key prognostic factor. Given the clear association of pulmonary hypertension with adverse outcomes, it may be appropriate to include this factor in future BPD classifications to aid risk-stratification.

Importantly, pulmonary hypertension is a potentially modifiable factor, therefore proactive screening and treatment of at-risk infants should be a priority. The European Paediatric Pulmonary Vascular Disease Network recommends a screening echocardiogram should be performed in any preterm infant <28 weeks with severe respiratory compromise, any infant with established BPD at 36 weeks CGA, and in any infant with a prolonged oxygen

requirement, poor growth or unsatisfactory clinical improvement, however national survey data suggests this does not happen in practice(Hansmann et al., 2020; Baczynski et al., 2020; Arjaans et al., 2021). The high morbidity and mortality associated with the presence of pulmonary hypertension in this cohort supports the need for optimisation of a standardised screening policy to ensure high-risk infants are identified and managed appropriately.

Retrospective studies have associated use of sildenafil with echocardiographic and clinical improvement in preterm infants with BPD, but these are small, single-centre studies with varying protocols for pulmonary hypertension screening and treatment, therefore have high levels of bias and lack generalisability(Trottier-Boucher et al., 2015; Wardle et al., 2015). In this cohort, 12/32 (37.5%) infants reported to have echocardiographic evidence of pulmonary hypertension did not receive treatment with sildenafil. Whilst supportive measures such as supplemental oxygen and use of non-invasive respiratory support may improve the clinical status of infants with pulmonary hypertension, the lack of standardised protocols for treatment of recognised pulmonary hypertension results in variation in practice, and it is possible some of these infants would benefit from pulmonary vasodilator therapy such as sildenafil(Hansmann et al., 2020). Prospective, collaborative studies are ultimately required to assess the optimal timing and dosing regimen for sildenafil in infants with BPD-associated pulmonary hypertension.

4.6.6 Infection in life-threatening BPD

Significant infection was common in this cohort, with culture positive sepsis reported in 47% and culture negative sepsis in 52% of affected infants. This is notably higher than the general preterm population, with a positive blood culture reported in only 16% of infants <32 weeks gestation in the UK, consistent with infection and inflammation contributing to the aetiology of severe BPD(National Neonatal Audit Programme (NNAP), 2020).

Ureaplasma has specifically been associated with the development of BPD in preterm infants, with azithromycin a potential therapeutic strategy(Razak & Alshehri, 2020). *Ureaplasma* was only identified in one infant in this cohort, however this requires specific culture techniques and screening rates were not surveyed therefore this may be an under-recognised modifiable factor.

4.6.7 Medications used in life-threatening BPD

Diuretics were very widely used in this cohort, with 87% of infants receiving diuretic therapy during their neonatal unit admission. This was started at a median age of 32 days, suggesting diuretics were generally used in the management of evolving BPD in these infants. Total duration of diuretic therapy was long, with a median duration of 76.5 days, and over 40% of infants remained on diuretic therapy on discharge from the neonatal unit.

There is little convincing evidence of clinical benefit from diuretic use in the prevention or management of BPD, therefore the high prevalence and long duration of diuretic exposure in this cohort is concerning. Diuretic use has been associated with associated with short-term improvements in oxygenation and pulmonary mechanics, likely due clearance of interstitial lung fluid, but evidence of long-term term benefit is currently lacking(Stewart & Brion, 2011; Stewart et al., 2011). A retrospective study of 835 preterm infants in the Prematurity and Respiratory Outcomes Programme (PROP) showed no improvement in respiratory status following initiation of diuretic therapy(Blaisdell et al., 2018), however differences in baseline infant characteristics and variation in diuretic use mean confounding factors cannot be excluded. In contrast, a retrospective cohort study including data from over 37,000 infants in the USA reported a statistically significant association between longer furosemide exposure and reduced rates of BPD, with a 4.6% reduction in BPD for each 10% increase in days exposed to furosemide(Greenberg et al., 2019). The authors of this study suggest that duration of exposure may be key to improving outcomes, as this benefit was not evident when infants were simply classified according to whether or not they received furosemide. No prospective trial evidence is currently available to support this approach, and the retrospective nature of this study makes exclusion of all potential confounding factors difficult. Side-effects of diuretics including electrolyte imbalance and nephrocalcinosis are common therefore prospective, randomised trials are required to assess the safety and efficacy of diuretic regimes in the prevention and treatment of BPD.

Inhaled bronchodilators were used infrequently and late in the disease course in this cohort, with only 8 (8.5%) infants receiving treatment at a median age of 125 days. Duration of bronchodilator therapy in this cohort was relatively short, with a median of 8 days, suggesting it was used as a short-term trial. This is notably different to the PROP cohort, in which 31.7% of infants born at <29 weeks received inhaled bronchodilator therapy during

their neonatal unit admission(Greenberg et al., 2020). High variation in bronchodilator use between centres is evident, reflecting the uncertain evidence of benefit(Slaughter et al., 2015). Short term improvements in airway resistance and lung compliance have been reported with inhaled bronchodilators in infants with evolving or established BPD, however this effect is variable and evidence of long-term benefit on clinical outcomes is lacking(Clouse et al., 2016). Infant lung function testing has shown a range of disease phenotypes in preterm infants with BPD, with varying patterns of obstructive, restrictive, and mixed disease. Rates of bronchodilator responsiveness are highest in those with obstructive disease, suggesting infant lung function testing and targeted therapy for those with obstructive disease may be a useful approach going forward(Shepherd et al., 2018).

Inhaled corticosteroids were similarly used late during admission, at a median age of 97 days in a relatively small number of infants with established BPD (16/94; 17%). Individual studies have variably reported earlier extubation, reduced duration of oxygen and improved respiratory mechanics with use of inhaled corticosteroids, but meta-analysis of trials using inhaled corticosteroids after 7 days of age showed no reduction the outcomes of death and/or BPD, duration of mechanical ventilation, or oxygen therapy(Clouse et al., 2016; Onland et al., 2017). However, heterogeneity in the included study populations, treatment regimes, and outcome definitions mean these results should be interpreted with caution. Strategies to prevent BPD should be clearly differentiated from the treatment of established BPD, and focus on management strategies for infants with severe, established BPD is required.

4.6.8 Outcomes of life-threatening BPD

By 1 year of age, 15/94 (16%) infants died, with most reporting BPD as the primary cause of death. As case reporting occurred at 38 weeks CGA, this definition does not include infants who died due to BPD before 38 weeks CGA, therefore overall BPD-related mortality is higher. However, this data is useful for clinicians counselling the families of infants remaining on respiratory support at 38 weeks; most infants (84%) do survive but the mortality rate (16%) is not insignificant.

Ultimately, 81% of infants were discharged home, with the majority requiring low flow oxygen and 9% requiring long-term ventilation. Discharge generally occurred post-term at a

median postnatal age of 143 days, or 46.6 weeks CGA, indicating this condition is associated with high resource use during a prolonged hospital admission and ongoing respiratory support post-discharge. Duration of home oxygen and/or long-term ventilation were not studied, but both are associated with significant healthcare resource use and impact on families' post-discharge. Furthermore, readmissions requiring respiratory support, particularly high flow, in the first year of life were frequent, highlighting that the consequences of BPD reach beyond the neonatal unit and long-term collaborative follow-up involving neonatologists and respiratory paediatricians is required.

Tracheostomy placement was uncommon, and generally performed very late at a median postnatal age of 260 days. Given the long duration of respiratory support received in this cohort, this suggests, although clinicians may be reluctant to perform a tracheostomy, most infants avoid the need for a tracheostomy with time. Retrospective data from 18 neonatal units in the US Neonatal Research Network suggests that although tracheostomy placement is associated with significantly increased risk of death or neurodevelopmental impairment, in those infants requiring a tracheostomy, early placement (<120 days of age) was associated with improved outcomes compared to late placement (≥120 days)(DeMauro et al., 2014). The authors postulate this is likely due to the improved mobility and social interaction allowed by tracheostomy insertion and suggest the procedure should not be delayed in infants likely to require a tracheostomy. Tracheostomy insertion is a major decision, and timing of the procedure must be carefully considered to avoid unnecessary insertion if an infant may manage without, but avoid unduly delaying tracheostomy formation in infants who inevitably require this.

Formal neurodevelopmental assessment was not performed in this cohort due to the timepoint of outcome evaluation at 1 year, however clinicians reported the presence of no, minor, or major concerns from the infants' medical records. Major neurodevelopmental concerns were reported in 22% infants, which is higher than the comparable general preterm population(Moore et al., 2012). This finding is consistent with others reporting significantly higher rates of neurodevelopmental impairment in infants with severe BPD compared to mild or moderate BPD, particularly when this was assessed near term(Malavolti et al., 2018; Isayama et al., 2017; Jensen et al., 2019). Many of the risk factors predisposing to BPD are also associated with neurodevelopmental impairment, such as lower gestational age and birth weight, therefore both are a marker of illness severity. In addition, in infants

with severe BPD recurrent episodes of hypoxia, hypercapnia and respiratory acidosis, and frequent postnatal steroid use may further exacerbate brain injury, independently increasing risk of neurodevelopmental impairment. This information should be considered when counselling families of infants with severe lung disease, and in future BPD definitions to ensure the highest risk infants can be identified appropriately.

4.6.9 Strengths and limitations of this study

This study collated data on infants with the most severe BPD at a national level, providing a comprehensive overview this important, understudied subgroup of infants. In an individual unit cases are rare but collecting data from across the country using the BPSU methodology allowed a detailed description of the characteristics, variation in management and outcomes of these infants, not possible in a single centre study.

The BPSU methodology is a well-established technique for study rare diseases, which allows active case surveillance to measure incidence. Compliance with case reporting is high (94.7% during this study period), but further ascertainment is limited by clinicians' responses. This study used a series of three data collection questionnaires to collect detailed data at different timepoints up to 1 year of age, however attrition inevitably occurred at each stage. Questionnaire 1 was used to confirm case eligibility and collect demographic data for affected infants. In total, complete questionnaire 1 data were provided for 153 confirmed cases. Data were not provided for an additional 86 potential cases despite multiple reminders, therefore the calculated minimum incidence is likely an underestimation. Questionnaire 2 was used to collect detailed neonatal unit admission and discharge data. This was completed for 94/153 confirmed cases. Questionnaire 2 data was not provided for 59/153 confirmed cases, again despite multiple reminders. Although a potential source of bias, there was no difference in baseline characteristics between infants with and without additional data, and a comprehensive description of infants from 57 different centres is provided. The major strength of the BPSU methodology is data is obtained from the infants' medical records, therefore specific data can be collected with a high level of detail and accuracy. The National Neonatal Research Database (NNRD) is an electronic database that collects routinely recorded data and is frequently used for epidemiological studies. However, the NNRD reports a limited number of data points and would not allow identification of infants requiring respiratory support at 38 weeks or provide the level of detail permitted by

the BPSU methodology. Furthermore, significant reporting error is known to exist in this database, including for important clinical outcomes. Information is entered into this database by all clinical and administration staff, with high potential for error. When data from the NNRD was compared to the Probiotics in Preterms Study randomised controlled trial dataset, a discordancy of 13.3% (95% CI 11.2-15.8%) was observed in whether an infant was receiving oxygen at 36 weeks corrected gestational age(Battersby et al., 2018). The BPSU methodology involves a single clinician obtaining data directly from the infants medical records, reducing the risk of error.

Case reporting occurred at 38 weeks corrected gestational age, therefore infants who died of BPD prior to this were not included, so overall BPD-related mortality is higher than reported. Although a large dataset was collected, there are some additional data points such as maternal smoking status, specific ventilation strategies and incidence of necrotising enterocolitis, which may modulate disease severity and would be useful to explore in the future. Finally, since the study notification period, new evidence and associated practice changes such as offering stabilisation at lower gestational ages, increased use of prophylactic hydrocortisone and less invasive surfactant administration may alter the incidence and characteristics of life-threatening BPD in the preterm population(BAPM, 2019; Baud et al., 2016; Aldana-Aguirre et al., 2017). Assessing the impact of such changes at a population level, possibly by development of a disease registry or integrating this into existing databases such as the NNRD, will be important to continually assess practice and identify areas for improvement.

4.6.10 Conclusions

In conclusion, life-threatening BPD occurred in 13.9 per 1000 infants born at <32 weeks gestation in the UK and Ireland during the study period. This study has identified an extremely high-risk subgroup of infants, with high morbidity and mortality not discernible using current definitions of BPD. These findings support the distinct classification of infants requiring positive pressure support near term and provide useful data for clinicians counselling families of affected infants.

Whilst there has been extensive research focus on prevention of BPD, there is little evidence to guide the management of established BPD, particularly in the most severely affected

infants. As a result, significant variation in practice was identified, particularly in key areas of postnatal steroid use and pulmonary hypertension management, which are important areas for future study.

Chapter 5. Lung function and ventilatory response to exercise measured using optoelectronic plethysmography in school age children born preterm

5.1 Introduction

Children who were born preterm show lung function abnormalities, with features of airflow obstruction and impaired gas exchange that persist with age(Kotecha et al., 2013; Simpson et al., 2018; L. W. Doyle et al., 2019). This is clearly a spectrum of disease, with most marked impairment in those with severe neonatal lung disease and a diagnosis of bronchopulmonary dysplasia, but preterm-born children without a diagnosis of BPD also show a degree of lung function impairment(Ronkainen et al., 2015; Simpson et al., 2018). This is associated with a higher burden of respiratory disease in childhood, with a higher prevalence of respiratory symptoms, respiratory related hospital admissions and respiratory medication use in preterm-born children(Hennessy et al., 2008; Fawke et al., 2010).

The longer-term impact of preterm birth on subsequent exercise capacity in childhood is unclear. A number of studies report reduced exercise capacity in children born preterm(Welsh et al., 2010; Maclean et al., 2016), although this is not universal with some reporting near-normal peak exercise capacity(Clemm et al., 2012; Joshi et al., 2013). Studies specifically assessing the ventilatory response to exercise have shown an altered pattern of breathing in children born preterm, with lower tidal volumes and higher respiratory rates at peak exercise(Welsh et al., 2010; Maclean et al., 2016). Expiratory flow limitation is more common at peak exercise in children with BPD and has been postulated as a mechanism for this altered ventilatory response. Expiratory flow limitation promotes dynamic hyperinflation, with an increase in end-expiratory lung volume and concomitant reduction in inspiratory capacity resulting in tidal volume restriction(Calverley & Koulouris, 2005). In adults with chronic obstructive pulmonary disease (COPD) this is known to contribute to impairment of respiratory muscle strength and the sensation of dyspnoea, however the potential contribution of this to exercise limitation in children born preterm is unclear(Vogiatzis et al., 2005).

No change in inspiratory capacity during exercise has been reported in children born preterm, suggesting that dynamic hyperinflation does not occur, however this technique is subjective and effort dependent(Maclean et al., 2016). Furthermore, standard

cardiopulmonary exercise testing involves use of tight-fitting facemask or mouthpiece and nose clip during exercise, which alters normal breathing patterns. Optoelectronic plethysmography is a non-invasive technique that measures changes in thoracoabdominal volumes at rest and during exercise, and can directly track changes in end-expiratory chest wall volume(Massaroni et al., 2017). It does not require use of a facemask, therefore has potential to overcome the limitations of standard cardiopulmonary exercise tests, and directly assess for evidence of dynamic hyperinflation. Optoelectronic plethysmography has been used to assess breathing patterns in children at rest, and to demonstrate dynamic hyperinflation during exercise in adults with asthma and chronic obstructive pulmonary disease, but it has not previously been used during exercise in children with preterm lung disease(Fregonezi et al., 2018; Vogiatzis et al., 2005).

5.2 Hypothesis

This study explored the hypothesis that dynamic hyperinflation contributes to exercise limitation in school-aged children born preterm.

5.3 Aims

This study aimed to explore lung function and exercise capacity of school-aged children born preterm compared to healthy term-born controls, specifically to:

- Assess baseline lung function in a contemporary cohort of children who were born preterm with and without a diagnosis of BPD in the neonatal period.
- Evaluate the feasibility of using optoelectronic plethysmography to assess the ventilatory response to exercise in school-aged children.
- Assess the changes in end-expiratory chest wall volume during exercise using optoelectronic plethysmography, to assess for evidence of dynamic hyperinflation in school-aged children born preterm.

5.4 Methods

5.4.1 Inclusion and exclusion criteria

Children aged 10-16 years of age were recruited to this study. The preterm group included children who were born at <32 weeks gestation and received neonatal care at the Royal

Victoria Infirmary (RVI), Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne. Preterm participants were classified as having significant BPD if they required oxygen and/or positive pressure respiratory support at 36 weeks corrected gestational age, or no BPD if they were in room air by 36 weeks. Positive pressure support included invasive ventilation, CPAP/BiPAP and nasal high flow at ≥2L/min. The healthy control group included children born at ≥37 weeks gestation. Informed, written parental consent was required prior to participation in the study.

Children unable to comply with the test procedure, and those with significant cardiac, neuromuscular disease or other respiratory pathology were excluded from the study as these factors may affect exercise capacity and study results. Children with controlled asthma requiring inhaled bronchodilators and/or inhaled steroids were not excluded; they were advised to continue their long-acting medications as normal and were permitted to participate if they had not required a short-acting bronchodilator in the preceding 24 hours. Children with an acute respiratory illness in the previous 2 weeks were excluded, or appointments rearranged.

5.4.2 Participant recruitment

Eligible preterm participants were identified using the neonatal unit database. All admissions from 2005-2009 were screened for eligibility in August 2019. Those born at <32 weeks, who were alive at the point of discharge from the neonatal unit, without any major documented congenital anomaly were shortlisted. The electronic health record of all shortlisted children was screened to ensure they were still alive, living in the local area, and did not have any major exclusion criteria. As the RVI is a tertiary referral centre infants are referred from across the North East and Cumbria. Children with postcodes in Newcastle, Gateshead, North Tyneside, and Northumberland were identified; those living outside this area were excluded to avoid excessive travel for families. Their general practitioner (GP) details were recorded from the National Health Service (NHS) Spine portal. A letter was sent to the GP of all potential participants, to ensure there were no medical or social reasons not to approach the family. Positive confirmation of this by letter, email or telephone was required before approaching the family. An invitation letter was then sent to eligible families in the post. This included a cover letter and copies of the parent and participant information sheets. This was

followed up by a telephone call one week later to discuss recruitment and any questions the family may have.

In addition, participants were recruited via the Tiny Lives, the Newcastle Neonatal Unit charity. Information about the study was posted on their website and social media accounts, so volunteers (preterm and controls) could contact the research team directly. Healthy control subjects, born at ≥37 weeks gestation were also recruited. This was planned to be via local schools, however due to the restrictions imposed by the Covid-19 pandemic, a smaller volunteer sample was recruited.

5.4.3 Background information

Demographic and detailed neonatal information was obtained from the medical records of preterm participants. This included gestation, birth weight, steroid exposure, types and duration of respiratory support and comorbidities. All participants completed a questionnaire assessing current respiratory health, physical activity levels and their own perceptions of their exercise capacity. The questionnaire was completed by the participant and their parent/guardian(s) together.

5.4.4 Study protocol

The study involved two visits to the study centres. The first was to the children's outpatient department at the Great North Children's Hospital for standard lung function tests. Height and weight were recorded, and the study questionnaire completed prior to lung function tests.

Lung function tests included spirometry, body plethysmography, gas transfer testing and fraction of exhaled nitric oxide. These were carried out according to standard European Respiratory Society standards as detailed in chapter 2. Reversibility testing was performed, measuring change spirometry variables following administration of 400 micrograms of salbutamol via a metered dose inhaler and spacer.

The second visit was to the gait analysis laboratory of the Department of Sport, Exercise and Rehabilitation, Sport Central, Northumbria University, Newcastle upon Tyne. Pre-exercise spirometry was performed using a hand-held spirometer to assess FEV_1, FVC, FEV_1/FVC, and peak expiratory flow. This was repeated a minimum of three times, until repeatability

criteria were met i.e. the difference between the two largest FEV_1 and FVC values were ≤0.1L or 10% of the highest value, whichever was greater(Graham et al., 2019). An exercise test was then performed using optoelectronic plethysmography to assess ventilatory changes during exercise. The OEP system (BTS bioengineering, Italy) was set up and calibrated, and 89 reflective markers applied to the participants' chest, back and abdomen as detailed in chapter 2. Three minutes of quiet breathing were recorded as a baseline before starting the exercise test. During this time, three inspiratory capacity manoeuvres were performed.

The exercise test was performed on a cycle ergometer (Ergoselect 200, Ergoline, Germany). Three minutes of unloaded cycling were performed as a warm-up to familiarise the child with the environment and equipment. Following this, a ramped exercise test using a modified Godfrey protocol was performed so the child would be expected to reach peak exercise within 8-10minutes as detailed in chapter 2. Cycling cadence was maintained at 50-60 revolutions per minute throughout the test.

The test was terminated at the point of voluntary exhaustion when the child was unable to continue or maintain the required cadence despite verbal encouragement. Heart rate and saturations were monitored throughout using a pulse oximeter (Nonin Onyx Vantage 9590, USA). Following the exercise test, spirometry was repeated as above, specifically assessing for evidence of exercise induced bronchoconstriction. The exercise study protocol is outlined in Figure 5.1.

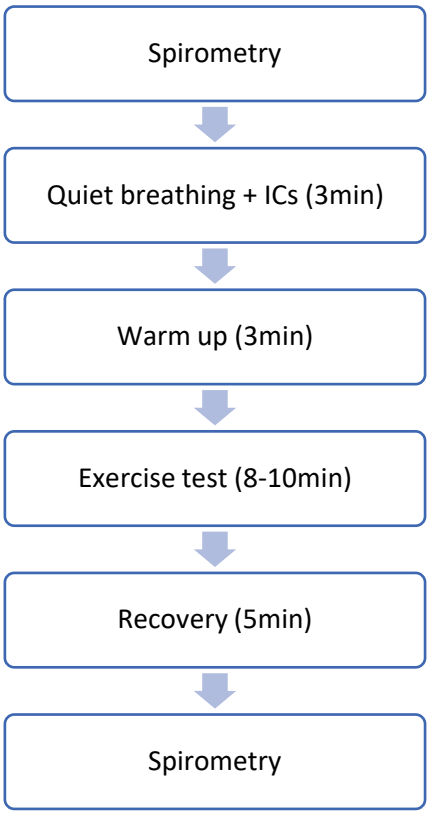

Figure 5.1 Exercise study protocol. IC: Inspiratory capacity manoeuvre.

5.4.5 Data analysis

Lung function values are reported as z-scores adjusted for age, height and sex. OEP data was analysed using dedicated reconstruction software (Smart Tracker, BTS bioengineering, Italy). Recordings were made for 3 minutes of quiet breathing, the last one minute of the warm-up, then for the last 30 seconds of each minute until peak exercise. Data was analysed in 30 second blocks at rest (0%), 20%, 40%, 60%, 80%, and at 100% of peak exercise. All artefact free breaths in each 30second recording were included. At each time point, absolute values and change from baseline (0%) were recorded for tidal volume, respiratory rate and minute ventilation, in addition to total and compartmental thoracoabdominal wall volumes at peak inspiration and maximal expiration.

5.4.6 Statistics

As this was a feasibility study, with no existing OEP data available for children born preterm during exercise, a formal power calculation was not undertaken. Initially, a target sample size of 20 children per group (preterm with BPD, preterm without BPD and controls) was

planned as this was a feasible number to recruit that would provide informative data, however due to the disruption caused by the Covid-19 pandemic, the number of participants recruited was reduced. As a result, the data provided is largely descriptive. Data were analysed using frequencies and measures of central tendency and dispersion; median and interquartile range (25^{th} – 75^{th} centile) were reported as data were non-normally distributed.

Some exploratory statistical analysis was performed to compare groups, although this is limited due to the sample size. The Wilcoxon signed rank test was used to assess longitudinal changes. Fisher's exact test was used to compare categorical variables, and the Mann-Whitney U or Kruskal Wallis tests were used to compare non-parametric continuous variables between two or three groups respectively. A p-value of <0.05 was considered significant, and a Bonferroni correction was applied for multi-group comparisons. All data were analysed using IBM SPSS statistics version 27.

5.4.7 Ethical approval and safety considerations

This study was designed with input from the Young Persons Advisory Group for North England (YPAG-NE), who reviewed the study protocol and participant information sheets to ensure they were understandable to young people, and they felt comfortable with the study procedure.

Although some of the ex-preterm children taking part in the study had significant lung disease, all were able to take part in normal physical activity at school, therefore the exercise test procedure was not expected to be associated with any adverse effects. The child's heart rate and saturations were monitored throughout the exercise test, and I (a paediatric registrar) supervised all tests. As a precaution, oxygen and a salbutamol inhaler were available at the test site.

Ethical approval was obtained from the NHS North-East (York) Research Ethics Committee (reference 19/NE/0005).

5.5 Results

5.5.1 Participant demographics

Study recruitment commenced in September 2019 and was planned to run over 12-18 months, however, due to the Covid-19 pandemic all study activity was stopped in March 2020. At this point, 39 children were enrolled in the study and had provided data. This included 19 children born preterm with a history of significant BPD, 11 children born preterm without BPD and 9 healthy, term-born controls. All participants completed the lung function tests, and 29 completed the exercise test (Figure 5.2).

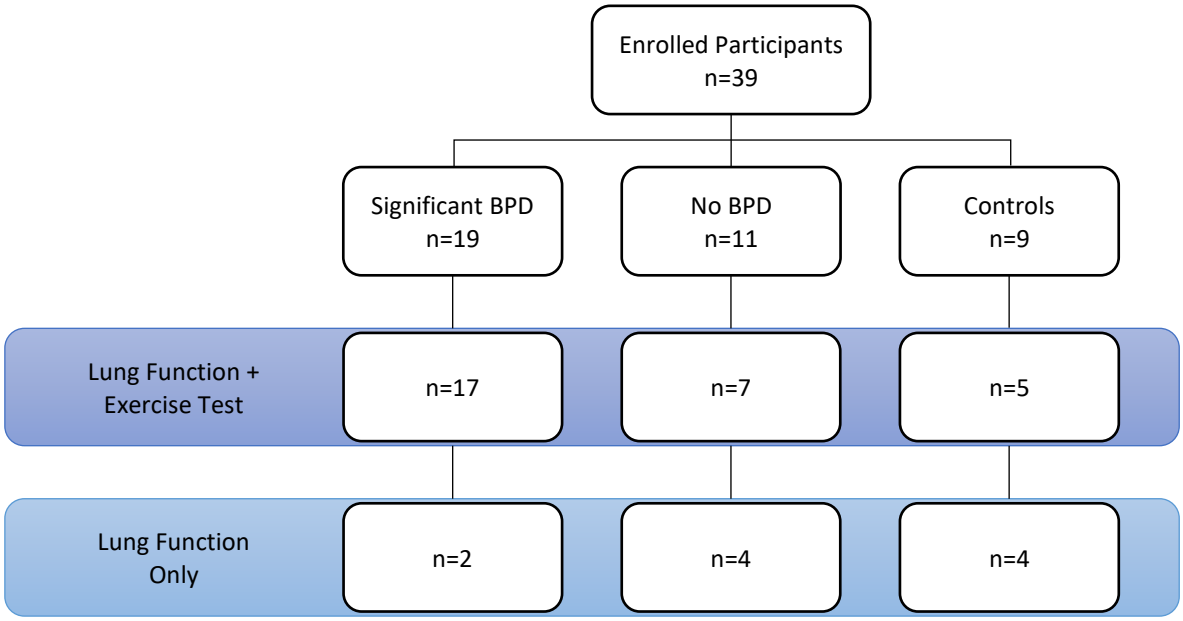

Figure 5.2 Participant recruitment and tests undertaken. BPD: Bronchopulmonary dysplasia defined as need for oxygen and/or positive pressure respiratory support at 36 weeks corrected gestational age.

Demographic and perinatal details of the participants are summarised in Table 5.1. There were no significant differences in age, sex, current height, or weight between the groups at the point of study enrolment. Children with BPD were born extremely preterm with a median gestational age of 26.7 weeks (IQR 25.1-28.2) and extremely low birth weight (median 0.89kg [0.74-0.99]). During the neonatal period, children with BPD were significantly more likely to receive surfactant, required a longer duration of positive pressure

respiratory support and were more likely to require home oxygen than those without BPD or controls.

The preterm group without BPD were generally born very preterm, at a median gestational age of 29.7 weeks (IQR 28.4-30.7) and very low birth weight (median 1.43kg [IQR 1.04-1.55]). They were also more likely to receive surfactant and required a longer duration of respiratory support than the healthy control group.

	Significant BPD n=19	**No BPD n=11**	**Controls n=9**
Current Demographics			
Age (years)	13.3 (12.5-14.3)	12.5 (12.2-13.5)	12.25 (11.3-13.8)
Male	12/19 (63%)	6/11 (55%)	4/9 (44%)
Current height (cm)	158.4 (152.4-164)	156.8 (146.7-160.1)	158.2 (155-161)
Current weight (kg)	52.2 (40.1-57.3)	44.1 (40.6-52.9)	44.4 (37.8-50)
Neonatal Details			
Birth gestation (weeks)	26.7 (25.1-28.2)[a,b]	29.7 (28.4-30.7)[c]	39.0 (38-39.7)
Birth weight (kg)	0.89 (0.74-0.99)[a,b]	1.43 (1.04-1.55)[c]	3.30 (2.70-3.54)
Caesarean section	8/19 (42%)	6/11 (55%)	3/9 (33%)
Prolonged rupture of membranes	6/19 (32%)	3/11 (27.3%)	0/9 (0%)
Chorioamnionitis	4/19 (21%)	0/11 (0%)	0/9 (0%)
Received antenatal steroids	12/19 (63%)[a]	6/11 (55%)	1/9 (11%)
Received postnatal steroids	3/19 (16%)	0/11 (0%)	0/9 (0%)
Received surfactant	18/19 (95%)[a,b]	7/11 (64%)[c]	0/9 (0%)
Duration respiratory support (days)	46 (21.5-58)[a,b]	7 (5-15.5)[c]	0 (0-0)
Received home oxygen	17/19 (90%)[a,b]	0/11 (0%)	0/9 (0%)

Table 5.1 Demographic and neonatal details of study participants. All data presented as number (%) or median (IQR). BPD: Bronchopulmonary dysplasia. [a]BPD group significantly different to controls ($p<0.05$). [b]BPD group significantly different to no BPD group ($p<0.05$). [c]No BPD group significantly different to controls ($p<0.05$).

5.5.2 Respiratory health and activity

Questionnaire data regarding participant's baseline respiratory health and exercise capacity is displayed in Table 5.2. Over 50% (10/19) of children with a history of BPD had received a salbutamol inhaler, compared to only 9% (1/11) of preterm children without BPD and 22% 2/9) of the control group, although only 16% (3/19) children with BPD had a formal diagnosis of asthma. Rates of asthma diagnosis, respiratory related hospital admissions and steroid use were not different between groups, although overall numbers were small.

Children born preterm with and without BPD reported significantly lower activity levels than the control group, with the majority reporting they exercise for 30 minutes or more ≤4 times per week, whilst all the control group reported exercising >4 times per week. Children with a history of BPD were significantly more likely to self-report their fitness as below average compared to both the preterm group without BPD and term-born controls, with 37% (7/19) of the BPD group reporting their fitness level to be lower than their peers. In contrast, 67% (6/9) of the control group reported their fitness to be above average.

	Significant BPD n=19	No BPD n=11	Controls n=9
Respiratory Health			
Diagnosed asthma	3/19 (16%)	0/11 (0%)	1/9 (11%)
Other atopic history	5/19 (26%)	4/11 (36%)	3/9 (33%)
Family history atopy	13/19 (68%)	8/11 (73%)	3/9 (33%)
Respiratory related hospital admission	6/19 (32%)	5/11 (46%)	1/9 (11%)
Salbutamol inhaler (ever)	10/19 (53%)[b]	1/11 (9%)	2/9 (22%)
Inhaled and/or oral steroid (ever)	2/19 (11%)	1/11 (9%)	0/9 (0%)
Smokers in household	3/19 (16%)	0/11 (0%)	0/9 (0%)
Exercise			
Frequency per week			
0-1	4/19 (21%)	1/11 (0%)	0/9 (0%)
2-4	9/19 (47%)[a]	7/11 (64%)[c]	0/9 (0%)
4-6	4/19 (21%)[a]	3/11 (27%)[c]	7/9 (78%)
7	2/19 (11%)	1/11 (9%)	2/9 (22%)
Exercise induced symptoms			
Breathlessness	9/19 (47%)	4/11 (36%)	1/9 (11%)
Wheeze	6/19 (32%)	4/11 (36%)	1/9 (11%)
Cough	5/19 (26%)	4//11 (36%)	1/9 (11%)
Self-rated fitness			
Below average	7/19 (37%)[a]	1/11 (9%)	1/9 (0%)
Average	10/19 (53%)	8/11 (73%)	3/9 (33%)
Above average	2/19 (11%)[a]	2/11 (18%)[c]	6/9 (67%)

Table 5.2 Respiratory health and self-reported activity data. BPD: Bronchopulmonary dysplasia. Other atopic history: Eczema or hay fever. Family history: First degree relative. Exercise frequency: Days per week with 30 minutes of more exercise. [a]BPD group significantly different to controls ($p<0.05$). [b]BPD group significantly different to no BPD group ($p<0.05$). [c]No BPD group significantly different to controls ($p<0.05$).

5.5.3 Baseline lung function

Lung function results are summarised in Table 5.3. Preterm children with a history of BPD showed clear features of airflow obstruction, with median z-scores for FEV_1 -1.48 (IQR -2.2 to -0.4), FEV_1/FVC -1.38 (IQR -1.38 to 0) and $FEF_{25-75\%}$ -1.75 (IQR -2.1 to -1.2). These were all significantly lower than the term born control group, and suggest marked airflow obstruction in this group. Preterm children without a history of BPD showed a similar obstructive pattern, but less marked abnormalities with median z-scores for FEV_1 -0.85 (IQR -1.4 to -0.4), FEV_1/FVC -0.82 (IQR -1.37 to -0.1) and $FEF_{25-75\%}$ -1.35 (-1.7 to -0.7). In this group, FEV_1/FVC and $FEF_{25-75\%}$ were significantly lower than the healthy control group; differences in FEV_1 did not reach statistical significance, although the sample size is small.

Assessing the response to a bronchodilator, a trend toward a greater increase in FEV_1 post-bronchodilator was evident in the preterm groups compared to healthy controls. In the preterm group with BPD FEV_1 increased by a median of 8.4% (IQR 2.7 to 10.7) compared to a median increase of 5.1% (IQR 3.7 to 6.3) in the preterm without BPD and 3.2% (IQR 0 to 5.2) in the control group. A similar trend was observed in change in FEV_1/FVC and $FEF_{25-75\%}$ post-bronchodilator, with the greatest increase in the preterm group with BPD and the smallest increase in control group. Only the difference in change in FEV_1/FVC between the preterm group with BPD and controls was statistically significant in this cohort, although sample size limitations mean a significant difference cannot be excluded in other parameters.

No difference in lung volumes including total lung capacity, residual volume or inspiratory capacity was observed between groups. Similarly, residual volume to total lung capacity was not different, suggesting gas trapping is not a significant feature in this cohort. Gas exchange abnormalities were evident, with median z-scores for DLCO -1.02 (IQR -1.5 to -0.4) and KCO -1.9 in the preterm BPD group which were significantly lower than controls. The preterm group without BPD showed a similar trend, with a median z-scores of -0.35 (IQR -0.6 to 0.3) for DLCO and -1.47 (IQR -2.0 to -0.9) for KCO respectively. These were not significantly different to controls but the sample size is again limited. Fraction of exhaled nitric oxide was not different between groups.

	Significant BPD n=19	No BPD n=11	Controls n=9
FEV_1 z-score	-1.48 (-2.2 - -0.4)[a]	-0.85 (-1.4 - -0.4)	-0.25 (-0.7 - 0.03)
FVC z-score	-0.9 (-1.5 - -0.01)	-0.48 (-0.8 - 0.0)	-0.42 (-1.2 - -0.07)
FEV_1/FVC z-score	-1.38 (-1.8 - 0.0)[a]	-0.82 (-1.37 - -0.1)[c]	0.4 (0.1 - 0.8)
FEF_{25-75} z-score	-1.75 (-2.1 - -1.2)[a]	-1.35 (-1.7 - -0.7)[c]	-0.24 (-0.5 - 1.0)
TLC z-score	-0.05 (-1.1 - 0.7)	-0.13 (-0.5 - 0.5)	-0.09 (-0.7 - 0.9)
RV z-score	0.16 (-0.7 - 0.7)	-0.51 (-0.7 - 0.2)	-0.06 (-0.6 - 0.4)
RV/TLC z-score	0.55 (-0.3 - 1.5)	-0.23 (-0.9 - 0.5)	0.06 (-0.2 - 1.0)
VC z-score	-0.69 (-1.5 - -0.1)	-0.34 (-0.7 - 0.1)	-0.44 (-0.8 - 0.3)
ERV z-score	-0.48 (-1.4 - 0.2)	-0.44 (-0.8 - 0.4)	0.59 (-0.5 - 0.8)
IC z-score	-0.85 (-2.0 - -0.2)	-0.07 (-0.6 - 0.5)	-0.82 (-1.2 - 0.2)
DLCO z-score	-1.02 (-1.5 - -0.4)[a]	-0.35 (-0.6 - 0.3)	0.59 (-0.2 - 0.7)
KCO z-score	-1.9 (-2.8 - -1.5)[a]	-1.47 (-2 - -0.9)	-0.79 (-1.2 - -0.4)
VA z-score	1.21 (-0.2 - 2.0)	1.32 (1.0 - 2.7)	1.28 (0.1 - 2.4)
ΔFEV_1 post-bronchodilator (%)	8.4 (2.7 - 10.7)	5.1 (3.7 - 6.3)	3.2 (0 - 5.2)
ΔFEV_1/FVC post-bronchodilator (%)	5.7 (3 - 7.8)[a]	4.2 (1.3 - 4.8)	2.0 (0.1 - 2.7)
$\Delta FEF_{25-75\%}$ post-bronchodilator (%)	19.1 (12.1 - 30.6)	16.4 (10 - 21)	10.4 (2.8 - 16.8)
FeNO (ppb)	21 (10 - 31)	10 (6.5 - 24)	18 (7 - 29)

Table 5.3 Baseline lung function results. All data reported as median (IQR). BPD: Bronchopulmonary dysplasia. FEV_1: Forced expiratory volume in 1 second. FVC: Forced vital capacity. FEF_{25-75}: Forced expiratory flow at 25-75% vital capacity. TLC: Total lung capacity. RV: Residual volume. VC: Vital capacity. ERV: Expiratory reserve volume. IC: Inspiratory capacity. DLCO: Diffusion capacity for carbon monoxide. KCO: Carbon monoxide transfer coefficient. VA: Alveolar volume. FeNO: Fraction of exhaled nitric oxide. PPB: Parts per billion. [a]BPD group significantly different to controls ($p<0.05$). [c]No BPD group significantly different to controls ($p<0.05$).

5.5.4 Exercise test results

Results of the exercise test are summarised below in Table 5.4. In total, 29 participants completed the exercise test, and OEP data were collected successfully in all children. The overall exercise time, maximum workload and peak heart rate were not different between the three groups, suggesting participants achieved a similar relative peak intensity of exercise. No children showed evidence of desaturation (oxygen saturation <95%) during exercise. All participants terminated exercise due to leg fatigue, and no participants terminated exercise due to breathlessness.

The changes in tidal volume, respiratory rate, and minute ventilation from rest to peak exercise are displayed in Figure 5.3 to Figure 5.5. At peak exercise, minute ventilation was significantly lower in the BPD group than in the healthy controls (median 0.88L/kg/min [IQR 0.83-0.99] and 1.31L/kg/min [IQR 1.13-1.37] respectively; $p<0.05$). The BPD group showed both a lower peak tidal volume and peak respiratory rate compared to the control group, although these differences were not statistically significant, likely due to the small sample size (median respiratory rate 38 [IQR 33-45] and 47 [IQR 43-49], and tidal volume 22.4ml/kg [IQR 20.4-24.3] and 31.8ml/kg [IQR 29.3-33.4] in BPD group and control groups respectively). The pattern of change in tidal volume, respiratory rate and minute ventilation were similar between both preterm groups.

One child with BPD was unable to perform spirometry post-exercise. FEV_1 decreased post-exercise in 12/16 (75%) children with BPD, showing a median change of -3.7% from baseline (IQR -6.8-1.7). There was no change in FEV_1 with exercise in the preterm group without BPD (median change -0.6% [IQR -3.0-3.6]) but a significant increase in FEV_1 the control group, showing a median change of 9.9% (IQR 9.4-10.2; Figure 5.6).

	Significant BPD n=17	No BPD n=7	Controls n=5
Exercise time (min)	6.9 (6.2-7.6)	7.5 (7.2-7.8)	8 (7-8)
Maximum work (W/kg)	2.2 (1.9-2.7)	2.5 (2.2-2.7)	3.0 (2.6-3.0)
Heart rate (per min)			
Pre	90 (87-95)	91 (82-96)	86 (79-96)
Post	168 (158-182)	170 (159-176)	169 (151-185)
Oxygen saturations (%)			
Pre	99 (98-99)	99 (99-100)	100 (99-100)
Post	98 (97-98)	99 (98-99)	99 (98-99)
Respiratory rate (per min)			
Pre	17 (15-20)	17 (15-18)	19 (19-20)
Post	38 (33-45)	39 (30-47)	47 (43-49)
Tidal volume (ml/kg)			
Pre	9.0 (7.4-11.2)	10.9 (9.6-13.3)	9.1 (8.3-9.8)
Post	22.4 (20.4-24.3)	26.4 (25.1-27.9)	31.8 (29.3-33.4)
Minute ventilation (L/kg/min)			
Pre	0.15 (0.12-0.18)	0.17 (0.15-0.21)	0.17 (0.15-0.2)
Post	0.88 (0.83-0.99)[a]	1.11 (0.91-1.27)	1.31 (1.13-1.37)
ΔFEV_1 post exercise (%)	-3.7 (-6.8-1.7)[a]	-0.6 (-3.0-3.6)	9.9 (9.4-10.2)
Change EEVcw (ml/kg)	-1.2 (-3.2-1.4)	2.3 (0.1-5.4)	-1.3 (-5.7-0.2)
Change EEVrc (ml/kg)	2.7 (1.2-5.4)	3.4 (2.8-6.0)	0.5 (-1.7-1.9)
Change EEVab (ml/kg)	-4.7 (-6.0 - -2.3)	-2.4 (-4.2 - -0.9)	-3.2 (-3.7 - -1.6)

Table 5.4 Exercise test results. All data displayed as median (IQR). BPD: Bronchopulmonary dysplasia. W/kg: Watts per kilogram. ΔFEV_1: Change in forced expiratory volume in 1 second. EEVcw: End-expiratory volume of the chest wall. EEVrc: End-expiratory volume of the rib cage. EEVab: End-expiratory volume of the abdomen. [a]BPD group significantly different to controls ($p<0.05$).

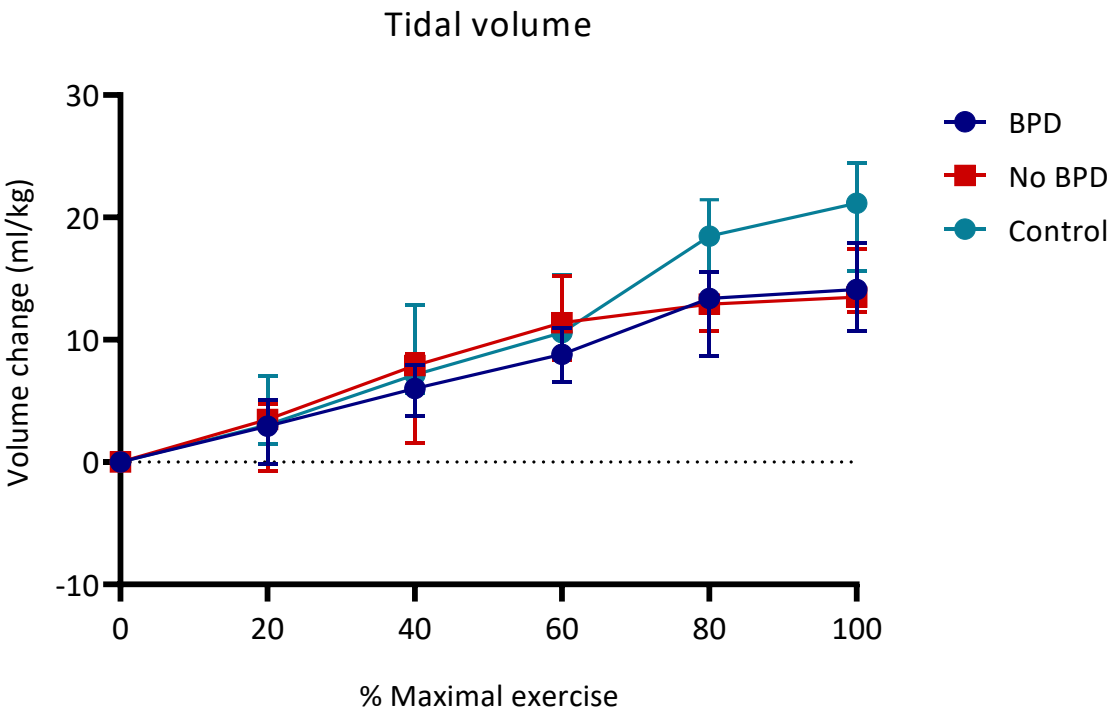

Figure 5.3 Change in tidal volume during exercise. Data displayed from rest (0%) to maximal exercise (100%) in preterm children with bronchopulmonary dysplasia (BPD), preterm children without BPD and healthy term-born controls.

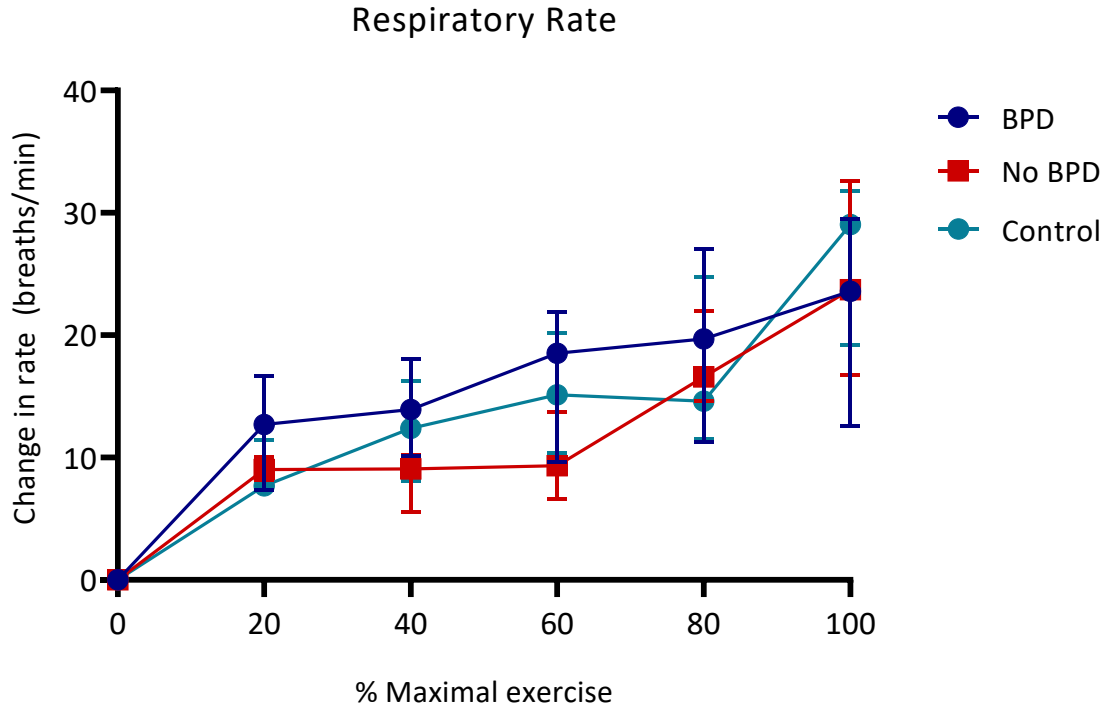

Figure 5.4 Change in respiratory rate during exercise. Data displayed from rest (0%) to maximal exercise (100%) in preterm children with bronchopulmonary dysplasia (BPD), preterm children without BPD and healthy term-born controls.

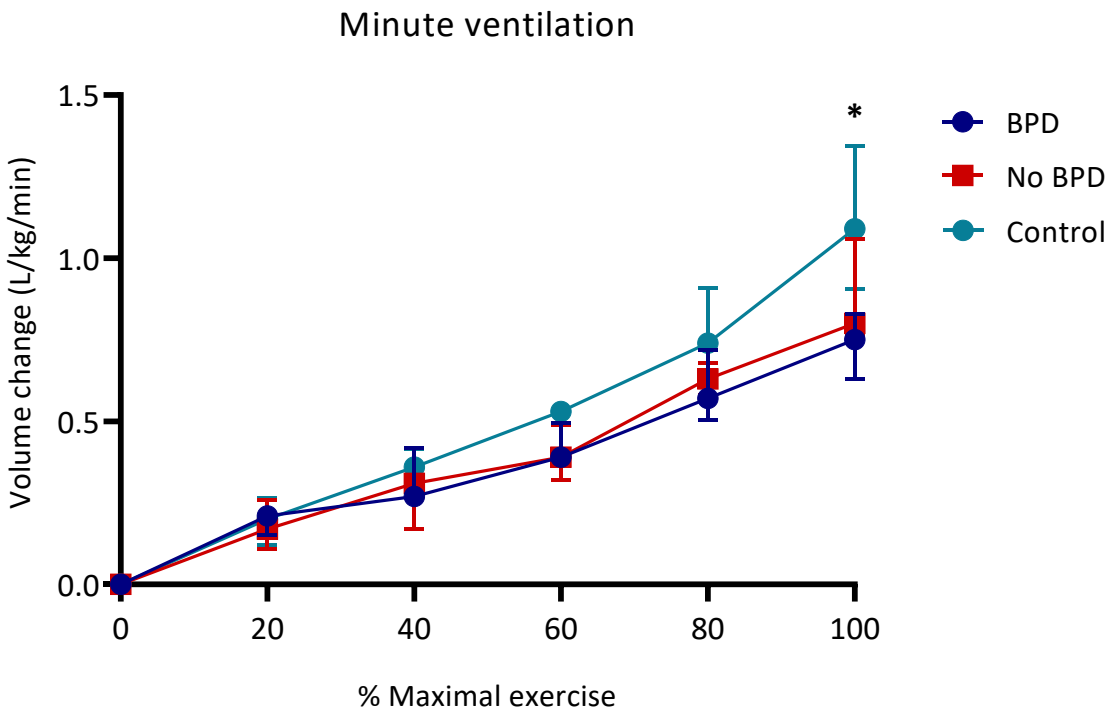

Figure 5.5 Change in minute ventilation during exercise. Data displayed from rest (0%) to maximal exercise (100%) in preterm children with bronchopulmonary dysplasia (BPD), preterm children without BPD and healthy term-born controls. *BPD significantly different to control ($p<0.05$)

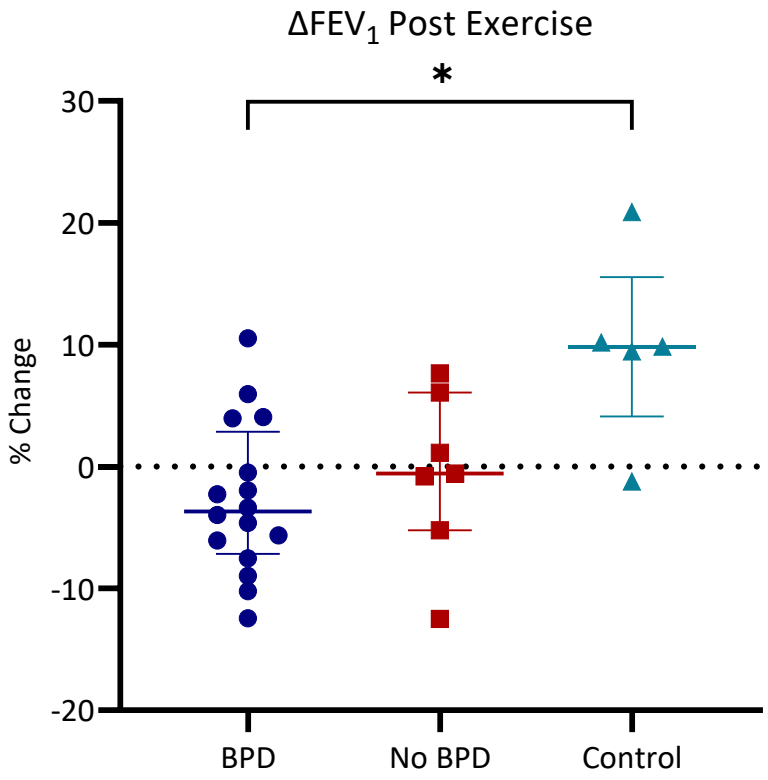

Figure 5.6 Percentage change in forced expiratory volume in 1-second (FEV_1) post exercise test in preterm children with bronchopulmonary dysplasia (BPD), preterm children without BPD and healthy term-born controls. *BPD significantly different to control ($p<0.05$)

5.5.5 Thoracoabdominal volume changes during exercise

Total and compartmental thoracoabdominal volume changes are displayed in Figure 5.7 - Figure 5.9. Specifically assessing end-expiratory volumes for evidence of dynamic hyperinflation, there was no significant change in total end-expiratory chest wall volume from baseline to maximal exercise in the cohort overall or in any of the three subgroups. Total end-expiratory chest wall volume changed by median -0.03L (IQR -0.19-0.14; p=0.54) in the cohort overall, with a median change of -0.06L (IQR -0.15-0.08) in the BPD group, 0.1L (IQR -0.15-0.2) in the preterm group without BPD, and -0.32L (IQR -1.26-0.06) in the term-born control group. There was no difference in absolute or weight-adjusted total end-expiratory chest wall volume changes at maximal exercise (Figure 5.7).

Total end-expiratory rib cage volumes increased significantly during exercise with a median change from baseline of 0.19L (IQR 0.03-0.3; p=0.001) in the cohort overall. There was no difference in weight-adjusted end-expiratory rib cage volume change between the subgroups at maximal exercise (Figure 5.8). Total end-expiratory abdominal volumes showed a compensatory decrease at maximal exercise, with a median change of -0.14L (IQR -0.25 to -0.07; p<0.001) during exercise in the combined cohort overall. There was similarly no change in weight-adjusted end-expiratory abdominal volume change at maximal exercise between subgroups (Figure 5.9).

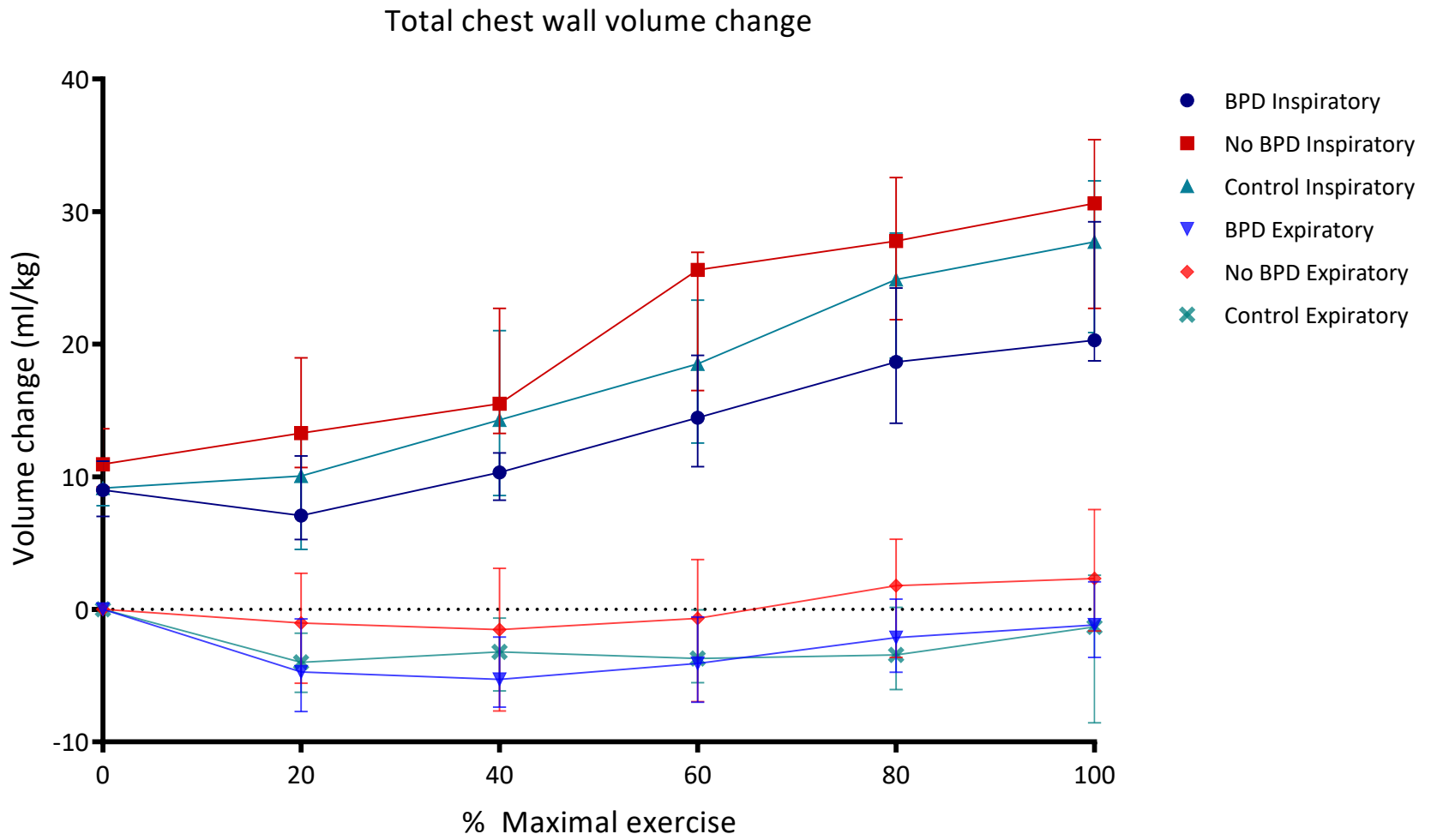

Figure 5.7 Change in total inspiratory and expiratory chest wall volumes during exercise. Data displayed from rest (0%) to maximal exercise (100%) in preterm children with bronchopulmonary dysplasia (BPD), preterm children without BPD (no BPD), and term-born controls.

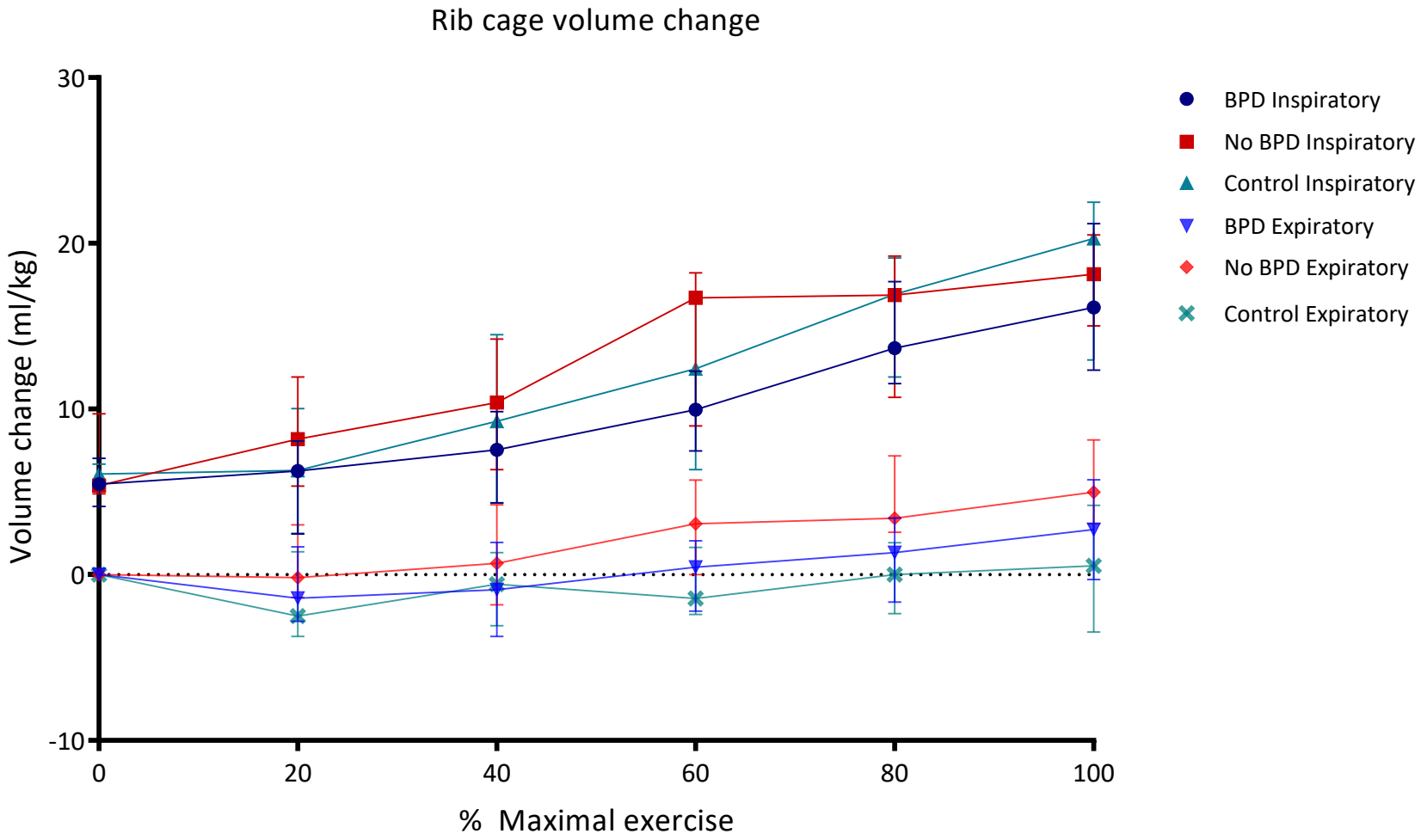

Figure 5.8 Change in inspiratory and expiratory rib cage volumes during exercise. Data displayed from rest (0%) to maximal exercise (100%) in preterm children with bronchopulmonary dysplasia (BPD), preterm children without BPD (no BPD), and term-born controls.

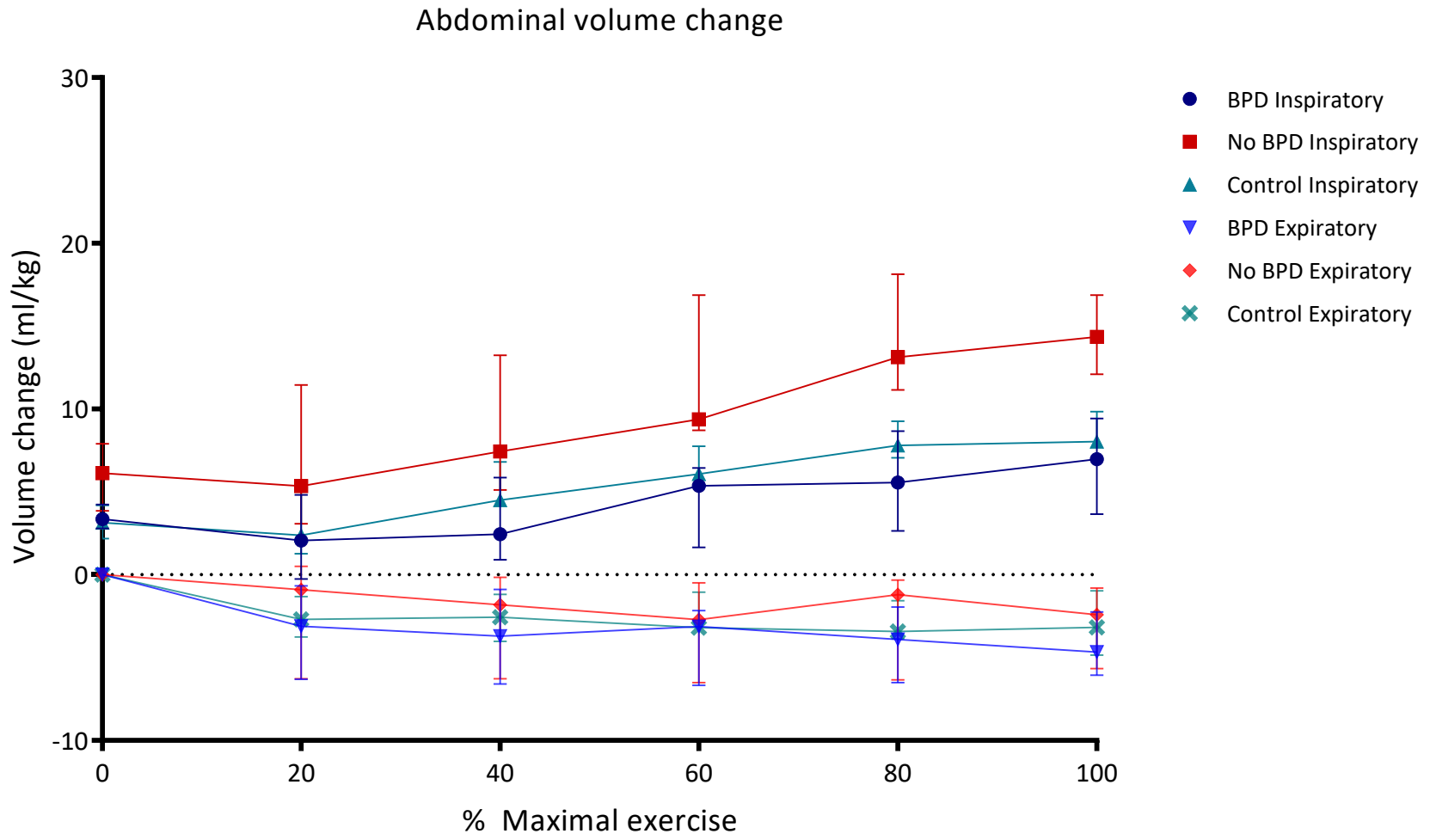

Figure 5.9 Change in inspiratory and expiratory abdominal volumes during exercise. Data displayed from rest (0%) to maximal exercise (100%) in preterm children with bronchopulmonary dysplasia (BPD), preterm children without BPD (no BPD), and term-born controls.

Although total chest wall volumes did not change in the cohort overall, a number of children did show an overall increase in end-expiratory chest wall volume during exercise, suggestive of dynamic hyperinflation. This occurred in 13 children in total: 6/17 (35%) of the BPD group, 5/7 (71%) and 2/5 (40%) of the control group. The clinical features of children showing an overall increase and decrease in end-expiratory chest wall volume are compared in Table 5.5.

The group showing an increase in end-expiratory chest wall volume were slightly younger than those showing a decrease in volume (median age 12.5 [IQR 11.8-13.0] v 13.8 [IQR 12.3-14.4]; $p<0.05$), but there was no difference in other demographics including height or weight between the groups. There was no difference in exercise time, maximal workload, peak respiratory rate, tidal volume, or minute ventilation between the groups suggesting this pattern was not associated with a ventilatory limitation to exercise. Inspiratory reserve volume, calculated as the difference between total lung capacity measured during the baseline inspiratory capacity manoeuvre and peak tidal volume, was not different between groups. Furthermore, degree of airflow limitation as assessed by FEV_1 at baseline was not different between the groups, and there was no correlation between change in end-expiratory chest wall volume and change in FEV_1 with exercise (Figure 5.10).

The total and compartmental volume changes in children showing evidence of hyperinflation are compared to those showing a decrease in end-expiratory volume in Figure 5.11 - Figure 5.13. Total chest wall volume shows a normal decrease to 60% maximal exercise, then increases above functional residual capacity from 60% to 100% maximum exercise (Figure 5.11). This is associated with a greater increase in end-inspiratory chest wall volume to maintain tidal volume. The increase in end-expiratory volume appears to be due to a greater increase in rib-cage volume (Figure 5.12) as end-expiratory abdominal volume still decreased with progressive exercise in this group (Figure 5.13).

	Hyperinflation (n=13)	No Hyperinflation (n=16)
Volume changes		
Total chest wall volume change	0.18 (0.08-0.27)	-0.17 (-0.38 - -0.10)*
Rib cage volume change	0.32 (0.22-0.36)	0.07 (-0.12-0.19)*
Abdominal volume change	-0.11 (-0.14 - -0.07)	-0.24 (-0.31 - -0.13)*
Demographics		
Age	12.5 (12.3-13.0)	13.8 (12.5-14.4)*
Height	158.8 (153-161)	159.1 (156-165.9)
Weight	52.2 (43-56.8)	51.4 (37.0-60.2)
Male	4/13 (30.8%)	10/16 (62.5%)
Gestational age (weeks)	28.9 (26.7-30.4)	27.8 (25.0-30.3)
Birth weight (g)	895 (820-1440)	988 (702-1532)
Asthma diagnosis	3/13 (23.1%)	1/16 (6.3%)
Baseline FEV_1 z-score	-1.12 (-1.5 to -0.4)	-1.46 (-2.2 to -0.1)
Exercise Test		
Exercise time (minutes)	7.3 (7.0-8.0)	7.2 (6.3-8.2)
Maximal workload (W/kg)	2.5 (2.2-2.8)	2.2 (1.9-2.7)
Maximal respiratory rate	39 (33-47)	41 (32-47)
Maximal tidal volume (ml/kg)	26.4 (21.7-28.3)	23.8 (21.1-31.7)
Maximal minute ventilation (L/kg/min)	1.0 (0.92-1.24)	0.89 (0.80-1.13)
Inspiratory reserve volume at peak exercise (ml/kg)	17.6 (12-20)	13.0 (7.7-16.3)
FEV_1 change post-exercise (%)	-3.3 (-8.9-6.9)	-0.7 (-3.7-5.0)

Table 5.5 Comparison of demographics and physiological changes during exercise in children showing an overall increase in end-expiratory thoracoabdominal volume (hyperinflation) during exercise and those without. Data displayed as median (IQR) or number %). FEV_1: Forced expiratory volume in 1-second. *Hyperinflation group significantly different to no hyperinflation group ($p<0.05$).

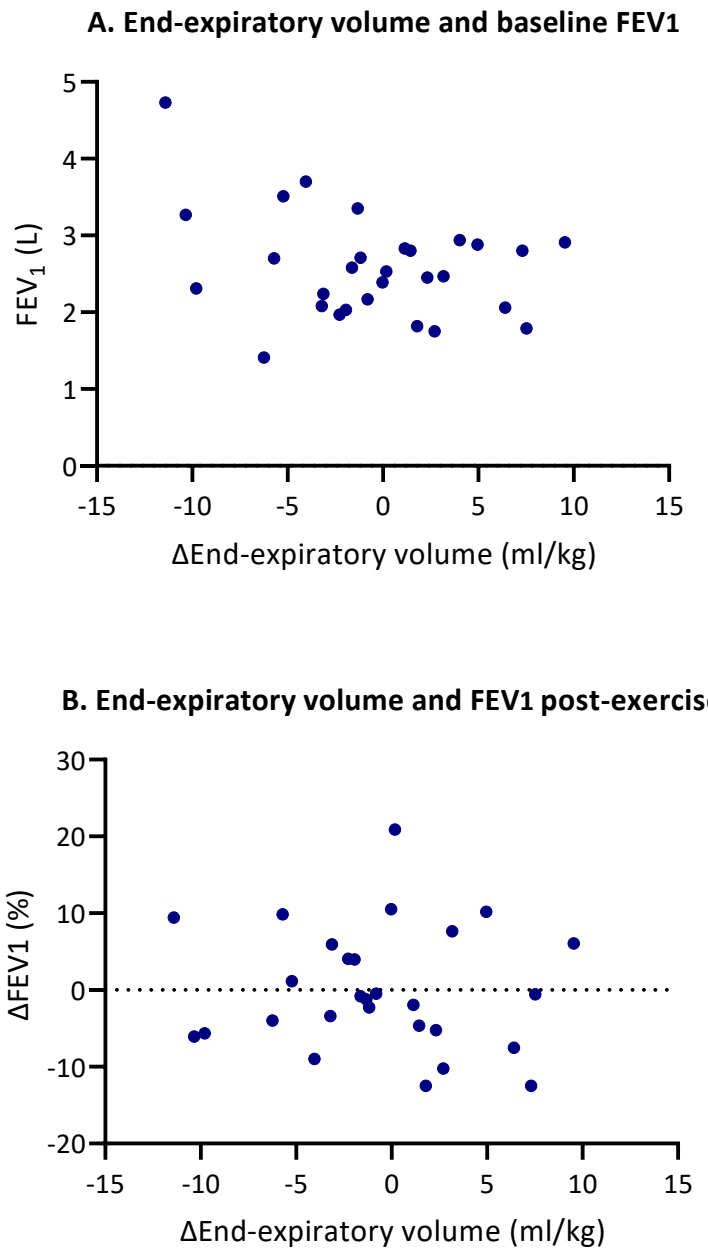

Figure 5.10 Scatterplots showing no correlation between change in end-expiratory chest wall volume (ml/kg) and A: Forced expiratory flow in 1-second (FEV_1) at baseline. Pearson correlation coefficient = -0.32; p= 0.09 and B: Percentage change in FEV_1 post exercise. Pearson correlation coefficient = -0.08; p= 0.7.

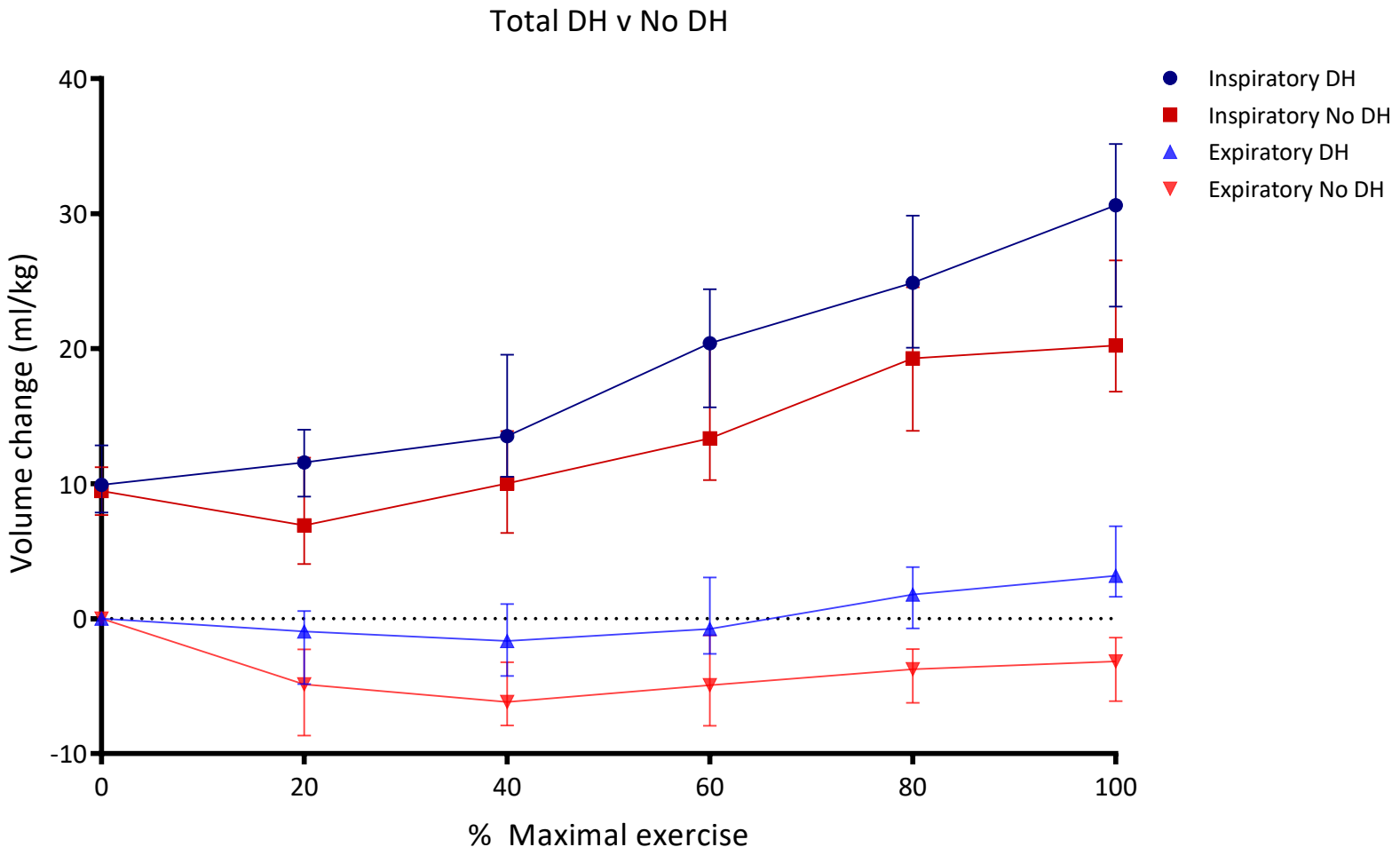

Figure 5.11 Total inspiratory and expiratory chest wall volume change in children showing an overall increase in end-expiratory volume (dynamic hyperinflation; DH) compared to those showing an overall decrease in end-expiratory volume (no dynamic hyperinflation; No DH) at maximal exercise.

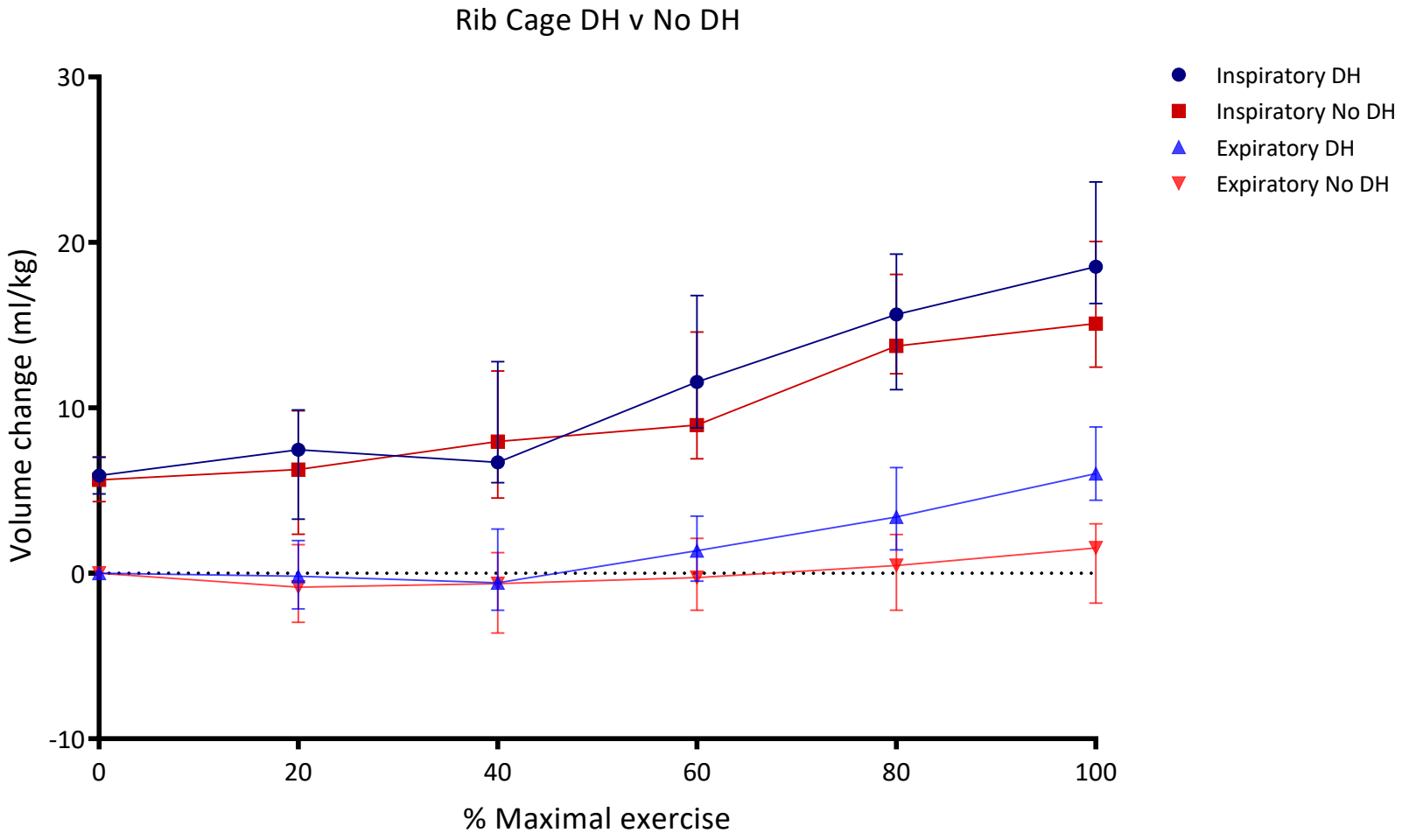

Figure 5.12 Total inspiratory and expiratory rib cage volume change in children showing an overall increase in end-expiratory volume (dynamic hyperinflation; DH) compared to those showing an overall decrease in end-expiratory volume (no dynamic hyperinflation; No DH) at maximal exercise.

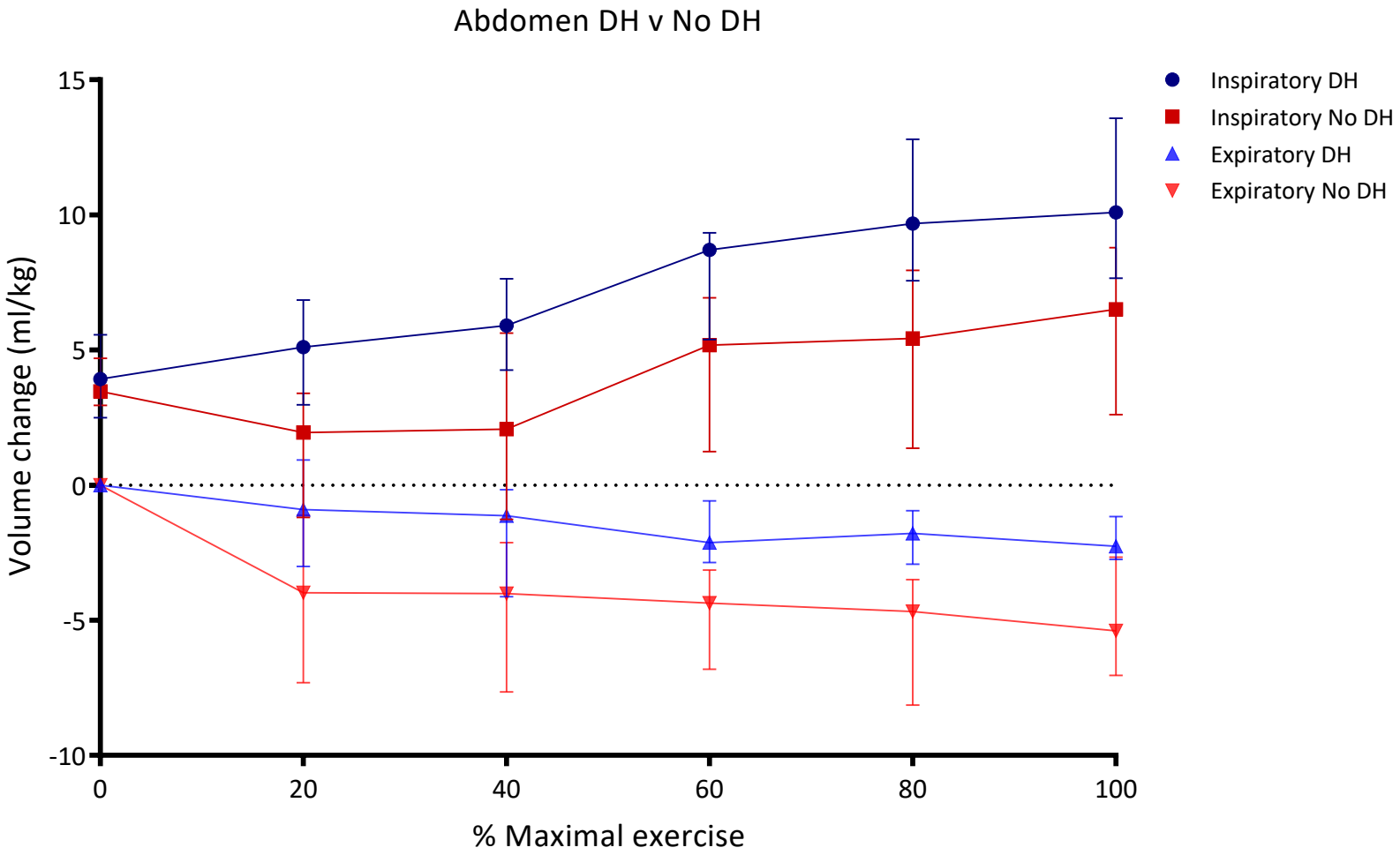

Figure 5.13 Total inspiratory and expiratory abdominal volume change in children showing an overall increase in end-expiratory volume (dynamic hyperinflation; DH) compared to those showing an overall decrease in end-expiratory volume (no dynamic hyperinflation; No DH) at maximal exercise.

5.6 Discussion

It is well established that children born preterm have lung function abnormalities that persist throughout childhood and into adult life(Islam et al., 2015). Airflow obstruction is a key feature of preterm-term lung disease, and expiratory flow limitation during exercise is common. However, the functional impact of this on exercise capacity and the ventilatory response to exercise is unclear. Optoelectronic plethysmography has the potential to allow further characterisation of this, measuring thoracoabdominal volumes non-invasively, and directly tracking changes in end-expiratory volumes to assess directly for dynamic hyperinflation. This study explored the feasibility of using OEP to assess the ventilatory response to exercise in children, and described the changes observed in a cohort of children born preterm.

5.6.1 Study recruitment and participants

The primary aim of this study was to explore to feasibility of using OEP to assess the ventilatory response to exercise in children born preterm. As there are no published exercise study data available in children born preterm using OEP, a formal power calculation was not undertaken. In designing the study, a target of 20 children per group (preterm with BPD, preterm without BPD and term-born controls) was chosen as a feasible number to study that would provide informative data, and ethical approval was obtained for this number. Recruitment to the study commenced in September 2019 and planned to run over 12-18 months. Initial recruitment was good, with 39 children (19 preterm children with BPD, 11 preterm children without BPD and 9 term-born controls) completing parts of the study in the first 6 months.

Unfortunately, in March 2020 all research activity stopped unexpectedly due to the Covid-19 pandemic. As a result, recruitment to the study is considerably less than initially planned and the number of participants in each group is unbalanced. Although this limits our ability to compare groups, the original study objectives can still be addressed. Lung function results are expressed as z-scores, using reference data for age, height and sex, therefore comparison to a control group not essential. Pilot work was undertaken to optimise the OEP system for paediatric use and 29 children completed an exercise test using OEP, therefore feasibility of using OEP to assess the ventilatory response to exercise in children can be

addressed. Finally, the pattern of thoracoabdominal volume changes during exercise in a group of children born preterm can be described.

5.6.2 Baseline lung function is reduced in children born preterm

Lung function abnormalities, with features of airflow obstruction and impaired gas exchange are well described in preterm-born children, particularly those with a history of BPD(Islam et al., 2015). Children in this study showed the anticipated pattern of lung function impairment, with evidence of significant airflow obstruction (lower z-scores for FEV_1, FEV_1/FVC and $FEF_{25-75\%}$) and impaired gas exchange (lower z-scores for DLCO and KCO) in those with a history of BPD. A similar pattern of abnormality was evident in the preterm children without a history of BPD, although differences were less marked. This trend highlights that preterm lung disease is a spectrum of abnormality, and even those children with less severe neonatal lung disease, who do not meet criteria for a diagnosis of BPD, are at risk of long-term respiratory morbidity.

5.6.3 Respiratory health and self-reported fitness in children born preterm

In this cohort, children born preterm with a history of BPD were more likely to have a diagnosis of asthma, and significantly more likely to have received a salbutamol inhaler than both preterm children without a history of BPD and controls. There was no difference in rates of atopy or FeNO levels between groups, which is consistent with previous studies and supports the theory that this pattern of wheeze and obstructive airway disease is distinct from asthma, and not mediated by eosinophilic inflammation but is likely due to structural airway disease(Course et al., 2019).

Although the sample size is small, it is notable that only children in the BPD group reported presence of smokers at home. This is an important, modifiable factor as smoking is independently associated with increased risk of preterm birth, higher rates of BPD in preterm infants, and an accelerated decline in lung function in affected children(Morrow et al., 2017; Simpson et al., 2018; L. W. Doyle et al., 2019). Public health initiatives to reduce exposure to cigarette smoke are vitally important to both reduce the development of BPD and to improve the longer-term health of affected children.

In this cohort, children born preterm reported exercising less frequently and rated their self-perceived fitness lower than control children. This may reflect a real difference between groups; however, selection bias may also contribute as the control children were healthy volunteers who likely had an interest sport and exercise. Others have reported lower physical activity levels in preterm born children, but a similar positive association between physical activity and exercise capacity in preterm and term-born children, suggesting that they have similar training potential and physical activity should be encouraged in preterm-born children(Clemm et al., 2012).

5.6.4 Feasibility of using optoelectronic plethysmography during exercise in children

The primary aim of this study was to assess the feasibility of using OEP to assess the ventilatory response to exercise in preterm children, specifically to track end-expiratory chest wall volume. Previously published studies have reported using OEP in children before and after exercise, but none have reported using OEP to assess dynamic changes during exercise(Lima et al., 2014; Feitosa et al., 2018). Several adjustments to the OEP system set-up were required to optimise it for paediatric use prior to commencing the study. This was achieved in a series of pilot tests by maximising the camera zoom and adjusting the camera position to focus on a smaller area, and modifying the participants arm position to ensure the view of the lateral markers was not obscured. Following these adjustments, satisfactory recordings were able to be made in all study participants.

This system has the major advantage of allowing non-invasive measurement of changes in thoracoabdominal volumes, not requiring a facemask or mouthpiece and nose clip, therefore allowing more natural breathing. It also allows direct measurement of changes in end-expiratory chest wall volumes to assess for hyperinflation, avoiding the difficulty of indirect measures such as serial inspiratory capacity manoeuvres which is highly effort dependent to assess this. There are however a number of limitations to the OEP system. The OEP analysis software automatically connects markers to reconstruct a 3D model of the thoracoabdominal wall. However, when there is significant movement and the markers are close together, such as in paediatric exercise studies, the automated analysis is not always successful, and the markers need to be joined manually which is a very time-consuming process. Furthermore, the system is expensive and requires a large, dedicated space to operate. The cost, physical limitations and time required for analysis mean OEP is not

practical for use in a clinical setting, and its utility clearly limited to the research setting at present.

5.6.5 Exercise test results

This study used a standard exercise test protocol, with the workload increment stratified so that the participant would be expected to reach peak exercise within 8-10 minutes. This was to ensure the duration of exercise was long enough to observe an adaptive response to exercise, but short enough to prevent boredom and lack of concentration with a prolonged test. The average duration of incremental exercise was slightly shorter than this in all groups, however total exercise time, maximal workload and peak heart rate were not different between the groups suggesting participants reached a similar peak relative intensity of exercise. All participants discontinued exercise due to leg fatigue rather than breathlessness, suggesting that a ventilatory constraint does not limit exercise in this cohort of children born preterm.

Although the number of control children in this study is limited, a number of differences between the exercise test results in preterm children and term-born controls can be observed. Children with BPD achieved a lower peak minute ventilation than controls (median 0.88 L/kg/min [IQR 0.83-0.99] compared to 1.31 L/kg/min [IQR 1.13-1.37]), which is statistically significant despite the small sample size and consistent with other studies using standard cardiopulmonary exercise testing (CPET)(Welsh et al., 2010; Maclean et al., 2016; Hestnes et al., 2017). An altered ventilatory response to exercise has been reported in preterm born children, particularly those with a history of BPD, with higher respiratory rates and lower tidal volumes than healthy term-born controls when assessed using standard CPET. In this cohort, a similar trend toward a lower median tidal volume at peak exercise was observed in both preterm groups (22.4ml/kg [IQR 20.4-24.3] in preterm children with BPD and 26.4ml/kg ([IQR 5.1-27.9] in preterm children without BPD) compared to the control group (31.8ml/kg [IQR 29.3-33.4]). These differences were not statistically significant in this study, although this likely reflects the small sample size of the control group.

The peak tidal volumes recorded using OEP were highly consistent with other studies using standard CPET in preterm and term-born children, although peak respiratory rates recorded in this cohort were generally lower. At peak exercise, Welsh *et al* reported respiratory rates

of 57.2 and 50.9 breaths per minute in extremely preterm and control children, whilst MacLean et al reported rates of 48.0 and 47.5 breaths per minute respectively. In this cohort, peak respiratory rates were 38 breaths per minute (IQR 33-45) in the preterm group with BPD and 47 (IQR 43-49) breaths per minute in the controls. This lower respiratory rate may reflect differences in the measurement technique, as OEP is less invasive and does not require a facemask or mouthpiece therefore this may be a more physiological breathing pattern. Alternatively, this may reflect differences in the exercise protocol. A well-recognised exercise protocol was used, but all children in the study terminated exercise due to leg fatigue rather than breathlessness therefore it is possible that peak cardiorespiratory exercise capacity was not achieved. However, the peak workload achieved in this study was similar to others, therefore it is unlikely this contributes to the differences in respiratory rate observed (Welsh et al., 2010).

5.6.6 Thoracoabdominal volume changes

In healthy subjects, total end-expiratory chest wall volume decreases with exercise to facilitate increasing tidal volume and minute ventilation. However, in healthy subjects with superimposed expiratory flow limitation and adults with obstructive airway disease due to COPD, dynamic hyperinflation occurs, causing an increase in end-expiratory chest wall volume during exercise(Iandelli et al., 2002; Vogiatzis et al., 2005). Individuals showing dynamic hyperinflation have reduced exercise capacity and use a higher respiratory rate and achieve lower tidal volumes during exercise. Children born preterm have higher rates of expiratory flow limitation during exercise, and a similar ventilatory pattern has been observed in this group(O'Dea et al., 2018; Welsh et al., 2010). It is currently unclear whether dynamic hyperinflation occurs in preterm-born children, and this study aimed to explore this using OEP to directly measure changes in end-expiratory chest wall volumes during exercise.

Overall, no significant change in total end-expiratory chest wall volume was observed from baseline to peak exercise in the combined cohort, or any of the subgroups although all showed a normal trend to decreased end-expiratory chest wall volume on commencing exercise. End-expiratory rib cage volume increased with exercise, but this was associated with a compensatory reduction in end-expiratory abdominal volume so total volume at peak exercise remained unchanged.

Considering individual participant data, 13 children showed an overall increase in end-expiratory chest wall volume with exercise with a median volume increase of 0.18L (IQR 0.08-0.27), which may suggest dynamic hyperinflation is occurring. However, there was no difference in exercise time or maximal workload between those who displayed an increase in total end-expiratory chest wall volume and those who showed in decrease in end-expiratory volume, and no participants terminated exercise due to breathlessness. This suggests that, if hyperinflation did occur, children were not symptomatic of this. Similarly, there was no difference in peak tidal volume or peak minute ventilation between those showing an increase in total end-expiratory chest wall volume and those showing an overall decrease, suggesting this is not associated with any mechanical ventilatory constraint. Although end-expiratory rib cage volume was higher in this group, there was a concurrent increase in end-inspiratory rib cage volume so tidal volume was maintained. Inspiratory reserve volume at peak exercise was not reduced in children showing an increase in end-expiratory chest wall volume, consistent with previous studies showing no difference in inspiratory capacity between preterm and term-born children during exercise. Finally, an overall increase in end-expiratory chest wall volume was observed in 2/5 healthy controls, and there was no correlation between baseline FEV_1 z-score or change in FEV_1 during exercise and total chest wall volume change suggesting this was not directly associated with degree of airflow obstruction in this cohort. It therefore seems unlikely that these changes reflect dynamic hyperinflation due to expiratory flow limitation.

All changes were compared to baseline values obtained during a three-minute period of 'normal' breathing at rest. Although participants were encouraged to breathe normally and efforts were made to create a non-intimidating environment and minimise anxiety, it is possible that the conscious effort of breathing may cause deeper breathing and active exhalation below FRC during these baseline recordings. However, end-expiratory chest wall volume decreased on starting exercise in all participants and hyperinflation was not evident until ≥60% maximal exercise, suggesting this was not the case. Volume changes were not correlated with a pneumotachograph in this study to avoid use of a mouthpiece and allow more physiological breathing. Previous studies have shown strong correlation between chest wall volume changes measured using OEP and standard CPET during exercise, and the tidal volume changes recorded in this study are in line with other preterm cohorts. It is therefore unlikely that significant measurement error contributes to the volume changes observed,

but this cannot be completely excluded. Further work correlate OEP volume changes with this reference technique in children during exercise may be useful to clarify this.

In summary, an increase in total end-expiratory chest wall volume was observed in a subgroup of children in this study, but the mechanism and the functional impact of this is unclear. In this small cohort, change in end-expiratory chest wall volume was not clearly associated with degree of airway obstruction, and it did not appear to limit exercise capacity although numbers are small and assessment in a larger cohort required.

5.6.7 Strengths and limitations of OEP study

This study has demonstrated that it is feasible to use OEP to assess the ventilatory response to exercise in children. This has the benefit of allowing non-invasive measurement of volume changes without the need for a facemask or mouthpiece and allows direct tracking of end-expiratory volume changes. There are limitations to the use of OEP in paediatric practice as discussed above, particularly the time required for manual reconstruction of the chest wall model during analysis, but this may be useful in the research setting.

The major limitation in this study is the sample size, particularly the small number of healthy controls that were able to be recruited. This was unavoidable due to the restrictions imposed by the Covid-19 pandemic but despite this, the original study aims have been addressed. The small number of controls does however limit our ability to compare groups and further work to explore the relationship between prematurity, exercise capacity and changes in end-expiratory chest wall volume during exercise in a larger cohort of children is required. A volunteer sample of children were recruited and preterm children with significant neurodevelopmental or other medical problems were excluded as ability to comply with the test procedure was required, therefore selection bias may limit generalisability of the results.

As the focus of this study was on the feasibility of using OEP to measure end-expiratory chest wall volumes in preterm children, volume changes were not correlated with a pneumotachograph. This was an intentional decision to avoid use of a mouthpiece and allow normal breathing, but as OEP measures total chest wall volumes it is possible that redistribution of blood volume may contribute to the volume changes measured. In adults, a very strong correlation between volume changes measured using OEP and those measured

using a pneumotachograph have been reported during exercise, suggesting that any contribution of blood volume changes is minimal. Similarly, gas analysis and tidal flow-volume loops were not recorded as they require use of a mouthpiece. It was not possible to directly measure the frequency of expiratory flow limitation or correlate this with change in end-expiratory chest wall volume, however, FEV_1 and change in FEV_1 post-exercise were measured as indicators of airflow obstruction, and have previously been shown to correlate with the presence of expiratory flow limitation during exercise(O'Dea et al., 2018).

5.7 Conclusions

In conclusion, this study explored lung function and exercise capacity of school-aged children who were born preterm, and has shown that it is feasible to use OEP to measure the ventilatory response to exercise in school-age children born preterm. Children born preterm with a history of BPD showed significant baseline lung function abnormalities with features of both airflow obstruction and impaired gas exchange. During exercise, preterm children with a history of BPD achieved a lower peak minute ventilation than controls. In assessing the ventilatory response to exercise, a number of children showed an increase in end-expiratory volume of the chest wall at peak exercise although the relevance of this is unclear. This does not appear to be due to expiratory flow limitation induced dynamic hyperinflation, as it was not associated with any ventilatory limitation, it did not correlate with degree of airflow obstruction, and was also observed in some healthy controls. Further work in a larger cohort is required to compare volume changes between preterm and term-born groups using OEP.

Chapter 6. Discussion

6.1 Overview

This final discussion will summarise the key findings of each chapter with relevance to clinical practice and suggested areas for future study to complement the previous detailed discussions. This is followed by a more general discussion regarding the evaluation and outcomes of preterm lung disease.

6.2 Longitudinal cohort study of changes in diaphragm electrical activity with weaning nasal high flow in preterm infants

6.2.1 Summary

The primary aim of this study was to explore in detail the longitudinal changes in respiratory muscle effort that occur when weaning nasal high flow therapy in preterm infants. A weaning protocol was developed as a framework for the study, based on current practice and published consensus guidelines and a series of measurements made at each weaning step. Oesophageal pressure measurement and electrical activity of the diaphragm were assessed as objective markers of respiratory muscle effort for use in this study. Oesophageal pressure measurement is well-established as the gold-standard technique for assessment of work of breathing, however measurement is difficult, particularly in the preterm population(Bellani & Pesenti, 2014). Traditional balloon catheters are not designed for this group of infants and this study has shown the micro-tipped catheters used in previous studies are not suitable as they show marked baseline drift, an inadequate frequency response, and are relatively invasive as they require insertion of an additional oesophageal catheter. In contrast, diaphragm electrical activity can be measured using a modified feeding tube in an essentially non-invasive manner therefore well tolerated by infants and highly acceptable to parents and clinicians. The integration of this technology into the Maquet Servo-n ventilator has real potential for clinical use, both as a monitoring tool and to directly guide respiratory support in neurally-adjusted ventilatory assist modes. As a result, diaphragm electrical activity was chosen as the primary outcome of this study as an objective measure, relevant to clinical practice.

The weaning protocol used in this study was highly successful and provides a framework for clinical practice and future research studies. No significant change in any Edi parameter was observed during flow rate reduction steps in this study but a significant increase in both Edi max and Edi delta were observed in the 24-hours post discontinuation of high flow. These findings have direct relevance to clinical practice when weaning high flow in preterm infants. The lack of change in Edi when reducing flow rates and the high success of weaning steps in the study supports weaning in decrements of at least 1L/min, as smaller changes will be clinically inconsequential. The significant increase in Edi max and Edi delta when discontinuing high flow from 2L/min shows that even this relatively low flow rate does unload diaphragmatic inspiratory effort to some extent, therefore we recommend weaning high flow to 2L/min before discontinuing in preterm infants. There was no change in Edi min, a measure of tonic diaphragm activity required to maintain functional residual capacity at the end of expiration with discontinuation of high flow from 2L/min and end-expiratory pressures delivered at this flow rate are low, suggesting the effect on inspiratory respiratory muscle effort may be mediated by reduced nasopharyngeal resistance rather than positive end-expiratory pressure(Liew et al., 2020). Some individuals advocate discontinuing high flow from higher flow rates, therefore comparing weaning success and the magnitude of Edi change when discontinuing from flow rates of 2, 3, and 4L/min is a logical area for future study.

No difference in Edi parameters was observed between successful and unsuccessful weaning steps in this study, however the number of unsuccessful steps was small. The feasibility of using Edi parameters to proactively guide weaning cannot be addressed at present, but is an area for future study. The high success rate of the protocol does lead to consideration of whether weaning could occur more quickly in this group. The introduction of high flow therapy in neonates has been associated with longer duration of respiratory support and increased rates of bronchopulmonary dysplasia in several retrospective studies(Taha et al., 2016; Heath Jeffery et al., 2017; Sand et al., 2022). Confounding by indication clearly contributes to this in some cohorts, as high flow is used as a step down from CPAP in infants requiring a longer duration of respiratory support, therefore exposure to high flow simply reflects severity of lung disease. However, inherent differences in respiratory support may also contribute, as it is feasible that the highly variable pressure delivered by high flow contributes to lung injury and a prolonged respiratory support requirement. Alternatively,

the high tolerance and perception of high flow as a less invasive mode of support may promote less proactive weaning than would occur with CPAP. A structured approach to weaning, such as that used in this study, provides a framework for practice to promote active weaning and overcome this problem. It may be feasible to refine the protocol to encourage faster weaning, although in this population the key end point needs consideration. Whilst duration of respiratory support is an important outcome, this cannot be considered in isolation. In preterm infants, weaning respiratory support occurs in conjunction with establishing oral feeding, growth and maturation therefore establishing stability and a holistic approach to care is essential. It is likely that if solely focusing on respiratory support, infants in the study could be weaned off high flow faster, however other aspects of care may be compromised, therefore a hybrid outcome such as corrected gestational age at discharge may be more clinically relevant. Future study to refine this weaning protocol may facilitate more rapid weaning, but the primary endpoint should be carefully considered.

6.2.2 Clinical Implications

The weaning protocol used in this study is safe and effective, providing a structured, evidence-based approach to weaning in clinical practice. Implementation of change in a clinical context requires engagement of staff and families, using a quality improvement approach to support and sustain change.

Implementation of the weaning protocol in our neonatal unit during the study was achieved by development of a formal high flow guideline and staff education. Engagement of senior medical and nursing staff was ensured by involving them in the protocol design and guideline development process, and responding to feedback. Posters and copies of the flowchart were displayed in bays and next to the cot-space of infants enrolled in the study to promote awareness. Interestingly, this empowered nursing staff and parents to contribute decisions regarding weaning, and both informally reported that they found the structure helpful in caring for their infant. The benefits of family-integrated care, in which parents act as the primary care giver, are increasing recognised in neonatology, and providing parents with a simple framework such as this may help them guide care and advocate for their infant. Wider implementation of the protocol may be achieved by development of regional and network-level guidelines, and collaborative working to share best-practice nationally.

6.2.3 Future Study

As discussed above, the high success of the weaning protocol used in this study, and minimal change in Edi with flow rate reductions suggests this is a safe and effective protocol, but does lead to consideration of whether weaning could occur more quickly. Nationally, there is variation in minimum flow rates used and it is unclear whether discontinuation from a higher flow rate is less successful, or associated with a greater increase in Edi. To address this further, I would propose a study randomising preterm infants to discontinuation of high flow at 4L/min or 2L/min. As both are used in clinical practice this would be ethical, and easily addressed using a similar protocol to this current study. High flow would be weaned according to the current weaning protocol, but discontinuation would occur from 4L/min or 2L/min. Edi would be measured before and after discontinuation to assess whether there is a greater increase, indicating an increase in work of breathing, with discontinuation from 4L/min compared to discontinuation from 2L/min, and whether this correlates with success of weaning. The primary outcome would ideally be success of weaning or total duration of respiratory support, as this is likely most important to the infant and families although this would require a larger sample size than a physiological outcome such as change in Edi. This data would be useful to determine the optimal flow rate for discontinuation of high flow and further refine the weaning protocol.

6.3 National surveillance study of life-threatening bronchopulmonary dysplasia in preterm infants

6.3.1 Summary

It is evident that preterm lung disease encompasses a wide spectrum of disease, and current definitions of BPD are limited in their ability to differentiate severity and predict longer-term outcomes. This study aimed to explore in detail the characteristics, management, and short-term outcomes of infants with life-threatening BPD in the United Kingdom. Life-threatening BPD was defined in infants requiring positive pressure respiratory support and/or pulmonary vasodilator therapy at or beyond 38 weeks corrected gestational age. During the study period, 153 confirmed cases of life-threatening BPD were identified, meaning each level 3 neonatal intensive care unit in the country can expect to see around 1 such infant per year. As a result, in an individual unit, opportunities for developing practice, management

pathways and experience for counselling are limited, but collating cases at a national level provides a comprehensive picture of this group of infants.

Infants in the study were generally born extremely preterm and extremely low birth weight, and received a prolonged period of respiratory support during a protracted hospital admission. Significant variation in management in several important aspects of care was identified, particularly postnatal steroid use, other medical use, and management of pulmonary hypertension. This variation in practice is likely multifactorial, reflecting disease heterogeneity, individual unit practice and often a lack of clear randomised controlled trial evidence. There is major research focus on early strategies to prevent BPD, but little focus on the management of established BPD, particularly severe BPD requiring positive pressure support near term. It is difficult to completely differentiate prevention and treatment of BPD, as by definition BPD cannot be diagnosed until 36 weeks corrected gestational age, but it is clear that early interventions to reduce lung damage should be distinguished from later interventions to manage and improve established lung disease. Postnatal steroid use is a key example of this. Postnatal dexamethasone used after the first week of life reduces death or BPD in preterm infants without increasing rates of cerebral palsy therefore it is notable that 40% of this cohort did not receive any postnatal steroid despite the severity of their lung disease(Doyle et al., 2021b). Whilst concern regarding adverse neurodevelopmental effects of dexamethasone appropriately limit its use, risk-stratification and identification of high-risk infants who have potential to benefit from steroid treatment is essential. The most widely used steroid regime in this cohort was that used in the DART study. This study showed significantly higher rates of extubation in infants ventilated beyond the first week of life who received dexamethasone compared to placebo but was not powered to assess the impact of dexamethasone on BPD or longer-term outcomes(Doyle et al., 2006). Despite these limitations, the DART regime has become the default steroid regime for use in preterm infants of any age in many units. The benefit observed in this small study cannot be extrapolated to all situations, therefore future work should focus on targeted interventions in the management of established BPD. Performing randomised controlled trials specifically in infants with life-threatening BPD will be challenging, as they are relatively small in number so a difficult group to study, but ongoing prospective study such as via a national disease registry may be useful to identify progress in management and longer-term outcomes.

In this cohort, need for invasive ventilation near term and presence of pulmonary hypertension were clearly identified as factors associated with adverse outcomes. Current BPD definitions would categorise such infants along with those requiring low flow oxygen, who clearly have a different risk profile and outcome in both the short and long-term. This highlights the limitation of current BPD definitions, and supports classification of infants requiring positive pressure support, particularly invasive ventilation near term as a distinct, high-risk subgroup(Jensen et al., 2019).

Despite the complexity and high burden of respiratory disease in this group of infants, their overall outcomes were perhaps more positive than anticipated. Ultimately, 81% of infants were discharged home, most in low flow oxygen, and neurological assessment at 1-year of age was normal in 62% of survivors. This study did not include respiratory deaths prior to 38 weeks, therefore overall BPD-related mortality is higher, however, the data provided will be useful for clinicians in decision making regarding direction of care and counselling families of infants requiring positive pressure respiratory support near term. Longer-term outcomes were not assessed due to the limitations of the study methodology, but an area for future study. Given the known trajectory of preterm lung disease, proactive follow-up with clear advice to parents to avoid exposure to cigarette smoke and to encourage physical activity where possible is particularly important in this high-risk group.

6.3.2 Clinical Implications

This study provides a detailed description of management and outcomes of infants with life-threatening BPD nationally. Although much of this data is descriptive, highlighting lack of evidence and variation in practice, there are a number of findings with direct implications for clinical practice, which will help clinicians caring for this complex group of infants.

Firstly, outcomes of this group have not previously been described and the data provided in this study permits more accurate, evidence-based decision making and discussion with families. Secondly, data provided in this study strongly supports screening for, and treatment of, pulmonary hypertension as an important, potentially modifiable factor associated with outcome. Clinicians should ensure this is included in local and national guidelines and consistent processes for screening are in place. Finally, this study highlights

the lack of evidence for many interventions, and should encourage clinicians to avoid non-evidence-based interventions that may actually cause harm.

6.3.3 Future Study

It is evident that the management and outcomes of infants with the most severe lung disease requires further study, and a multi-centre collaborative approach is essential to achieve this. Understanding of the outcomes of this group requires longer-term follow-up, to school-age and beyond. It is increasingly recognised that the historical approach of neonatal follow-up to 2-years of age is not enough, and many problems associated with prematurity are not apparent until later childhood. Furthermore, adults born preterm show and early and more marked age-related decline in lung function and it is likely this group will be particularly susceptible to this, potentially experiencing symptomatic lung disease earlier in life.

Long-term follow-up of this group of infants should be a priority for future study. Increasing use of electronic patient records may facilitate this using routinely collected data, but given the variation in reporting and lack of a core outcome set, this approach is not suitable for detailed assessment and follow-up at present. To explore this further, I would ideally develop a prospective cohort study to allow detailed, longitudinal follow-up of this group of infants. Given the relatively small number of infants with life-threatening BPD, a national collaborative approach would be required to identify and recruit infants to the cohort, and long-term surveillance throughout childhood and into adulthood is required. Core outcomes should be developed in collaboration with families, but should include periodic lung function testing, respiratory-related hospital admissions, medication use and of quality-of-life assessment to fully understand the impact on children and families.

6.4 Lung function and ventilatory response to exercise measured using optoelectronic plethysmography in school age children born preterm

6.4.1 Summary

Children born preterm show lung function abnormalities, particularly features of airflow obstruction and impaired gas exchange, that persist throughout childhood and into adult life(Islam et al., 2015). However, the functional impact of this on exercise capacity and the

ventilatory response to exercise is less clear. Children born preterm have higher rates of expiratory flow limitation during exercise and have been shown to reach a lower peak tidal volume during exercise than healthy term-born controls(Welsh et al., 2010; Maclean et al., 2016; O'Dea et al., 2018). Dynamic hyperinflation secondary to expiratory flow limitation has been postulated as a mechanism underlying this however previous assessment has relied on serial inspiratory capacity manoeuvres during exercise, which is difficult to perform and highly effort dependent. This study aimed to explore the feasibility of using optoelectronic plethysmography in preterm born children to directly measure changes in end-expiratory chest wall volume and assess for dynamic hyperinflation during exercise.

The study used the OEP system in the Department of Sport, Exercise and Rehabilitation at Northumbria University. A series of pilot tests were undertaken to optimise the system for paediatric use. This involved modifications to camera position and zoom, participant arm position and exercise protocol, which were successful in improving the quality of data obtained.

Children aged 10-15 years born preterm with and without a neonatal diagnosis of BPD were recruited, along with healthy term-born controls. Recruitment to this study was limited due to the Covid-19 pandemic, however the primary study objective, namely assessing the feasibility of using OEP during exercise in children was addressed. This study has shown that it is feasible to measure ventilatory changes during exercise in children, including those born preterm. OEP has the advantage of not requiring a facemask or mouthpiece, therefore does not disturb normal breathing patterns and continually tracks end-expiratory chest wall volumes therefore can directly assess for dynamic hyperinflation. This is particularly useful in children where cooperation may be limited. Although this study has shown it is feasible to use OEP during exercise in children, there are clear practical challenges that prevent its widespread use. Manual reconstruction of the chest wall model is generally required, which is a very time-consuming process, and the high cost of the equipment and physical space required mean it is not suitable for clinical use at present.

Baseline lung function tests were undertaken using standard testing methodologies as a reference to correlate with OEP data. Children with a history of BPD showed clear features of airflow obstruction and impaired gas exchange as anticipated, but preterm children without a diagnosis of BPD also showed marked abnormalities highlighting the spectrum of

preterm lung disease. During exercise, no difference in pattern of end-expiratory chest wall volume change was observed between groups, although an overall increase in end-expiratory chest wall volume was observed in 13 of the 29 children who undertook the exercise test, including 2 healthy control subjects. Whilst this may represent dynamic hyperinflation, there was no difference in baseline characteristics, exercise time, peak tidal volume or change in FEV_1 with exercise between children showing an increase in end-expiratory chest wall volume and those showing a decrease, and no children terminated exercise due to breathlessness. Exercise limitation due to symptomatic dynamic hyperinflation associated with expiratory flow limitation therefore seems unlikely. The mechanism behind the increase in end-expiratory chest wall volume in these children is unclear but may represent a degree of asymptomatic hyperinflation. Volume changes were not correlated with a pneumotachograph as previous studies have reported strong correlation between volume changes measured using OEP and standard CPET methodologies, and to avoid the use of a mouthpiece to allow more physiological breathing. Future work is required in a larger cohort, powered to assess changes between groups, and may consider addition of a pneumotachograph to correlate volume changes and directly quantify expiratory flow limitation.

6.4.2 Clinical Implications

It is well established that children born preterm have lung function abnormalities that persist with age, but the functional impact of this on daily activity is less well described. Whilst it was good to see that most children in the study were thriving and participating in normal physical activity at school and home, they showed significant impairments in lung function and this was not limited to children with a neonatal diagnosis of BPD. Ideally, children born preterm should undergo long-term respiratory follow-up, with monitoring of their lung function and targeted intervention if required but with current service pressures this is likely not realistic at present. Development of resources for families, young people and schools to increase awareness of the potential risks, promote respiratory health and address modifiable factors such as encouraging physical activity, nutrition and avoidance of cigarette smoke may be helpful. Sadly, many of the public health factors contributing to preterm birth are the same factors that contribute to poor respiratory health, namely obesity, smoking and low socioeconomic status, therefore targeted public health interventions will be the most important strategy to reduce the overall burden of preterm respiratory disease.

6.4.3 Future Study

With changes in neonatal care and increasing survival of progressively more immature infants, ongoing study into the longer-term respiratory impact of prematurity is undoubtedly required. However, this should focus on outcomes that are important to families and young people, and interventions to improve respiratory health rather than simply focus on lung function abnormalities which are well described. In taking this work forward, as a priority I would like to develop a core outcome set for respiratory health in infancy, early and late childhood in conjunction with families. This may include factors such as respiratory related hospital admissions, respiratory medication use, exercise capacity and breathlessness, but will allow more meaningful comparison of outcomes and the impact of interventions, and include factors that are important to quality of life.

The impact of a targeted exercise programme in children born preterm is also an important area for future study. In children born preterm, exercise capacity measured using VO_2max correlates more strongly with activity level than FEV_1 or BPD status, and pulmonary rehabilitation is effective in other chronic respiratory conditions such as asthma and COPD(Clemm et al., 2015). To study this, lung function, exercise capacity and quality of life, using the core outcome set, could be assessed before and after a targeted activity programme delivered using an app or web-based programme to increase physical activity. Whilst lifestyle modifications are difficult to implement and sustain, this is likely to have the most impact on longer term respiratory health and merits further investment.

6.5 Reflection: Evaluation and key outcomes of preterm lung disease

A recurring theme throughout this thesis is the continuum of preterm lung disease and limitations of current BPD definitions in reflecting this, both as a prognostic indicator and a trial outcome. It is highly unlikely that application of a single dichotomous outcome to all preterm infants <32 weeks can accurately reflect the wide spectrum of lung disease in these infants, and more refined outcome measures are clearly needed. The work described in this thesis clearly demonstrates this, describing a cohort of infants with life-threatening disease, not discernible using current definitions, whilst also highlighting abnormal lung function and longer-term respiratory morbidity in children who did not reach the threshold for a diagnosis of BPD in the neonatal period.

The ideal BPD definition must be pragmatic, therefore easily applicable in clinical practice, but accurately reflect both short and long-term outcomes, which is challenging. Current BPD definitions based on need for oxygen or respiratory support at 36 weeks corrected gestation were developed over 20 years ago, when clinical practice and the population of preterm infants cared for in neonatal intensive care units were markedly different to today(Jobe & Bancalari, 2001). As progressively more immature infants are admitted to, and surviving, neonatal care, accurate outcomes measures that are relevant to clinical practice are increasingly important. Newer proposed definitions, which stratify severity according to mode of positive pressure support near term, go some way to addressing these limitations and correlate more closely with short-term outcomes, but longer-term follow-up is lacking(Isayama et al., 2017; Jensen et al., 2019). Ultimately, comprehensive follow-up into childhood should be part of routine clinical care and future neonatal trials to ensure accurate outcome assessment. Furthermore, it is likely that preterm-born children born, their families and healthcare professionals perceive outcome priorities differently. Ideally a key respiratory outcome set in neonatology should be developed in conjunction with young people and their families, to facilitate a collaborative approach to improving the future respiratory health of preterm children.

6.6 Concluding remarks

In conclusion, the work in this thesis has explored various clinical and physiological aspects of preterm lung disease. A clear protocol for weaning nasal high flow therapy in preterm infants has been developed, and the longitudinal changes in diaphragm activity that occur when weaning described in a cohort of preterm infants. A prospective national cohort study of life-threatening bronchopulmonary dysplasia in preterm infants in the United Kingdom was performed, describing the characteristics, management, and outcomes of affected infants. Finally, the longer-term respiratory health of children born preterm has been discussed and the feasibility of using optoelectronic plethysmography to assess ventilatory changes in this group has been addressed.

Appendix A: High flow weaning paper

Original research

Diaphragm electrical activity during weaning of nasal high-flow therapy in preterm infants

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ABSTRACT

Objective To determine whether electrical activity of the diaphragm (Edi) changes with weaning nasal high-flow (HF) therapy in preterm infants according to a standardised protocol.

Design Prospective observational cohort study.

Setting Neonatal intensive care unit.

Patients Preterm infants born at <32 weeks gestation, receiving nasal HF as part of routine clinical care.

Interventions Infants recruited to the study had their HF weaned according to set clinical criteria. Edi was measured using a modified gastric feeding tube serially from baseline (pre-wean) to 24-hours post-wean.

Main outcome measures Change in Edi from baseline was measured at four time points up to 24 hours after weaning. Minimum Edi during expiration, maximum Edi during inspiration and amplitude of the Edi signal (Edi_{delta}) were measured. Clinical parameters (heart rate, respiratory rate and fraction of inspired oxygen) were also recorded.

Results Forty preterm infants were recruited at a mean corrected gestational age of 31.6 (±2.7) weeks. Data from 156 weaning steps were analysed, 91% of which were successful. Edi did not change significantly from baseline during flow reduction steps, but a significant increase in diaphragm activity was observed when discontinuing HF (median increase in Edi_{delta} immediately post-discontinuation 1.7 µV (95% CI: 0.6 to 3.0)) and at 24 hours 1.9 µV (95% CI: 0.7 to 3.8)). No significant difference in diaphragm activity was observed between successful and unsuccessful weaning steps.

Conclusions A protocolised approach to weaning has a high probability of success. Edi does not change with reducing HF rate, but significantly increases with discontinuation of HF from 2 L/min.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Weaning high flow in preterm infants is largely a trial-and-error process, and little is known about the physiological changes in breathing effort that occur with weaning in preterm infants.

⇒ Electrical activity of the diaphragm is an objective measure of respiratory muscle effort, and may be useful to guide weaning.

WHAT THIS STUDY ADDS

⇒ Electrical activity of the diaphragm does not change when reducing high flow by 1 L/min, but does increase significantly when discontinuing high flow from 2 L/min.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ A structured weaning protocol was developed, which may be useful for clinical practice.

⇒ Study findings support weaning high flow in decrements of 1 L/min, and show a flow of 2 L/min does reduce respiratory effort measured using diaphragm electrical activity.

INTRODUCTION

Nasal high flow (HF) is a widely used mode of non-invasive respiratory support in preterm infants. HF is popular due to its ease of use, improved comfort and reduced nasal trauma compared with continuous positive airway pressure (CPAP). Mechanisms of action include positive distending pressure, reduced nasopharyngeal resistance and upper airway washout to increase carbon dioxide (CO_2) clearance.[1] HF is generally not recommended for primary support of respiratory distress syndrome, but is extensively used as a step down from CPAP due to the aforementioned advantages.[2–4]

There are few objective parameters to guide weaning of HF support in preterm infants. Weaning is largely a 'trial-and-error' process based on clinical judgement, leading to variation in practice.[4–6] Retrospective studies have associated introduction of HF with longer duration of respiratory support and higher rates of bronchopulmonary dysplasia (BPD).[7–9] Due to the observational nature of these studies, it is unclear whether these findings reflect differences in infant characteristics, efficacy of support or a tendency to wean HF less aggressively than CPAP, but highlight weaning as an important area for prospective studies.

Diaphragm electrical activity (Edi) can be measured easily by electromyography using a modified gastric feeding tube or transcutaneous surface electrodes, providing an objective measure of respiratory effort.[10–13] The maximal Edi during inspiration (Edi_{max}) reflects inspiratory effort and is responsible for the size of a breath, while the minimal Edi at end expiration (Edi_{min}) reflects tonic activity required to maintain functional residual capacity (FRC) and prevent atelectasis.[10 14] Changes in Edi correlate with work of breathing, and in infants weaning from CPAP, diaphragm activity (Edi_{max}) increases most markedly in infants failing the weaning attempt, suggesting this may be a useful objective tool to guide weaning.[12 15] A small study of eight stable infants showed HF 6 L/min reduced diaphragm activity compared with low-flow nasal

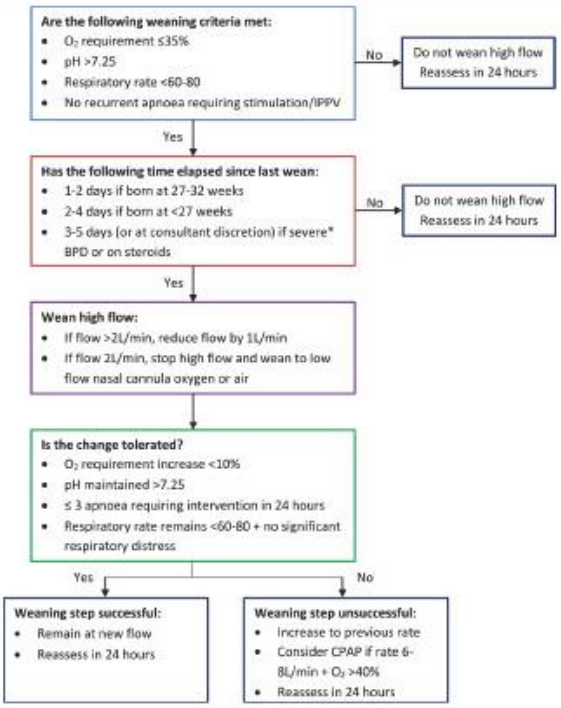

Figure 1 High-flow weaning protocol. *Severe BPD: need for respiratory support (invasive ventilation, CPAP or high flow) at ≥36 weeks' corrected gestational age. BPD, bronchopulmonary dysplasia; CPAP, continuous positive airway pressure; IPPV, intermittent positive pressure ventilation; O_2, oxygen.

cannula support, but it is not known if, or how, Edi changes with weaning nasal HF support.[16]

This study aimed to assess changes in Edi with weaning nasal HF in preterm infants. We hypothesised that Edi_{min} and Edi_{max} would increase with weaning.

METHODS

This was a prospective, observational study performed in the level 3 neonatal intensive care unit at the Royal Victoria Infirmary, Newcastle upon Tyne, UK, from August 2020 to September 2021. A volunteer sample of preterm infants born at <32 weeks gestation, receiving HF during routine clinical care, were recruited (online supplemental figure 1). Infants with major congenital, cardiac, or neuromuscular abnormalities, and contraindications to gastric tube insertion were excluded.

HF weaning

HF was delivered using a Fabien Therapy Evolution device (Acutronic Medical, Switzerland). Following study enrolment, HF was weaned according to a prespecified protocol (figure 1). This protocol was developed using local audit data, national survey data and international consensus statements.[4 6 17] Weaning steps included both flow reductions (decreasing flow by 1 L/min) and discontinuation steps (cessation of HF from 2 L/min to air or low-flow nasal cannula oxygen at <1 L/min). Weaning steps were classed as successful if the infant remained at the lower rate or off HF (or weaned further) for ≥72 hours and unsuccessful if increasing flow or restarting HF was required within 72 hours.

Table 1 Infant characteristics and high-flow (HF) parameters

Demographics and background	
Gestation (weeks)	26.3 (±1.9)
Birth weight (g)	805 (688–1008)
Male	23/40 (57.5%)
C-section delivery	23/40 (57.5%)
Received antenatal steroids	36/40 (90%)
Invasive ventilation	
Received	37/40 (92.5%)
Ventilator days	17 (3–27.5)
Received HFOV	12/40 (30%)
Received iNO	13/40 (32.5%)
Received surfactant	37/40 (92.5%)
CPAP	
Received	39/40 (97.5%)
CPAP days	18 (6.5–28.5)
Received postnatal steroids	22/40 (55%)
Received diuretics	11/40 (27.5%)
PDA medical therapy	12/40 (30%)
PDA ligation	4/40 (10%)
IVH grade ≥2	6/40 (15%)
Treatment for ROP	9/40 (22.5%)
HF therapy	
Age commenced HF (days)	35 (14–55.3)
Corrected gestational age (CGA) commenced HF (weeks)	31.6 (±2.7)
Weight at starting HF (kg)	1.39 (±0.44)
Starting flow (L/min)	6 (5–6)
Weight-adjusted starting flow (L/min/kg)	4.4 (±1.5)
Study HF days	15 (11–21)
Total HF days	18 (11–29.5)
Weight at discontinuation (kg)	1.8 (1.3–2.1)
Weight-adjusted flow at discontinuation (L/min/kg)	0.9 (0.7–1.1)
Respiratory outcomes	
Moderate/severe BPD	33/40 (82.5%)
Respiratory support at 36 weeks' CGA	
None	7/40 (17.5%)
Low-flow	19/40 (47.5%)
HF	11/40 (27.5%)
CPAP	3/40 (7.5%)
Home oxygen	32/40 (80%)

Data reported as number (%), mean (SD) or median (IQR).
BPD, bronchopulmonary dysplasia; CPAP, continuous positive airway pressure; HFOV, high-frequency oscillatory ventilation; iNO, inhaled nitric oxide; IVH, intraventricular haemorrhage; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity.

Measurements

Edi was measured using a specific gastric feeding tube containing miniaturised electrodes at the level of the diaphragm (6 F Edi catheter, Maquet, Sweden) positioned according to the manufacturer's instructions.[18] The catheter was connected to a Servo-n ventilator (Maquet, Sweden) where the signal was filtered and processed.[19] The digital Edi signal was transferred directly to a multichannel recorder (PowerLab, ADInstruments, New Zealand) via a digital to analogue converter, with a sampling frequency of 20 Hz.

Heart rate and oxygen saturation were continually monitored using a pulse oximeter (Masimo Radical, USA). Uncalibrated respiratory inductance plethysmography used to monitor chest and abdominal excursion (Nims Respitrace 200, USA), to detect apnoea and identify periods of artefact. All signals, including

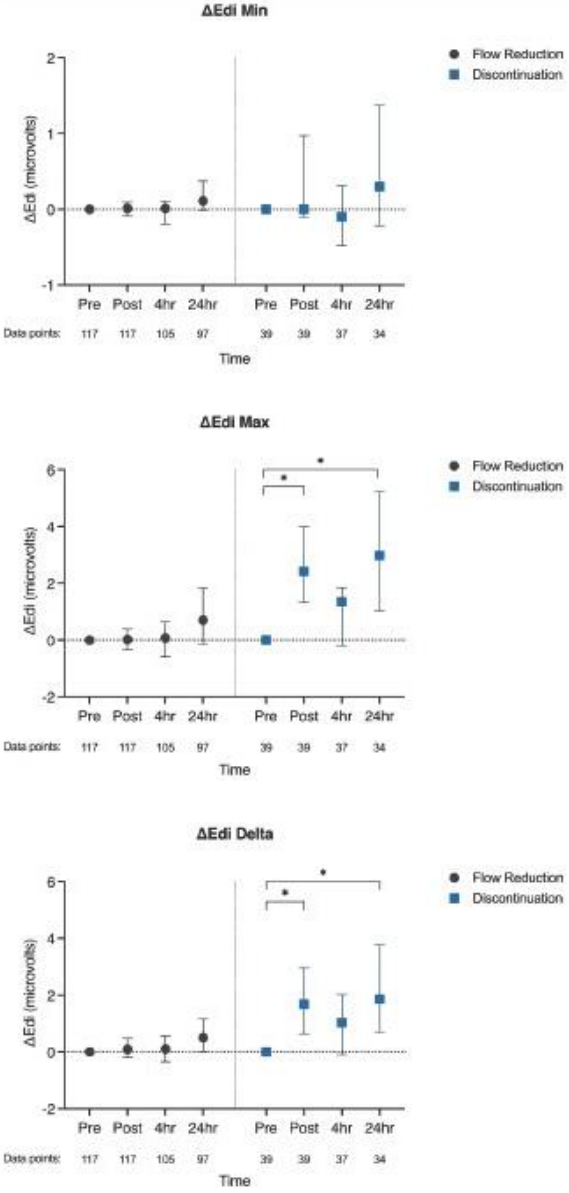

Figure 2 Change in Edi following flow reductions and discontinuation of high flow. Data presented as median (95% CI). Friedman test used to assess change with time, with post-hoc Dunn test for pairwise comparisons. *Statistically significant difference from pre-wean baseline value at time point ($p<0.05$). Edi, diaphragm electrical activity; Edi_{delta}, amplitude of the Edi signal; Edi_{max}, maximal Edi during inspiration; Edi_{min}, minimal Edi at end expiration.

Edi, were simultaneously recorded in the multichannel recorder. Fraction of inspired oxygen (FiO_2) was titrated throughout the study to maintain saturation in target range according to unit policy. A capillary blood gas was taken 4 hours post-wean to measure partial pressure of CO_2 (pCO_2). A pre-wean gas was not routine, but the most recent pCO_2 (within 24 hours) prior to weaning was recorded.

Measurements were made in continuous 10-minute blocks immediately before, immediately after, 4 hours and 24 hours after each flow change. For infants receiving bolus feeds, measurements were performed at least 1 hour post-feed and each series of measurements was made in either the prone or supine position.

Data analysis and statistics

All artefact free breaths during each 10-minute recording were analysed. Periods of movement, central apnoea and sigh breaths were excluded, but all other breaths included to accommodate the high physiological variability in infant breathing. For each breath, Edi_{max}, Edi_{min} and amplitude of the Edi signal (Edi_{delta} = Edi_{max}–Edi_{min}), measured in microvolts (μV) were recorded and median change from baseline (pre-wean) calculated for each time point. Neural respiratory rate was calculated from the Edi trace, and the number of central respiratory pauses, defined as Edi amplitude <1 μV for >5 s, in each 10-minute period was recorded.[20] Analysis was performed using ADInstruments Labchart V.8 software.

Using published preterm Edi data, a sample size of 40 infants was estimated to allow detection of a 25% increase in Edi_{max} with 90% power and significance 0.05.[14] Data were summarised as frequencies and percentages for categorical variables, and mean (SD) or median (IQR) for continuous parametric and non-parametric variables, respectively. Summary statistics are presented as mean or median and their 95% CI. Longitudinal changes were analysed using repeated measures analysis of variance for parametric data, and Friedman test for non-parametric data. A Bonferroni correction was applied to post-hoc pairwise comparisons. Group comparisons used the independent Student's t-test or Mann-Whitney U test according to distribution. A p value of <0.05 was considered significant. Analysis was performed using SPSS V.28 and GraphPad Prism V.9.0.

RESULTS

Infant demographics

A total of 40 infants participated in the study. Demographics details of infants recruited are in table 1. Mean gestational age at birth was 26.3 (±1.9) weeks, and median birth weight 805 g (IQR 688–1008). Most infants received invasive ventilation and CPAP before HF (92.5% and 97.5%, respectively). All ventilated infants received surfactant. On commencing HF, mean corrected gestational age (CGA) was 31.6 (±2.7) weeks and weight 1.39 kg (±0.44). Thirty-three (82.5%) infants had moderate/severe BPD defined as need for oxygen and/or positive pressure respiratory support at 36 weeks CGA.[21]

Measurements

Measurements were made for 162 weaning steps; six were excluded due to technical issues, therefore 156 weaning steps (117 flow reductions and 39 discontinuation steps) were analysed. Median steps per infant was 4 (IQR 3–5). Data were available immediately pre-wean and post-wean for all 156 steps, at 4 hours for 142, and 24 hours for 131 steps. Missing data points were due to researcher unavailability (26 of 39), removal of Edi gastric tube (9 of 39) or further change in flow (4 of 39). Median number of breaths analysed per 10-minute recording was 306 (IQR 236–420).

Weaning protocol

Weaning occurred per protocol in 132 of 156 (85%) steps. Of those that occurred outside the protocol, 13 of 24 (54%)

Table 2 (A) Physiological changes with weaning high flow; (B) comparison of successful and unsuccessful steps

	Pre-wean	Immediately post-wean		4 hours post-wean		24 hours post-wean	
(A) Physiological changes with weaning high flow							
Flow reduction steps							
Number	117	117		105		97	
Edi_{min} (µV)	1.1 (1.0 to 1.3)	1.1 (0.9 to 1.5)	p>0.99	1.1 (0.9 to 1.3)	p>0.99	1.2 (1.1 to 1.5)	p=0.87
Edi_{max} (µV)	8.6 (6.9 to 10.1)	8.7 (7.4 to 10.2)	p>0.99	8.2 (6.9 to 9.5)	p>0.99	8.7 (7.8 to 10.0)	p=0.20
Edi_{delta} (µV)	7.0 (5.5 to 8.2)	6.7 (6.0 to 7.8)	p>0.99	6.5 (5.5 to 7.8)	p>0.99	6.8 (6.1 to 7.4)	p=0.07
HR	154 (152 to 157)	156 (151 to 158)	p>0.99	155 (151 to 157)	p>0.99	157 (154 to 160)	p>0.99
RR	59 (56 to 64)	62 (55 to 64)	p>0.99	60 (56 to 64)	p>0.99	62 (59 to 67)	p=0.02
Central pause >5s	2 (1 to 2)	2 (1 to 3)	p>0.99	2 (1 to 3)	p=0.15	1 (1 to 2)	p=0.37
Discontinuation steps							
Number	39	39		37		34	
Ed_{min} (µV)	1.9 (1.1 to 2.2)	2.2 (1.5 to 3.4)	p>0.99	1.6 (1.3 to 2.3)	p>0.99	2.2 (1.5 to 2.8)	p>0.99
Edi_{max} (µV)	10.9 (8.5 to 13.1)	13.1 (11.5 to 15.7)	p<0.001	10.5 (8.7 to 13.4)	p>0.99	13.6 (10.6 to 16.5)	p=0.004
Edi_{delta} (µV)	8.2 (6.2 to 10.7)	9.4 (8.4 to 12.5)	p<0.001	8.3 (6.7 to 11.8)	p>0.99	9.8 (8.3 to 12.2)	p=0.001
HR	157 (153 to 160)	158 (154 to 163)	p=0.34	152 (144 to 161)	p=0.29	157 (152 to 163)	p>0.99
RR	63 (56 to 69)	63 (53 to 69)	p>0.99	66 (57 to 70)	p>0.99	68 (59 to 73)	p=0.18
Central pause >5s	1 (0 to 1)	0 (0 to 1)	p=0.48	0 (0 to 1)	p>0.99	0 (0 to 1)	p=0.89

	Pre-wean			Immediately post-wean			4 hours post-wean			24 hours post-wean		
(B) Comparison of successful and unsuccessful steps												
	Successful	Unsuccessful	P value	Successful	Unsuccessful	P value	Successful	Unsuccessful	P value	Successful	Unsuccessful	P value
Number of steps	142	14		142	14		128	14		120	11	
Edi_{ea} (µV)	1.2 (1.0 to 1.5)	1.3 (0.6 to 2.0)	0.92	1.4 (1.1 to 1.7)	1.3 (0.6 to 1.9)	0.5	1.2 (1.0 to 1.4)	1.4 (0.9 to 4.0)	0.17	1.5 (1.2 to 1.9)	1.4 (0.6 to 3.5)	0.9
Edi_{max} (µV)	8.9 (7.5 to 10.4)	10.9 (4.3 to 13.0)	0.78	10.4 (8.8 to 11.3)	10.2 (6.5 to 15.8)	0.92	8.7 (7.5 to 10.0)	12.7 (6.2 to 18.6)	0.16	9.4 (8.7 to 10.9)	11.1 (6.6 to 14.3)	0.7
Edi_{delta} (µV)	7.1 (6.1 to 8.3)	8.9 (3.1 to 11.7)	0.77	7.8 (6.7 to 8.6)	8.5 (5.0 to 13.4)	0.63	6.7 (5.8 to 7.8)	8.4 (5.2 to 12.9)	0.22	7.4 (6.4 to 8.4)	8.8 (5.0 to 12.4)	0.67
HR	154 (152 to 157)	161 (153 to 169)	0.11	155 (153 to 157)	159 (153 to 166)	0.38	153 (150 to 155)	162 (154 to 170)	0.04	156 (154 to 158)	161 (152 to 170)	0.23
RR	60 (57 to 63)	61 (53 to 70)	0.4	60 (57 to 63)	59 (50 to 69)	0.2	60 (57 to 63)	62 (52 to 71)	0.21	63 (60 to 66)	70 (62 to 78)	0.21
Central pause >5s	1 (1 to 2)	1 (0 to 4)	0.89	1 (1 to 2)	0.5 (0 to 4)	0.68	1 (1 to 2)	1.5 (0 to 4)	0.7	1 (0 to 1)	1 (0 to 9)	0.61

Data displayed as mean or median (95% CI). Repeated measures ANOVA or Friedman test used to assess significance of changes with time, and Bonferroni correction applied to post-hoc pairwise comparisons; p value displayed for comparison with pre-wean value on pairwise analysis. Successful and unsuccessful groups compared using the independent samples Student's t-test or Mann-Whitney U test and p value displayed for test.
ANOVA, analysis of variance; Edi, electrical activity of the diaphragm; Edi_{delta}, amplitude of the Edi signal; Edi_{max}, maximal Edi during inspiration; Edi_{min}, minimal Edi at end expiration; HR, heart rate; RR, respiratory rate.

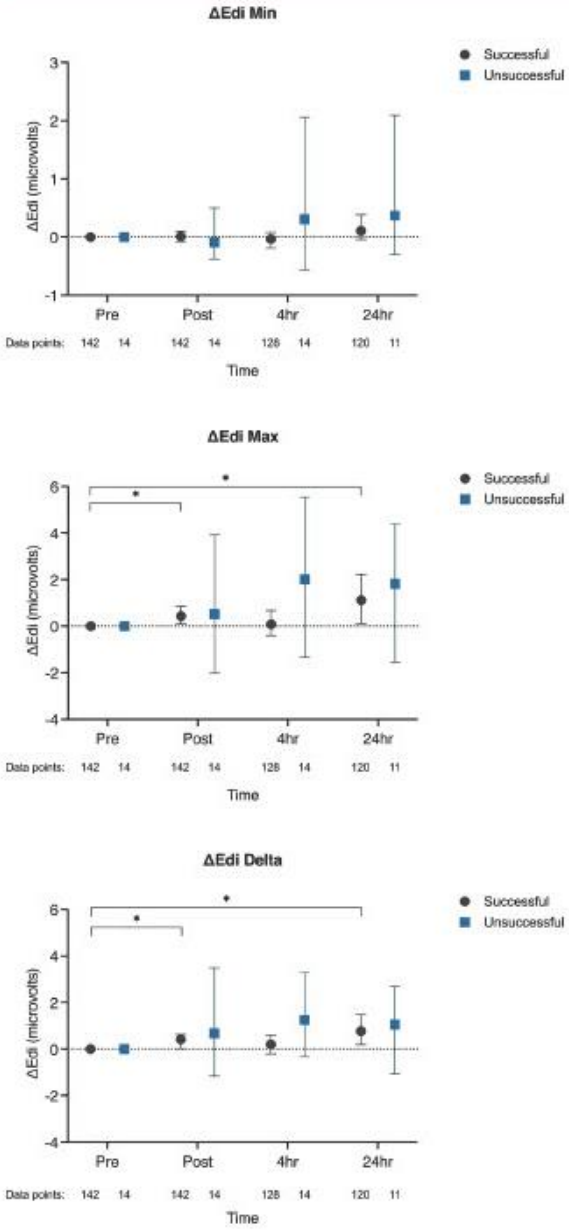

Figure 3 Change in Edi with successful and unsuccessful weaning steps. Data presented as median (95% CI). Friedman test used to assess change with time, with post-hoc Dunn test for pairwise comparisons. *Statistically significant difference from pre-wean baseline value at time point ($p<0.05$). Edi, diaphragm electrical activity; Edi_{delta}, amplitude of the Edi signal; Edi_{max}, maximal Edi during inspiration; Edi_{min}, minimal Edi at end expiration.

occurred earlier than recommended, and 11 of 24 (46%) later than recommended at the discretion of the treating clinician. Overall, 142 of 156 (91%) weaning steps were successful.

The unsuccessful steps were nine flow reductions and five discontinuation steps. Reasons for unsuccessful weaning were increased apnoea/desaturation in 9 of 14 (64%), increased respiratory distress in 3 of 14 (21%) and increased FiO_2 in 2 of 14 (14%). Two infants required re-escalation to CPAP during the study period due to deterioration associated with sepsis.

Change in Edi with flow reductions

No significant change in any Edi parameter was evident in the combined flow rate reduction steps (figure 2). Data for individual flow changes from 6 to 2 L/min, and longitudinal changes with weaning are provided in online supplemental tables 1 and 2.

Change in Edi with discontinuation of HF

Following discontinuation of HF to air or low-flow oxygen, a statistically significant increase in Edi_{max} from a median baseline of 10.9 µV (95% CI: 8.5 to 13.1) was evident immediately (median increase 2.4 µV (95% CI: 1.3 to 4.0)) and at 24 hours post-wean (median increase 3.0 µV (95% CI: 1.0 to 5.2)). A statistically significant increase in Edi_{delta} from baseline of 8.2 µV (95% CI: 6.2 to 10.7) similarly occurred immediately (median increase 1.7 µV (95% CI: 0.6 to 3.0)) and at 24 hours post-discontinuation of HF (median increase 1.9 µV (95% CI: 0.7 to 3.8); figure 2). Edi_{min} did not change significantly with discontinuation of HF (table 2). There was no statistically significant correlation between weight-adjusted flow and change in any Edi parameter at discontinuation (online supplemental figure 2).

Change in clinical parameters

There was no statistically significant change in median FiO_2 (0.26 (IQR 0.22–0.28) vs 0.28 (IQR 0.22–0.30); p=0.06) or capillary pCO_2 (6.6 kilopascal (IQR 6.0–7.3) vs 6.7 kilopascal (IQR 6.1–7.3); p=0.17) from baseline to 4 hours post-weaning. Respiratory rate was increased at 24 hours post-flow reduction, but no other statistically significant change in clinical parameters was identified at any time point (table 2).

Successful versus unsuccessful weaning

No statistically significant difference in Edi values was identified between successful and unsuccessful weaning steps (table 2). Edi_{max} and Edi_{delta} showed a statistically significant increase from baseline immediately and at 24 hours following successful weaning steps, but no statistically significant change was evident in the unsuccessful group (figure 3).

DISCUSSION

This study was designed to measure the changes in breathing that occur with weaning HF nasal cannula support in preterm infants using Edi. We observed no change in any Edi parameters when reducing HF rates, but identified a significant increase in Edi_{max} and Edi_{delta} following discontinuation of HF.

The weaning protocol used in this study was effective, with 90% of steps successful. There is little prospective clinical evidence to guide HF weaning, therefore this protocol was based on an audit of our own unit practice and published consensus statements.[4–6 17] Compliance with the protocol was high suggesting it is acceptable to clinicians, and provides a framework for future clinical practice.

The success of weaning and minimal change in Edi observed following flow reduction steps support weaning in 1 L/min decrements, as smaller changes are unlikely to be clinically meaningful. This is consistent with physiological studies showing that average end-expiratory pressure changes by only 0.6 cmH_2O per 1 L/min flow.[1] The high success of the protocol raises the question of

whether weaning could have been more rapid. Weaning support in preterm infants is complex, as a balance between progressing off support and stability for growth and maturation is needed, but a potential area for future study.

No significant change in any Edi parameter was observed during flow reduction steps. This is consistent with both Hough *et al* and Jeffreys *et al* who reported similar diaphragm activity measured transcutaneously at randomly applied flows of 4, 6 and 8 L/min.[22 23] The Edi technique we used measures activity of the crural diaphragm, and shows strong correlation with work of breathing measured using oesophageal pressure changes, but it does not consider intercostal muscle activity.[12] Intercostal muscle activity precedes diaphragm activation during inspiration and contributes to maintenance of FRC; therefore, it is possible that changes in intercostal muscle activity compensate for the reduction in flow.[24 25] However, Hough *et al* reported no difference in intercostal muscle activity, measured using transcutaneous electromyography, at different HF rates suggesting this is not the case.[22]

In contrast, a significant increase in Edi_{max} and Edi_{delta} was observed following discontinuation of HF at 2 L/min, both increasing >30% from baseline at 24 hours. Some centres advocate discontinuing HF from higher rates, for example, 4 L/min; given the minimal change in Edi with each flow reduction step, it is unclear whether discontinuing from a higher rate would have a greater physiological effect but is an area for future study. Edi_{max} and Edi_{delta} showed a statistically significant increase following discontinuation of HF, indicating that even 2 L/min does reduce diaphragmatic work of breathing to some extent, but the clinical implication of this requires consideration. The median increase in Edi_{max} post-discontinuation of HF was relatively small (3.0 µV (95% CI: 1.0 to 5.2)), but there was wide interindividual variation, suggesting a clinically significant increase occurred in some individuals. Further work is required to delineate clinically significant thresholds for changes in Edi, and assess the utility of Edi measurements to prospectively guide weaning in a personalised manner.

Interestingly, Edi_{min}, which reflects the tonic diaphragm activity required to maintain FRC and is altered by positive end-expiratory pressure, did not change with discontinuation of HF.[26] This likely reflects the low and variable level of distending pressure generated by HF at 2 L/min, and suggests its effect on inspiratory work of breathing is more related to other mechanisms such as reduced nasopharyngeal resistance.[1] Although the physiological effects of HF are related to weight, in this cohort, exploratory analysis showed no correlation between weight-adjusted flow and change in Edi when discontinuing HF. This may reflect the way HF was used in this cohort, as infants receiving HF at later gestational age and higher weight likely have more severe lung disease therefore intrinsically higher Edi.[1 27]

No difference in any Edi or clinical parameter was observed between successful and unsuccessful weaning steps in this study, although the small number of unsuccessful steps limits our ability to draw firm conclusions. One previous study reported significantly higher Edi in infants unsuccessfully weaned from CPAP, while another found no difference in Edi in infants unsuccessfully transitioning from CPAP to HF, but both were similarly limited by small numbers of unsuccessful changes.[15 28] Although no difference in raw Edi values was identified, the successful weaning steps showed an increase in Edi_{max} and Edi_{delta} from baseline, which was not observed in the unsuccessful group. While this likely simply reflects lack of power to detect a change in the unsuccessful group, in preterm infants failing extubation, a smaller increase in Edi_{max} and Edi_{delta} has been observed, suggesting inability to increase work of breathing with increased demand may contribute to failure.[29] Ultimately, further work is needed to determine the association and predictive value of changes in Edi and weaning success.

A major strength of this study is the detailed, longitudinal assessment and large number of weaning steps included, providing comprehensive data regarding changes in Edi with weaning in preterm infants. Recordings were made in 10-minute blocks to avoid intrusion on other clinical care. Although this may be considered a limitation, measurements were repeated longitudinally over a 24-hour period after each weaning step to capture both immediate and later changes. Furthermore, all artefact free breaths were analysed (average >1000 per step), which, given the high variability in infant breathing, is a more informative approach than selecting short periods for analysis. This Edi measurement technique was chosen as it is minimally invasive, well tolerated and suitable for clinical use unlike other oesophageal pressure-based techniques to assess work of breathing; however, it does not take into account the contribution of other respiratory muscles.[30 31] Infants in the study had a range of gestational and postnatal ages, and varying severity of lung disease, but each infant acted as their own control for assessing changes in Edi and clinical parameters. In our unit, HF is generally used as a step down from CPAP in infants requiring prolonged respiratory support, therefore the study population had relatively severe lung disease, reflected by the high rates of invasive ventilation, BPD and home oxygen use. All infants were in the stable, weaning phase but the relationship between flow reduction and Edi may be different in acute illness.

CONCLUSION

In conclusion, protocolisation of HF weaning was successful in this cohort. No change in Edi was identified when reducing HF rate, but a significant increase in Edi_{max} and Edi_{delta} occurred when discontinuing HF from 2 L/min. Further work is needed to assess the utility of Edi measurement as an objective marker of readiness to wean HF in preterm infants.

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Contributors RN, ACF, MB, SH and CO'B conceptualised and designed the study. RN collected data. RN, SH, MB and CO'B analysed and interpreted data. RN drafted the initial manuscript. MB, SH, CO'B, ACF and RN reviewed and revised the initial manuscript. RN is guarantor.

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Competing interests RN, ACF, SH, CO'B: None. Not related to this work, MB received investigator-led research grants from Pfizer and Roche Diagnostics; speaker fees paid to Newcastle University from Novartis, Roche Diagnostics and TEVA; travel expenses to educational meetings from Boehringer Ingelheim and Vertex Pharmaceuticals.

Patient consent for publication Not required.

Ethics approval This study involves human participants and was approved by the Newcastle and North Tyneside Research Ethics Committee (reference: 19/NE/0317). Written informed parental consent was obtained prior to enrolment.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplemental information.

of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

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Appendix B: High flow study participant information sheet and consent form

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PARENT/GUARDIAN RESEARCH STUDY INFORMATION SHEET

High Flow Weaning in **P**reterm Infants: **P**hysiology and **O**utcomes (HiPPO)

IRAS Project ID: 265622

We would like to invite your baby to take part in a research study investigating weaning of high flow in preterm infants. Please read this information carefully and as us if you have any questions.

What is this study about?

High flow is a commonly used type of breathing support on the neonatal unit. It delivers heated and humidified air and oxygen via small nasal prongs, at flow rates of 2-8L/minute.

As a baby matures and their breathing improves, the rate of high flow is reduced. It is important to get the timing of weaning high flow correct, as weaning too quickly may lead to instability, poor growth and re-escalation of breathing support. In contrast, weaning too slowly may prolong hospital admission, duration of respiratory support and delay oral feeding.

This study will investigate how breathing changes when high flow is weaned, aiming to improve the timing and success of high flow weaning in premature babies.

Why have I been invited?

You have been invited as your baby was born prematurely, and is on, or may soon be on, high flow support.

Does my baby have to take part?

No. While we would be very grateful for your help in this research, participation is entirely voluntary. If you do decide to take part, we will ask you to sign a consent form, but you are free to withdraw from the study at any time. This will not affect any future medical care you or your child receives.

What will happen if my baby takes part?

When your baby joins the study, they will start high flow at a time and rate decided by the consultant looking after them as usual. Their high flow will be weaned according to a set guideline, based on clinical features such as their oxygen requirement, blood gases and breathing effort. This is very similar to what happens normally, but will be more structured.

Over the days or weeks their high flow is being weaned, we will monitor their breathing closely and carry out a series of measurements with each flow rate change. This will give us information about how hard they are working to breathe, and how their breathing is changing.

We will take two main measurements:

1. *Electrical activity of the diaphragm*

The diaphragm is the main muscle responsible for breathing. It is controlled by nerves from the respiratory centres in the brain, which send impulses to make it contract. These nerve impulses are tiny electrical signals that activate the diaphragm.

We can detect these impulses using a specialised feeding tube that has miniature sensors built into the tube. This simply connects to a monitor to tell us about their respiratory drive, and how hard they are working to breathe. The tube is inserted, used for feeding and changed as normal.

2. *Pressure Measurements*

When a baby breathes, air moves in and out of their lungs due to changes in pressure in the chest. The size of the pressure changes tells us how hard they are working to breathe. This is also measured directly by connecting their feeding tube to another monitor. The tube is pulled back 2-3cm for these measurements, but will be put back to the original length after.

During the study, we also monitor heart rate and saturations using a pulse oximeter and measure chest and abdominal movement using soft cotton bands placed on their chest and abdomen.

What are the possible benefits and risks of being involved?

During the study your baby's high flow will be weaned according to set criteria. We think these criteria are associated with the best chance of success.

On enrolment to the study your baby's feeding tube will be replaced by a specialised feeding tube that can also measure the electrical activity of the diaphragm. This tube remains in and is used for feeding as normal. Like all tube changes this may cause your baby to become upset, but we will try to time insertion with their routine tube change to reduce this.

Will information about my baby be kept confidential?

Yes. We will ensure that all information about your child is kept secure and confidential. We will let your GP know you are taking part in this study.

Data Protection Statement
The Newcastle upon Tyne Hospitals NHS Foundation Trust is the sponsor for this study. We will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. We will keep identifiable information about you for 5 years after the study has finished.

Your right to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

Individuals from The Newcastle upon Tyne Hospitals NHS Foundation Trust and regulatory organisations may look at your medical and research records to check the accuracy of the research study. You can find out more about how we use your information by contacting nuth.dpo@nhs.net

What will happen to the results?

All medical information and study results are highly confidential and no information that identifies you or your child will be shared. At the end of the study the results will be analysed and published in a medical journal to share with other health professionals looking after babies on high flow, and non-identifiable information may be used in future research. This will also be submitted as a study report (thesis) to Newcastle University as part of a higher educational degree.

If you and your child are interested, we can give you a summary of the results of the study when it is finished. Please email Rebecca Naples (details below) if you would like to receive this.

Who has organised and funded the study?

The study has been organised by neonatal and children's respiratory doctors at the RVI. It has been funded by Tiny Lives, the Newcastle Neonatal Unit Charity.

Who has reviewed the study?

All healthcare research must be approved by an NHS Research Ethics Committee before it goes ahead. The ethics committee ensures that the study is safe, the expected benefits outweigh the potential risks, your rights will be respected, and that you have been given sufficient information before taking part. This study has been approved by the Newcastle and North Tyneside 1 Research Ethics Committee.

What if I have any problems with the study?

If you have any concerns about the study or the way the study has been carried out, you can contact any member of the research team who will do their best to answer your questions (contact details below). If you prefer to raise your concerns with someone not involved in your care, you can contact the Patient Advise and Liaison Service (PALS). This service is confidential and can be contacted on Freephone: 0800 032 0202

Alternatively, if you wish to make a formal complaint you can contact the Patient Relations Department through any of the details below:
Telephone: 0191 223 1382 or 0191 223 1454
Email: patient.relations@nuth.nhs.uk
Address: Patient Relations Department
The Newcastle upon Tyne Hospitals NHS Foundation Trust
The Freeman Hospital
Newcastle upon Tyne, NE7 7DN

What happens now?

Once you have read this leaflet and discussed the study with a member of the research team we will give you some time to think about whether you would like to take part. Please do not hesitate to ask us if you have any questions.

Thank you for reading.

Contacts

Main contact:

Dr Rebecca Naples
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Royal Victoria Infirmary
Newcastle upon Tyne

Email: rebecca.naples@nhs.net

Phone: 0191 2139898

Research Group Members:

Dr Sundeep Harigopal – Consultant Neonatologist
Dr Alan Fenton – Consultant Neonatologist
Dr Malcolm Brodlie - Consultant in Paediatric Respiratory Medicine
Dr Christopher O'Brien – Consultant in Paediatric Respiratory Medicine

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust
Newcastle Neonatal Service
Royal Victoria Infirmary
Newcastle upon Tyne
NE1 4LP
Tel: 0191 2336161

RESEARCH STUDY PARENTAL CONSENT FORM

Study Title: High Flow Weaning in Preterm Infants: Physiology and Outcomes (HiPPO)

Study Site: Ward 35, Royal Victoria Infirmary, Newcastle upon Tyne.

Researchers: Dr R Naples, Dr M Brodlie, Dr A Fenton, Dr S Harigopal, Dr C O'Brien

IRAS project ID: 265622

Name of Child:

Participant ID:

Please read the following carefully, and initial the boxes if you agree to the statements.

1. I confirm that I have read the information sheet dated 9/2/21 (version 1.5) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that participation is voluntary and that I am free to withdraw my child at any time without giving any reason, without his/her medical care or legal rights being affected. ☐

3. I understand that relevant sections of my child's medical notes and data collected during the study, may be accessed by individuals within the research team, regulatory authorities or the NHS Trust, where it is relevant to him/her taking part in this research. I give permission for these individuals to have access to my child's records. ☐

4. I understand that the information collected about my child will be used to support other research in the future, and may be shared anonymously with other researchers. ☐

5. I agree to my child's General Practitioner being informed of participation in the study. ☐

6. I agree to my child participating in this study ☐

Name of Parent/Guardian	Signature	Date
Name of Person Taking Consent	Signature	Date

Appendix C: High flow survey paper

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DOI: 10.1111/apa.16135

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

BRIEF REPORT

Nasal high flow in extremely preterm infants: Current evidence and practice in the United Kingdom

Nasal high flow (HF) therapy has rapidly become a popular mode of respiratory support in the neonatal unit due to its ease of use and excellent tolerance. In recent years, clinical evidence to refine its role has accumulated, although there has been limited focus on the most extremely preterm infants. This survey aimed to assess HF practice in extremely preterm infants in the United Kingdom (UK) in line with current evidence and to identify areas for development.

An online survey was sent to the lead nurse and consultant in all UK neonatal units via the 13 neonatal networks. The survey was open from 1 June to 1 September 2020, and each network lead distributed the link twice. Duplicate responses (obtained from both the lead nurse and consultant) were collated, so responses relating to use of HF and devices are displayed per unit. Indications for HF use are reported for all respondents from level 2 (high dependency) or 3 (intensive care) units as relevant to their patient demographic, and all individual responses are displayed for questions regarding preferences.

Responses were obtained from all 13 neonatal networks. In total, 114 individuals (58 consultant neonatologists/paediatricians and 56 senior nurses) from 94/191 (49%) of all units, including 75/145 (52%) of level 2/3 units, responded. HF was used in 89/94 (94.7%) responding units; the 5 units not using HF were all level 1 special care units. Results relating to HF practice are summarised in Table 1. Sixty-four per cent (59/91) of respondents from level 2/3 units use HF for primary support of respiratory distress syndrome (RDS), 54.2% (32/59) of whom use at any gestational age. Similarly, 60% (55/91) use HF for post-extubation support, 65% of whom (36/55) use at any gestational age. HF is widely used as a weaning modality to transition from continuous positive airway pressure (CPAP [79/91; 86.8%]) at all gestational ages.

Clinicians in the survey reported a clear preference for HF in relation to infant comfort (101/108; 93.5% preferred HF), nasal trauma (100/108; 92.6%), parental bonding (97/108; 89.8%) and oral feeding (86/108; 79.6%); however, more preferred CPAP for provision of reliable and effective respiratory support (43/108 [39.8%] preferred CPAP; 43/108 [38.9%] expressed no preference; 22/108 [20.4%] preferred HF).

This national survey assessed high flow use in the UK in 2020. Since a similar survey in 2012, use of high flow has increased and a significant body of evidence has accumulated to optimise its use.[1] For primary support of respiratory distress syndrome (RDS), two large randomised controlled trials and a recent meta-analysis consistently report higher rates of treatment failure with use of HF compared to CPAP, but despite this HF is now widely used for this indication at all gestations.[2] No large trials have included infants <28 weeks; however, even in studies of more mature infants, risk of treatment failure is highest at lower gestations. Notably, Roberts et al reported a treatment failure rate of 33% when HF was used for primary support of RDS in infants <32 weeks gestation, compared to only 18% in infants >32 weeks. Although overall intubation rates do not differ with use of rescue CPAP, this approach risks exposing infants to a period of physiological instability, which is particularly hazardous in vulnerable extremely preterm infants, potentially contributing to adverse outcomes. Similarly, although overall treatment failure rates for HF or CPAP are comparable when used for post-extubation support, sub-analysis shows much higher rates of treatment failure with HF in the most immature infants. Manley et al reported a treatment failure rate of 81% when HF used for post-extubation support in infants <26 weeks (20% higher than CPAP); therefore, this approach cannot be recommended at present.[3]

HF is widely used as a weaning modality to transition from CPAP at all gestations, likely due to its benefits in relation to comfort and nasal trauma. There is little evidence to guide discontinuation of HF, and variation in weaning practice is evident in the survey, particularly regarding flow rate changes and oxygen thresholds. A recent large observational cohort study associated use of HF with prolonged respiratory support and increased odds of bronchopulmonary dysplasia in very preterm infants; whether this reflects differences in support, infant characteristics or clinicians' approach to weaning is unclear, but this identifies an important area for future prospective study.[4]

Physiological studies have shown the positive end-expiratory pressure generated by HF is highly variable and unpredictable, whilst the CO_2 washout effect is significant, highlighting that CPAP and HF are not directly interchangeable, but the relative benefits of each modality and specific needs of the infant should be considered when selecting or changing modes of support. Positive end-expiratory pressure generated by high flow is directly related to both increasing flow rate and decreasing infant weight, with the potential to generate pressures >10 cmH_2O in the smallest infants.[5] Given the fragility of the extremely preterm lung, the risk of barotrauma and volutrauma from uncontrolled, variable pressure

TABLE 1 High flow practice in neonatal units in the United Kingdom

	Number (%)
Total individuals responded	114
Individual units responded	94
Units using high flow	89/94 (94.7%)
High flow device used	
Vapotherm	39/89 (43.8%)
Fisher & Paykel	28/89 (31.5%)
Fabien	11/89 (12.4%)
Combination	9/89 (10.1%)
Subsequent data includes all respondents from level 2 and 3 units using nasal high flow ($n = 91$)	
Use high flow for primary support of RDS	59/91 (64.8%)
If yes, at what gestational age?	
No lower limit	32/59 (54.2%)
≥28 weeks	15/59 (25.4%)
≥32 weeks	8/59 (13.6%)
Other	4/59 (6.8%)
Use high flow for post-extubation support	55/91 (60.4%)
If yes, at what gestational age?	
No lower limit	36/55 (65.5%)
≥28 weeks	12/55 (21.8%)
≥32 weeks	4/55 (7.3%)
Other	3/55 (5.5%)
Use high flow to wean from CPAP	79/91 (86.8%)
If yes, at what gestational age?	
No lower limit	62/79 (78.5%)
≥28 weeks	14/79 (17.7%)
≥32 weeks	2/79 (2.5%)
Other	1/79 (1.3%)
Subsequent data include all respondents from units using nasal high flow ($n = 108$)	
Highest flow rate used (l/min)	
≤6	28/108 (25.9%)
7	6/108 (5.6%)
8	70/108 (64.8%)
>8	4/108 (3.7%)
Lowest flow rate used (l/min)	
2	67/108 (62%)
3	27/108 (25%)
≥4	14/108 (13%)
Flow rate change when weaning (l/min)	
0.5	33/108 (30.6%)
1	65/108 (60.2%)
Other	10/108 (9.3%)
Factors considered when weaning	
Oxygen requirement	103/108 (95.4%)
Clinical examination	101/108 (93.5%)
Blood gas	76/108 (70.4%)
Time since last weaned	59/108 (54.6)
Oxygen threshold for weaning	
≤25%	21/108 (19.4%)
≤30%	57/108 (52.8%)
≤35%	9/108 (8.3%)
>35%	18/108 (16.7%)
Not known	3/108 (2.8%)

generation in extremely low birth weight infants is a concern. No prospective clinical studies have yet been powered to assess the impact of HF use on bronchopulmonary dysplasia or longer-term respiratory outcomes in extremely preterm infants, and this should be a priority.

A strength of this study is that both doctors and senior nurses were included, as neonatal nurses are integral to the care of infants on respiratory support. It provides a novel focus on extremely preterm infants, highlighting the striking lack of evidence in this group. Responses were obtained from 94 units; therefore, reporting bias may be a limitation; however, geographically diverse units from all UK neonatal networks were included, providing a snapshot of current practice.

In conclusion, HF has clear advantages in relation to improved infant comfort and reduced nasal trauma, and evidence to optimise its role is accumulating. It is, however, widely used despite little clinical evidence in the most immature infants <28 weeks gestation, where treatment failure rates are high and physiological effects variable. We recommend caution in this vulnerable group, and future prospective studies are essential to clarify the role of HF in this population.

ACKNOWLEDGEMENT

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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No funding was received for this study.

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Appendix D: Life-threatening BPD Paper

Original research

OPEN ACCESS

Life-threatening bronchopulmonary dysplasia: a British Paediatric Surveillance Unit Study

Rebecca Naples [1,2] Sridhar Ramaiah,[1] Judith Rankin,[3] Janet Berrington,[1,2] Sundeep Harigopal [1]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/archdischild-2021-322001).

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ABSTRACT

Objectives To assess the minimum incidence of life-threatening bronchopulmonary dysplasia (BPD), defined as need for positive pressure respiratory support or pulmonary vasodilators at 38 weeks corrected gestational age (CGA), in infants born <32 weeks gestation in the UK and Ireland; and to describe patient characteristics, management and outcomes to 1 year.

Methods Prospective national surveillance study performed via the British Paediatric Surveillance Unit from June 2017 to July 2018. Data were collected in a series of three questionnaires from notification to 1 year of age.

Results 153 notifications met the case definition, giving a minimum incidence of 13.9 (95% CI: 11.8 to 16.3) per 1000 live births <32 weeks' gestation. Median gestation was 26.1 (IQR 24.6–28) weeks, and birth weight 730 g (IQR 620–910 g). More affected infants were male (95 of 153, 62%; p<0.05). Detailed management and outcome data were provided for 94 infants. Fifteen died at median age 159 days (IQR 105–182) or 49.6 weeks CGA (IQR 43–53). Median age last receiving invasive ventilation was 50 days (IQR 22–98) and total duration of pressure support for surviving infants 103 (IQR 87–134) days. Fifty-seven (60.6%) received postnatal steroids and 22 (23.4%) pulmonary vasodilators. Death (16%) and/or major neurodevelopmental impairment (37.3%) or long-term ventilation (23.4%) were significantly associated with need for invasive ventilation near term and pulmonary hypertension.

Conclusions This definition of life-threatening BPD identified an extremely high-risk subgroup, associated with serious morbidity and mortality. Wide variability in management was demonstrated, and future prospective study, particularly in key areas of postnatal steroid use and pulmonary hypertension management, is required.

What is already known on this topic?

- Bronchopulmonary dysplasia (BPD) is a common complication of preterm birth with significant respiratory and neurodevelopment consequences.
- Little is known about the outcomes of infants with the most severe BPD, particularly infants requiring positive pressure support near term.
- There is limited evidence to guide treatment of established BPD, and management strategies vary.

What this study adds?

- We defined 'life-threatening' BPD in preterm infants requiring positive pressure respiratory support or pulmonary vasodilators at, or beyond, 38 weeks corrected gestational age.
- Mortality and morbidity were high, and significant variation in practice was demonstrated.
- Invasive ventilation near term and presence of pulmonary hypertension were identified as key factors significantly associated with adverse outcomes within this cohort.

INTRODUCTION

Significant bronchopulmonary dysplasia (BPD), defined as need for oxygen or positive pressure respiratory support at 36 weeks corrected gestational age (CGA), affected 37% of infants born <32 weeks gestation in the UK in 2019, and is the most common major complication of preterm birth.[1] BPD is associated with adverse respiratory and neurodevelopmental outcomes throughout childhood and into adult life, and despite significant progress in neonatal respiratory care in recent decades, rates continue to increase.[2–4]

BPD is traditionally classified according to respiratory support or oxygen requirement at 36 weeks CGA,[5] but it is increasingly recognised that the predictive value of this classification is limited, and need for pressure support more closely associated with longer term morbidity.[6–8]

Although extensively studied as a broad group, there is little data on treatment and outcomes of infants with the most severe BPD, making management decisions, counselling and identification of research priorities difficult. This study aimed to identify the minimum incidence of 'life-threatening BPD', defined as a need for positive pressure respiratory support or pulmonary vasodilators at 38 weeks CGA in the UK and Ireland, and to describe infant characteristics, management strategies, and outcomes to 1 year. This pragmatic definition was chosen to capture infants with the most severe lung disease and include a feasible number of infants to survey in this manner, providing a novel detailed description of this group.

METHODS

This was an observational, descriptive surveillance study in the UK and Ireland, carried out via the British Paediatric Surveillance Unit (BPSU), a

well-established centre for paediatric rare disease surveillance, using their methodologies.[9] All paediatricians are sent monthly electronic reporting cards to notify cases or confirm they have seen none. Surveillance was undertaken for 13 months from 1 July 2017 to 31 July 2018 as standard for BPSU Studies.

Clinicians then completed up to three questionnaires using medical records: questionnaire 1 at notification (demographics, pregnancy and delivery details), questionnaire 2 at 8 weeks post-term (neonatal care and outcome at discharge/death), and questionnaire 3 at 1 year of age (post-discharge data). Presence of major or minor neurodevelopmental concerns at 1 year was reported from medical records. Up to three reminders were sent for each questionnaire by email and post.

Case definition

Life-threatening BPD was defined in any infant born at <32 weeks gestation, without significant congenital anomaly, requiring positive pressure support (ventilation, continuous/bilevel positive airway pressure (CPAP/BiPAP), or high flow ≥2 L/min) or pulmonary vasodilators at 38 weeks CGA, without intercurrent illness to explain this need.

Statistics

Descriptive statistics with measures of central tendency and dispersion were used. Categorical variables were compared using X^2 or Fisher's exact tests, and continuous, non-parametric variables using Mann-Whitney U test. A p value of <0.05 was considered significant. Binomial logistic regression was used to evaluate predictors of outcomes. Models included gestational age (GA), birth weight and sex, plus variables with p<0.1 on univariate analysis not showing multicollinearity. All analyses were performed using IBM SPSS V.26.

RESULTS

Case reporting

During the study period, overall monthly BPSU surveillance reporting was 94.7%. In total, 329 notifications were received; 90 were excluded as they did not fulfil inclusion criteria (n=68) or were duplicates (n=22). For a further 86 notifications, no data were provided despite multiple requests. One hundred fifty-three confirmed cases were finally included with detailed data up to discharge (questionnaire 2) provided for 94 infants and data to 1 year or death (questionnaire 3) for 77 infants (figure 1). All infants met the case definition by virtue of requiring positive pressure support at 38 weeks' CGA.

Incidence

Using national population estimates,[10–13] minimum incidence of life-threatening BPD during the surveillance period was 13.9 (95% CI 11.8 to 16.3) per 1000 live births <32 weeks gestation, or 0.17 (0.15 to 0.2) per 1000 of all live births, based on 153 confirmed cases.

Demographics

Cases were reported from 57 hospitals, with individual units reporting 0–12 cases. Median GA was 26.1 weeks (IQR 24.6–28), and birth weight 730 g (IQR 620–910 g). More affected infants were male (95 of 153, 62%; p<0.05) and most (120 of 153, 78%) white British (online supplemental table 1). No differences in baseline characteristics were identified between infants with and without discharge data (online supplemental table 2).

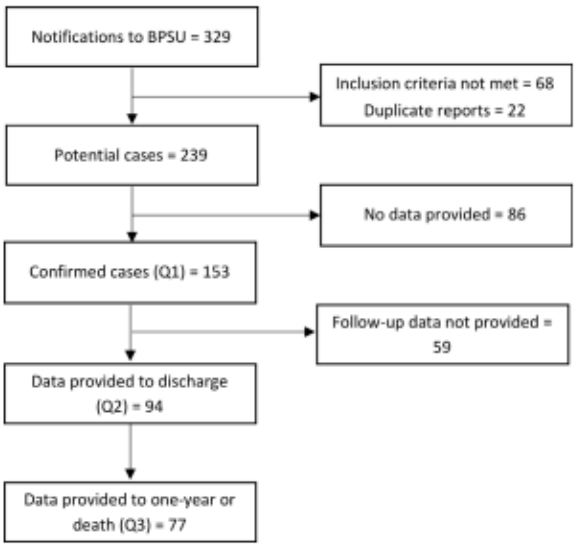

Figure 1 Cases reported to the BPSU. Q1/Q2/Q3=eligible questionnaire returned. BPSU, British Paediatric Surveillance Unit.

Antenatal steroids were given in 139 of 153 (90.8%) cases, with the last dose received a median of 2 days (IQR 1–6) before delivery (table 1).

Respiratory support

Episodes of respiratory support were considered separate if transfer to another device was achieved for >24 hours. Two of 94 cases provided incomplete respiratory data due to multiple postnatal transfers. Ninety-one (98.9%) infants received invasive ventilation: 85 of 91 (92.4%) on the first day of life and the remaining 6 within 72 hours. Infants were ventilated for median 29 days (IQR 17–51) in 2 (IQR 1–3) episodes, and median age last receiving invasive ventilation was 50 days (IQR 22–98).

All ventilated infants received surfactant, with a median first dose of 182 mg/kg (IQR 144–211) given at 11 min (IQR 7–23) of age. High-frequency oscillatory ventilation (HFOV) was used in 53 of 94 (56.4%); 30 of 94 (31.9%) received inhaled nitric oxide, and 4 of 94 (4.3%) had a pneumothorax.

Nasal CPAP/BiPAP and high flow were both extensively used (96.7% and 91.3%, respectively, table 2). High flow was generally started later and given for a significantly longer duration than CPAP (40.5 vs 27 days; p<0.05). Median duration of positive pressure support for infants discharged alive, off support was 103 days (IQR 87–134; max 258), which was discontinued at a median 41.3 weeks CGA (IQR 39.4–45.4; max 65.14). Seven infants required long-term ventilation post-discharge, all of whom survived to 1 year.

Postnatal steroids

Postnatal steroids were used for BPD in 57 of 94 (60.6%) infants, starting at a median age of 26 days (IQR 14–48). Initial steroid received was dexamethasone in the majority (52 of 57; 91.2%). Median steroid courses (defined as separate if >72 hours deliberately elapsed between doses) per infant was 1 (IQR 0–2, max 6). In total, infants in the study received 109 courses of steroid: 90 (82.6%) dexamethasone, 10 (9.2%) prednisolone, 5 (4.6%) methylprednisolone and 4 (3.7%) hydrocortisone. Two infants

Table 1 Demographic, antenatal and delivery details

Demographics	
Gestational age at delivery (weeks)	26.1 (24.6–28)
Birth weight (g)	730 (620–910)
Birth weight <10th centile	57/153 (37.3%)
Male	95/153 (62.1%)
Female	58/153 (37.9%)
Antenatal steroids	
Received any steroid	139/153 (90.8%)
Incomplete course only	16/139 (11.5%)
One complete course	109/139 (78.4%)
Two complete courses	13/139 (9.4%)
Courses not known	1/139 (0.7%)
None	13/153 (8.5%)
Not known	1/153 (0.7%)
Antenatal steroid received	
Betamethasone	66/139 (47.5%)
Dexamethasone	65/139 (46.8%)
Betamethasone and dexamethasone	1/139 (0.7%)
Not known	7/139 (5.0%)
Mode of delivery	
Caesarean section	85/153 (55.6%)
Vaginal	64/153 (41.8%)
Not known	4/153 (2.6%)
Rupture of membranes	
Prelabour	65/153 (42.5%)
Prolonged (>24 hours)	46/153 (30.1%)
Placenta	
Evidence of chorioamnionitis	21/153 (13.7%)
Other abnormality	21/153 (13.7%)
Apgar scores	
5 min	7 (5–8)
10 min	8 (7–9)
Surfactant	
Doses received	
None	1/153 (0.7%)
One	58/153 (37.9%)
Two	50/153 (32.7%)
≥Three	33/153 (21.6%)
Not known	11/153 (7.2%)
Respiratory support at 36 weeks' CGA	
Invasive ventilation	13/94 (13.8%)
CPAP/BiPAP	32/94 (34%)
High flow	43/94 (45.7%)
Not known	6/94 (6.4%)
Respiratory support at 38 weeks' CGA	
Invasive ventilation	13/94 (13.8%)
CPAP/BiPAP	20/94 (21.3%)
High flow	56/94 (59.6%)
Not known	5/94 (5.3%)

Data presented as number (%) or median (IQR).
BiPAP, bilevel positive airway pressure; CGA, corrected gestational age; CPAP, continuous positive airway pressure.

received Mini-Dex investigational medicinal product, one of whom also received open-label dexamethasone.[14]

Dexamethasone was given at a median starting dose of 135 µg/kg/day (IQR 50–150), and maximum dose 150 µg/kg/day (IQR 100–200) for 10 days (IQR 10–16) per course. Median total duration of steroid treatment was 23 days (IQR 14–44, range 2–163), and nine remained on steroid at discharge.

Management of patent ductus arteriosus

Medical therapy for patent ductus arteriosus (PDA) was used in 36 of 94 (38.3%) infants, and 8 (8.4%) received repeat courses (table 2). Seventeen (18.1%) underwent PDA ligation at median age of 43 days (IQR 37–78): 11 following medical therapy and 6 primary closures. Immediately before ligation, 9 of 17 (52.9%) infants were invasively ventilated.

Infections

Culture-positive sepsis occurred in 42 of 94 (44.7%) infants, most commonly coagulase-negative staphylococcus. Forty-nine (52.1%) experienced ≥1 episode of culture-negative sepsis, and 32 of 94 (34.0%) pneumonia, most commonly *Klebsiella* or *Staphylococcus aureus* (online supplemental table 3). Median number of treated infections was 2 (IQR 1–4), and age of first reported infection 7 days (IQR 1–28).

Pulmonary hypertension

Echocardiographic evidence of pulmonary hypertension (PHT) was identified in 32 of 94 (34%) infants. Sildenafil was used in 22 of 94 (23.4%) at a maximum dose of 3 mg/kg/day (IQR 1.6–4.3). One infant also received bosentan.

Other medications

Diuretics were frequently used (82 of 94, 87.2%), while inhaled steroids and bronchodilators were less common and started much later during admission (table 2).

Outcomes

Key outcomes are reported in table 3. By 1 year of age, 15 of 94 (16%) infants died; 14 before discharge, at median age 159 days (IQR 105–182) or 49.6 weeks CGA (IQR 43–52.9). Reported cause of death was BPD in 11 of 15 (73.3%), pulmonary stenosis in 1 of 15 (6.7%), and not known in 3 of 15 (20%).

Of 79 surviving infants, 1 (1.3%) remained an inpatient at 1 year. Median age of discharge home was 143 (IQR 117–185) days, or 46.6 (IQR 43–52.9) weeks CGA. Eighteen infants were transferred to respiratory paediatrics before discharge. At final discharge, 60 of 79 (75.9%) infants were documented as receiving low-flow oxygen, and 7 of 79 (8.9%) required long-term positive pressure support at home. Five had a tracheostomy at a median age of 260 days (range 177–278). Post-discharge, two infants required new invasive ventilation, one required CPAP and eight required high flow during readmissions in the first year of life.

One-year neurodevelopmental assessment was available for 60 of 79 (76%) surviving infants. No concerns were reported for 37 (61.7%), minor concerns in 10 (16.7%) and major concerns in 13 (21.7%) infants.

Characteristics of infants who died with and without major neurodevelopmental impairment (NDI) or required long-term ventilation are compared in table 4. Presence of PHT and need for any invasive ventilation at or beyond 38 weeks were significantly associated with these adverse outcomes on regression analysis.

DISCUSSION

Broad definitions of BPD do not facilitate focus on the most severely affected infants who merit separate approaches to their care. Infants requiring pressure support near term are an

Table 2 Respiratory support and medications received pre-discharge

	Number of infants	Starting age (days)	Starting CGA (weeks)	Total duration (days)	Postnatal age last received (days)
Respiratory support					
Invasive ventilation	91/92 (98.9%)	0 (0–0; 0–2)	26.4 (24.6–28.1; 23.3–31.3)	29 (17–51; 1–238)	50 (22–98)
Nasal CPAP/BiPAP	89/92 (96.7%)	20 (6–39; 0–152)	29.6 (27.7–32.1; 24.3–48.7)	27 (14–45; 2–297)	84 (49–103)
Nasal high flow	84/92 (91.3%)	49.5 (28–84; 0–161)	33.6 (31.1–37.1; 27.7–50.7)	40.5 (22–64; 4–156)	109 (89.5–143)
Medications					
PDA closure	36/94 (38.6%)	7.5 (5–14.5; 0–34)	26.3 (25.3–27.1; 23.9–31.9)	–	–
Ibuprofen	33 (91.7%)				
Paracetamol	4 (11.1%)				
Postnatal steroid	57/94 (60.6%)	26 (14–48; 0–185)	29.7 (27.9–33.4; 24.6–55.9)	23 (14–44)	91 (57–150)
Diuretics	82/94 (87.2%)	32 (17–51; 3–204)	31.1 (29.1–34.5; 25.4–34.5)	90 (49–123)	128 (101–169)
Inhaled steroid	16/94 (17.0%)	96.5 (60–126; 9–231)	39.4 (35.0–46.5; 26.4–61.1)	21 (5–74)	132 (104–183)
Inhaled bronchodilators	8/94 (8.5%)	124.5 (120–192; 100–231)	45.4 (42.4–56.6; 40.9–61.1)	14 (5–27)	148 (134–209)
Sildenafil	22/94 (23.4%)	–	–	44 (18–132)	–

Data presented as number (%) or median (IQR; ±range). Ages and duration displayed for infants who received intervention only.
BiPAP, bilevel positive airway pressure; CGA, corrected gestational age; CPAP, continuous positive airway pressure; PDA, patent ductus arteriosus.

extremely vulnerable subgroup, at high-risk of death, respiratory and neurodevelopmental morbidity.[6 15] This study describes in detail the demographics, management and clinical outcomes of infants with 'life-threatening' BPD; a group we defined based on assessment at 38 weeks to capture those with the most severe disease.

Table 3 Discharge details and outcomes

Outcomes	Number (%)
Status at 1 year	
Discharged home	76/94 (81)
Died	15/94 (16)
Remained inpatient	1/94 (1.1)
Not known	2/94 (2.1)
Age of discharge home (days)	143 (117–185)
CGA of discharge home (weeks)	46.6 (43–52.9)
Age of death (days)	159 (105–182)
CGA of death (weeks)	49.6 (42.6–52.6)
Respiratory support at discharge	
Air	8/79 (10.1)
Low-flow oxygen	60/79 (75.9)
Long-term ventilation (ventilation, CPAP, high flow)	7/79 (8.9)
Not known	4/79 (5.1)
Comorbidities	
Retinopathy of prematurity requiring treatment	26/94 (27.7)
Laser	20/94 (21.3)
Avastin	3/94 (3.2)
Both	3/94 (3.2)
Periventricular leukomalacia	7/94 (7.4)
Ventriculoperitoneal shunt inserted	5/94 (5.3)
Gastrostomy inserted	7/94 (7.4)
Tracheostomy	5/94 (5.3)
Neurological assessment at 1 year	
Normal	37/60 (61.7)
Minor concerns	10/60 (16.7)
Major concerns	13/60 (21.7)
Death or long-term ventilation (LTV)	22/94 (23.4)
Death or major neurodevelopmental impairment (NDI)	28/75 (37.3)*
Death or major morbidity (LTV, major NDI or readmission for respiratory support within 1st year)	42/94 (44.7)

Data presented as number (%) or median (IQR).
*Outcomes reported for infants with complete data only.
CGA, corrected gestational age; CPAP, continuous positive airway pressure.

There are certain limitations to this study. The well-established BPSU methodology was chosen to provide a collated overview of a condition seen rarely in individual units, with a high level of detail not possible using other methodologies. Compliance with reporting is high, but ascertainment and follow-up limited by clinician's responses. Our study of three questionnaires was designed to maximise data collected but, despite multiple reminders, attrition occurred at each stage, meaning detailed information was provided for 94 of 153 confirmed (or 239 potential) cases. Although a potential source of bias, baseline characteristics of infants with and without additional data were similar, and a detailed description of highly informative cases from 57 different centres is provided. Minimum incidence of life-threatening BPD was calculated using 153 confirmed cases, however true incidence is likely higher due to under-reporting. Finally, as cases were reported at 38 weeks CGA, deaths occurring before this time point or without meeting the case definition were not captured, therefore true BPD-related mortality is higher.

Our minimum annual incidence of life-threatening BPD is 13.9 (95% CI 11.8 to 16.3) per 1000 live births <32 weeks gestation. The associated high mortality, morbidity and significant resource use during a protracted neonatal admission make further study important. Furthermore, incidence is likely to increase as progressively more immature infants are supported from birth, and survival at the lowest gestation increases.[16]

By definition, infants received very prolonged pressure support (median 103 days). Most were ventilated on the first day of life, and it is unclear whether a more proactive approach to non-invasive support from birth would have a positive impact in this cohort.[17] Need for any invasive ventilation at or beyond 38 weeks CGA was significantly associated with death and major morbidity in this cohort (also significant when retrospectively assessed at 36 weeks). This is consistent with Jensen *et al* reporting significantly higher rates of death, serious respiratory and NDI in infants requiring invasive rather than non-invasive support at 36 weeks CGA, and supports the distinct classification of infants requiring invasive ventilation near term as an extremely high-risk subgroup.[6]

Table 4 Comparison of infants with and without outcomes of death, death/major neurodevelopmental impairment (NDI) and death/long-term ventilation (LTV) at 1 year

Association with outcomes on univariate analysis

	Died (n=15)	Alive (n=77)	P value	Death/NDI (n=28)	No death/NDI (n=47)	P value	Death/LTV (n=22)	No death/LTV (n=70)	P value
Gestational age (weeks)	27.0 (24.1–27.7)	26.1 (24.7–28.3)	0.816	26.4 (24.6–27.4)	27.0 (25.1–28.7)	0.179	26.8 (24.3–28.4)	26.1 (25–28.1)	0.826
Birth weight (g)	705 (570–869)	755 (621–930)	0.316	750 (610–892)	775 (604–1048)	0.511	706 (579–874)	775 (611–960)	0.385
Birth weight <10th centile	7 (46.7%)	29 (37.7%)	0.513	10 (35.7%)	22 (46.8%)	0.347	9 (40.9%)	27 (38.6%)	0.845
Male sex	7 (46%)	48 (62%)	0.257	16 (57.1%)	30 (63.8%)	0.565	11 (50%)	44 (62.9%)	0.283
Received antenatal steroids	15 (100%)	68 (88.3%)	0.346	24 (85.7%)	46 (97.9%)	0.061	20 (90.9%)	63 (90%)	1.0
Received postnatal steroids	12 (80%)	43 (55.8%)	0.081	20 (71.4%)	25 (53.2%)	0.119	17 (77.3%)	38 (54.3%)	0.055
Duration postnatal steroids (days)	31 (10–53)	8 (0–27)	0.029	23 (0–54)	0 (0–32)	0.030	29 (8–53)	4 (0–24)	0.009
Age first steroid (days)	23 (7–63)	11 (0–30)	0.081	13 (0–120)	0 (0–27.3)	0.134	18 (2–46)	10 (0–28)	0.093
Starting dose dexamethasone (µg/kg/day)	87.5 (15–142.5)	25 (0–120)	0.093	50 (0–120)	0 (0–120)	0.242	100 (0–150)	0 (0–120)	0.033
Maximum dose dexamethasone (µg/kg/day)	120 (30–120)	0 (0–120)	0.032	60 (0–150)	0 (0–120)	0.095	120 (0–200)	0 (0–120)	0.011
Duration initial ventilation (days)	23 (9–43)	16 (5–34)	0.269	22 (7–42)	11 (3–24)	0.069	24 (6–44)	16 (5–30)	0.213
Duration total ventilation (days)	23 (11–42)	30 (18–54)	0.215	23 (11–42)	34 (18–52)	0.108	24 (11–43)	33 (18–53)	0.145
Any ventilation ≥36 weeks	12 (80%)	24 (31.2%)	<0.001	17 (60.7%)	13 (27.7%)	0.005	15 (68.2%)	21 (30%)	0.001
Any ventilation ≥38 weeks	12 (80%)	18 (23.4%)	<0.001	15 (53.6%)	9 (19.1%)	0.002	14 (63.6%)	16 (22.9%)	<0.001
Any CPAP/BiPAP ≥38 weeks	11 (73.3%)	31 (40.3%)	0.019	15 (53.6%)	20 (42.6%)	0.355	10 (45.5%)	10 (14.3%)	0.052
Any high flow ≥38 weeks	8 (53.3%)	71 (92.2%)	0.001	20 (71.4%)	45 (95.7%)	0.004	14 (63.6%)	28 (40%)	0.002
Received inhaled nitric oxide	7 (46.7%)	23 (29.9%)	0.236	12 (42.9%)	14 (29.8%)	0.25	9 (40.9%)	20 (28.6%)	0.141
Received HFOV	12 (80%)	39 (50.6%)	0.036	17 (60.7%)	26 (55.3%)	0.648	14 (63.6%)	65 (92.9%)	0.061
Pulmonary hypertension*	12 (80%)	18/74 (24.3%)	<0.001	16 (57.1%)	10/46 (21.7%)	0.002	13 (59.1%)	46 (65.7%)	<0.001
Received sildenafil*	10 (66.7%)	12/75 (16%)	<0.001	11 (39.3%)	8/46 (17.4%)	0.037	14 (63.6%)	8/68 (11.8%)	<0.001

Association with outcomes on binomial logistic regression analysis

	Death aOR (95% CI)	P value	Death/NDI aOR (95% CI)	P value	Death/LTV aOR (95% CI)	P value
Gestational age (weeks)	1.42 (0.85 to 2.37)	0.183	0.96 (0.66 to 1.42)	0.849	1.33 (0.87 to 2.05)	0.188
Birth weight (g)	1.0 (0.99 to 1.00)	0.439	1.00 (1.0 to 1.0)	0.183	1.00 (1.0 to 1.0)	0.758
Male sex	0.40 (0.09 to 1.87)	0.242	0.70 (0.20 to 2.38)	0.562	0.40 (0.11 to 1.43)	0.159
Received antenatal steroids	–	–	0.02 (0.001 to 0.40)	0.010	0.71 (0.11 to 4.68)	0.721
Received postnatal steroids	3.42 (0.55 to 21.16)	0.186	4.33 (0.96 to 19.52)	0.057	2.91 (0.66 to 12.78)	0.158
Any ventilation ≥38 weeks	10.95 (1.97 to 60.79)	0.006	5.73 (1.45 to 22.70)	0.013	5.95 (1.51 to 23.46)	0.011
Received HFOV	2.52 (0.42 to 15.03)	0.309	0.47 (1.22 to 1.81)	0.273	1.33 (0.34 to 5.15)	0.681
Pulmonary hypertension	6.88 (1.47 to 32.28)	0.015	3.71 (1.001 to 13.72)	0.049	5.58 (1.61 to 19.40)	0.007

Results of univariate analysis reported as number (%) or median (IQR); results of regression analysis reported as aOR (95% CI).
*Reported for infants with complete data only.
aOR, adjusted OR; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; HFOV, high-frequency oscillatory ventilation.

HFOV was common (56.4%) and associated with increased risk of death, presumably reflecting use as 'rescue' therapy. Similarly, inhaled nitric oxide use was higher than the general preterm population (31.9% vs 16.6%), indicating severe respiratory disease, and knowledge of such associations with poorer outcomes may facilitate risk stratification for future treatment intervention studies.[18]

Although most infants received both CPAP and high flow (97% and 92%, respectively), high flow was generally started later and continued for a significantly longer duration. A number of retrospective studies have reported increased BPD, longer respiratory support and hospitalisation since introduction of high flow, although this is not universal.[19–21] Randomising infants with evolving BPD to weaning via CPAP only or CPAP and high flow to explore this relationship further would be helpful.

Postnatal dexamethasone reduces BPD, but optimal timing, dosing and duration of postnatal steroids to prevent and treat BPD are unknown.[22 23] Only 61% of infants received any postnatal steroid, despite the severity of their BPD, and significant variability in use demonstrated. Treatment commenced at an average age of 26 days, but recent retrospective studies suggest benefit from earlier treatment in the second postnatal week.[24] Risk stratification and prospective assessment of the optimal steroid regimes both to prevent BPD in high-risk infants and to treat established BPD should be a priority.

Diuretics were widely used (87%) despite no convincing evidence for long-term respiratory benefit and frequent side-effects.[25 26] Inhaled steroids and bronchodilators were used uncommonly (17% and 8.5%, respectively) and later in the inpatient course, likely reflecting a shift to treatment of established BPD. Neither have proven efficacy in prevention or treatment of BPD but evidence is scarce, and further work to clarify the role of these medications is needed.[27–29]

Nosocomial infections are implicated in the pathogenesis of BPD, and colonisation with *Ureaplasma* spp specifically associated with >2-fold risk of BPD on meta-analysis.[30] *Ureaplasma* was only isolated in one infant, but screening for atypical organisms, and conditions such as cytomegalovirus were not surveyed; an area for potential development addressed by the ongoing AZTEC Study (ISRCTN11650227).

Abnormalities of pulmonary vascular structure and function are common in BPD, with a subset of infants developing

clinical PHT proportional to BPD severity.[31 32] In our cohort, 34% had confirmed PHT, however screening rates were not surveyed, so this may be an underestimation. Recognised PHT was significantly associated with death, major NDI and/or long-term ventilation, highlighting this as an important prognostic factor potentially amenable to treatment.[33] Retrospective studies have associated sildenafil use with haemodynamic improvement and reduced mortality, although efficacy data are limited, and prospective studies to establish optimal PHT screening and treatment regimens required.[33 34]

By 1 year of age, 16% infants died, however this cohort did not include BPD-related deaths before 38 weeks, so overall mortality is higher. Ultimately, 81% infants were discharge home at a median 46.6 weeks CGA. While most were weaned to low-flow oxygen, 9% required long-term ventilation and major NDI was evident at 1 year in one of five survivors; significantly higher than the general preterm population.[35] The associated substantial ongoing healthcare resource use and impact on families make this condition a priority for future investment.

CONCLUSIONS

Life-threatening BPD occurred in 13.9 per 1000 infants born at <32 weeks gestation during the study period, with death or major morbidity in 45% of affected infants. There is little evidence to guide management of severe BPD, and we demonstrate significant variation in practice. Optimisation of non-invasive respiratory support, targeted postnatal corticosteroid use and universal screening for PHT are recommended priority actions. We have identified an extremely high-risk subgroup not discernible using current definitions of BPD, and better identification, possibly through a dedicated register, and research focus on this group of infants is urgently needed.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Approved by the North East Tyne and Wear South Research Ethics Committee (reference 16/NE/0343). Permission to access data obtained from the Health Research Authority via Section 251 Confidentiality Advisory Group, and the Public Benefit and Privacy Panel for Health and Social Care in Scotland.

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Appendix E: OEP participant information sheets, parent information sheet and consent form

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

RESEARCH STUDY INFORMATION SHEET FOR PARTICIPANTS (< 12 YEARS)

Hello,

We are doing a project looking at lung health and exercise in young people. We would like to invite you to take part.

This leaflet tells you what the project is about and what we are asking you to do to help us.

Please read this leaflet carefully then:

- **Talk** to your mum, dad or the person that looks after you about it
- **Ask us** if you have any questions

Thank you!

THE great north CHILDREN'S HOSPITAL

Who are we?

We are doctors that look after babies and children with lung problems.

What is this about?

Some babies are born earlier than expected.

We are doing this to see how their lungs work when they are older.

We want to see if this is different to children born at the correct time.

Why have I been invited?

You have been invited as you are 8-11 years old, and were early.

We need children born children born early and children born at the correct time to take part so we can compare results.

Do I have to take part?

No. It is up to you and your family to decide if you would like to take part.

What will happen if I take part?

We will do some exercises to look at how your lungs are working. Your parent will be with you during the study.

Visit 1

The first visit is to the children's hospital.

We will talk to you and your parent about your health. We will record this if you are happy.

We will then do some exercises to see how your lungs are working. We will ask you to breathe in and out, and blow into a tube.

Visit 2

The second visit is to a sports centre. We will look at your breathing whilst you cycle on an exercise bike.

We will put some stickers on your chest and back. There will be cameras around the bike that detect movement of the stickers. The cameras don't film you, they just detect the stickers!

We will ask you to cycle for about 10 minutes but you can stop anytime.

What is good about taking part?

You will learn about how your lungs are working, and what happens when you exercise.

What is bad about taking part?

You will need to visit us for a few hours.

You will be given an inhaler. This is very safe but can make you feel a bit shaky. This goes away very quickly.

What happens with the results?

All your information is private, so no one else will know your results.

At the end of the study we will combine the results from everyone that took part. We will use this to teach other doctors about how children's lungs work.

Thank you for reading!

Contact: Dr Rebecca Naples
Email: rebecca.naples@nhs.net
Phone: 0191 2139898

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

RESEARCH STUDY INFORMATION SHEET FOR PARTICIPANTS (≥ 12 YEARS)

Hello,

We would like to invite you to take part in a research study. The study is investigating lung health and exercise in young people born prematurely.

We need young people born prematurely and people born at the correct time to take part.

This leaflet tells you what the project is about and what we are asking you to do to help us.

Please read this leaflet carefully then:

- **Talk** to your parents about it
- **Ask us** if you have any questions

Thank you!

THE great north CHILDREN'S HOSPITAL

Who are we?

We are doctors that look after newborn babies and older children with lung problems.

Why are we doing this study?

Some babies are born earlier than expected. These babies are premature.

Premature babies are born before their lungs are fully developed. They often need extra care and help with breathing when they are born.

We have set up this study to learn more about lung health in older children and young people who were born prematurely.

When you exercise, your lungs have to work harder to provide oxygen to your body, so exercise is a good way to assess lung function.

Why have I been invited?

You have been invited as you are 12-16 years old, and were born prematurely.

We are also inviting people of the same age who were at the correct time as a comparison group.

Do I have to take part?

No. While we would be very grateful for your help in this research, it is entirely up to you and your family whether you take part.

What will happen if I take part?

We will ask you to attend two sessions with us.

Visit 1

This will be to the children's hospital. We will ask you to complete a questionnaire then discuss your respiratory health and exercise. We will make an audio recording of this discussion with your consent.

We will then do a basic assessment of your lung function. This will mainly involve breathing in and out and blowing into a mouthpiece. You will also be given 2 puffs of an inhaler to see if there is any increase in the amount of air you breathe out.

Visit 2

This will be to the sports centre at Northumbria University.

We will monitor your breathing whilst cycling on an exercise bike using small reflective stickers on your chest, back and abdomen. Cameras around the bike track the movement of the stickers, telling us about your breathing. You will not be filmed, as the cameras only detect the reflective markers!

You will cycle for around 10 minutes but can stop at any time.

During the test you will need to take the clothing off the top half of your body so we can apply the stickers (girls can keep a sports bra or crop top on). This will be in a private area, and supervised by a member of the research team of the same sex. Your parent will also be present if you wish.

What are the possible benefits of being involved?

You will learn about your lung function and how this changes with exercise.

What are the possible disadvantages of being involved?

We will require a few hours of your time to visit the study centres.

You will be given 2 puffs of a salbutamol inhaler during the test. This is very safe but occasionally makes people feel shaky or causes an increase in heart rate. These side effects quickly go away and you will be closely monitored throughout the test.

What will happen with my information?

Your information is private, so your details and results will not be shared with anyone. When the study is finished we will combine the results from everyone in the study to help other doctors looking after children born prematurely.

We can give you a summary of the results of the study when it is finished. Please email Rebecca Naples if you would like this.

Thank you for reading this leaflet!

Please take time to decide if you would like to take part, and get in touch if you have any questions.

Contact: Dr Rebecca Naples
Email: rebecca.naples@nhs.net
Phone: 0191 2139898

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

Royal Victoria Infirmary
Queen Victoria Road
Newcastle upon Tyne
NE1 4LP

Tel: 0191 233 6161

PARENT/GUARDIAN RESEARCH STUDY INFORMATION SHEET

Study Title: Lung Function and Exercise Response Measured By Optoelectronic Plethysmography (OEP) in School-Age Children Born Preterm

We are doing a research study investigating lung function and respiratory health in children born prematurely, and would like to invite your child to take part.

The study will involve a review of your child's lung function, a discussion about their respiratory health, and an assessment their breathing during exercise. This will provide us with more information about long-term lung health in premature children.

Please take time to read this information sheet, and do not hesitate to get in touch with us if you have any questions or would like any more information.

Questions answered in this information sheet: **Page**

Who are we?

We are a group of clinicians and researchers based in the neonatal unit at the Royal Victoria Infirmary (RVI) and the children's respiratory department at the Great North Children's Hospital (GNCH) in Newcastle upon Tyne. We look after newborn infants and older children with lung problems.

Why are we doing this study?

Preterm babies are born before their lungs are fully developed, and often need breathing support after delivery. Some will develop a condition called bronchopulmonary dysplasia (also known as chronic lung disease) in which they need oxygen for weeks or months, and can have long-term lung problems.

When you exercise, your lungs have to work harder to provide oxygen to your body, therefore exercise tests are a good way to assess lung function. We know children born prematurely have different breathing patterns and respond differently to exercise compared to children born at full term. Improving our knowledge of this may give us a better understanding of preterm lung disease, and allow us to provide better treatment.

Why have I been invited?

We are inviting children age 8-16 years old that were born very preterm (less than 32 weeks) to take part in our study. We are also inviting children of the same age who were born at full term (37 weeks or more) for comparison.

Does my child have to take part?

No. While we would be very grateful for your help in this research, participation is entirely voluntary. If you do decide to take part we will ask you to sign a consent form, but you are free to withdraw from the study at any time. This will not affect any future medical care you or your child receives.

What will happen if my child takes part?

If you and your child agree to take part you will be required to attend two sessions with us.

Visit 1
The first visit will be to the respiratory department at the Great North Children's Hospital in Newcastle for lung function testing.

We will first ask you to complete a brief questionnaire and discuss your child's respiratory health and activity levels. We will make an audio recording of this discussion with your consent. We will then do a range of standard tests to assess your child's lung function. This will include:

- Spirometry – This is a simple test where we ask your child to blow out as fast as they can into a mouthpiece that measures how much air they breathe out.

- Plethysmography – This involves sitting in a booth like a telephone box and breathing into a mouthpiece to measure lung volumes.

- Reversibility testing - We will give your child 2 puffs of a salbutamol inhaler and repeat some of the tests to see if there is any increase in the amount of air they can breathe out. This is commonly done to diagnose asthma in children.

More information about spirometry and reversibility testing is available on the British Lung Foundation website (https://www.blf.org.uk/support-for-you/breathing-tests).

Visit 2
The second visit will be to Sport Central at Northumbria University where we will complete the exercise test. This is on a bike and last about 10 minutes.

Your child will be asked to remove the clothing from the top half of their body (girls can keep a sports bra or crop top on) and we apply a number of small reflective marker stickers to their chest and abdomen. Several cameras placed around the bike track the movement of the marker stickers during exercise so we can monitor breathing patterns and calculate lung volumes. This is in a private area, and supervised by a member of the research team of the same sex. Your child will not be filmed during the test as the cameras only detect the movement of the reflective markers.

After the exercise test, the spirometry test will be repeated to see if there is any change in the amount of air they can blow out. If there is a significant reduction this can be a sign of airway narrowing with exercise. Some children with this will benefit from a salbutamol inhaler to take before exercise.

What are the possible benefits and risks of being involved?

If you take part in this research, you will be offered information about your child's lung function. If any significant abnormality is found you will be offered follow-up in a paediatric respiratory clinic, and we will inform your GP.

We will require you and your child to attend the respiratory department at the Great North Children's Hospital, and Sport Central on the Northumbria University Campus in Newcastle city centre on separate occasions (this can be morning and afternoon, or different days). We expect each visit to last 1 ½ - 2 hours. Parking facilities will be available and we can reimburse you for travel expenses.

Your child will be given a salbutamol inhaler during the test. This is very commonly used in paediatric respiratory medicine, and is very safe. Side effects are rare, but can include feeling shaky or an increase in heart rate. These side effects quickly go away and your child will be closely monitored throughout. A paediatric doctor will be present at all times.

Will information about my child be kept confidential?

Yes. We will ensure that all information about you and your child is kept secure and confidential.

<u>Data Management Statement</u>
The Newcastle upon Tyne Hospitals NHS Foundation Trust is the sponsor for this study. We will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for

looking after your information and using it properly. We will keep identifiable information about you for 5 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

Individuals from The Newcastle upon Tyne Hospitals NHS Foundation Trust and regulatory organisations may look at your medical and research records to check the accuracy of the research study. You can find out more about how we use your information by contacting nuth.dpo@nhs.net

Interviews will be recorded on a cassette tape using a Dictaphone then transcribed. Recordings will only be listened to by the person transcribing the interview, and regulatory authorities to ensure accuracy of the study if required. Recordings will be stored securely in a locked cabinet then erased.

What will happen to the results?

All medical information and study results are highly confidential and no information that identifies you or your child will be shared. At the end of the study the results will be analysed and published in a medical journal to share with other health professionals looking after preterm children. This will also be submitted as a study report (thesis) to Newcastle University as part of a higher educational degree.

If you and your child are interested, we can give you a summary of the results of the study when it is finished. Please email Rebecca Naples (details below) if you would like to receive this.

Who has organised and funded the study?

The study is being organised by members of the neonatal and paediatric respiratory teams at the RVI and GNCH in Newcastle. We will be using the OEP system belonging to Northumbria University who are also helping us with this study. The Newcastle upon Tyne Hospitals NHS Foundation Trust are overseeing and providing indemnity arrangements for the study.

Who has reviewed the study?

All healthcare research must be approved by an NHS Research Ethics Committee before it goes ahead. The ethics committee ensures that the study is safe, the expected benefits outweigh the potential risks, your rights will be respected, and that you have been given sufficient information before taking part. This study has been approved by the North East (York) Research Ethics Committee.

What if I have any problems with the study?

If you have any concerns about the study or the way the study has been carried out, you can contact any member of the research team who will do their best to answer your questions (contact details below).

If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from your hospital. In addition, the local Patient and Liaison Service (PALS) can provide very useful information if you have any concerns. The PALS website www.pals.nhs.uk will provide you with up to date details, or you can contact The Patient Advice and Liaison Service, New Victoria Wing, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP; 0800 032 0202.

What happens now?

If you would like to take part in this study, have any questions or would like any more information please get in touch by email or phone using the details below.

A member of the research team will give you a call in a few days to discuss your thoughts and answer any questions you may have. Once you have read this leaflet and discussed with study with a member of the research team we will give you some time to think about whether you would like to take part.

Thank you for taking the time to read this information.

If you have any questions or would like to discuss any aspect of the study, please do not hesitate to contact us using the details below.

Contacts

Main contact:

Dr Rebecca Naples
Neonatal Research Fellow
Royal Victoria Infirmary
Newcastle upon Tyne

Email: rebecca.naples@nhs.net

Phone: 0191 2139898

Team Members:

Dr Christopher O'Brien – Consultant in Paediatric Respiratory Medicine, GNCH
Dr Malcolm Brodlie - Consultant in Paediatric Respiratory Medicine, GNCH
Dr Alan Fenton – Consultant Neonatologist, RVI
Dr Sundeep Harigopal – Consultant Neonatologist, RVI

Newcastle Neonatal Service
Royal Victoria Infirmary
Newcastle upon Tyne
NE1 4LP
Tel: 0191 2336161

RESEARCH STUDY PARENTAL CONSENT FORM

Study Title: Lung Function and Exercise Response Measured By Optoelectronic Plethysmography in School-Age Children Born Preterm

Study Sites: Great North Children's Hospital, Newcastle upon Tyne
Department of Sport, Exercise and Rehabilitation, Northumbria University

Researchers: Dr R Naples, Dr M Brodlie, Dr A Fenton, Dr S Harigopal, Dr C O'Brien, Prof I Vogiatzis.

IRAS project ID: 249128

Participant ID:

Please read the following carefully, and initial the box if you agree to the following statements.

Please Initial

1. I confirm that I have read the information sheet dated 11/1/19 (version1.1) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that participation is voluntary and that I am free to withdraw my child at any time without giving any reason, without his/her medical care or legal rights being affected. ☐

3. I understand that relevant sections of my child's medical notes and data collected during the study, may be accessed by individuals within the research team, regulatory authorities or the NHS Trust, where it is relevant to him/her taking part in this research. I give permission for these individuals to have access to my child's records. ☐

4. I understand that the information collected about my child will be used to support other research in the future, and may be shared anonymously with other researchers. ☐

5. I agree to my child's General Practitioner being informed of participation in the study. ☐

6. I agree to participate in a structured interview, and am aware this will be recorded using a Dictaphone. ☐

7. I agree to my child participating in this study ☐

Name of Child		
Name of Parent/Guardian	Signature	Date
Name of Person Taking Consent	Signature	Date

Appendix F: Publications, presentations and prizes resulting from this thesis

Publications

Naples, R., Fenton, A., Brodlie, M., Harigopal, S. & O'Brien, C. (2022) Diaphragm electrical activity during weaning of nasal high-flow therapy in preterm infants*. Archives of Disease in Childhood: Fetal and Neonatal Edition*. Published online ahead of print. doi:10.1136/archdischild-2022-324112

Naples, R. & Harigopal, S. (2022) Nasal high flow in extremely preterm infants: Current evidence and practice in the United Kingdom. *Acta Paediatrica*. 111 302–304

Naples, R., Ramaiah, S., Rankin, J., Berrington, J. & Harigopal, S. (2022) Life-threatening bronchopulmonary dysplasia: a British Paediatric Surveillance Unit study. *Archives of Disease in Childhood: Fetal and Neonatal Edition.* 107 13-19

Prizes

Young Investigators Award (First Prize) at International Congress Paediatric Pulmonology 2021 for presentation of 'Use of optoelectronic plethysmography to assess the ventilatory response to exercise in school-aged children born preterm'

Oral Presentations

'Use of optoelectronic plethysmography to assess the ventilatory response to exercise in school-aged children born preterm' International Congress Paediatric Pulmonology 2021.

'Life-threatening bronchopulmonary dysplasia' Northern Neonatal Network Research Conference 2021.

'Use of optoelectronic plethysmography to assess the ventilatory response to exercise in school-aged children with bronchopulmonary dysplasia' European Academy of Paediatric Societies Conference 2020.

Published Abstracts and Poster Presentations

‘Diaphragm electrical activity during weaning of nasal high flow therapy in preterm infants’ European Academy of Paediatric Societies Conference 2022 and British Association of Perinatal Medicine Conference 2022.

‘Nasal high flow use in the United Kingdom: current evidence and practice’ Joint European Neonatal Societies Conference 2021

‘Weaning high flow nasal cannula therapy on the neonatal unit: clinical predictors of success’ Joint European Neonatal Societies conference 2019

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