Optimisation of Neonatal Ventilation

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Optimisation of Neonatal Ventilation
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Abstract

Background: Survival of neonates requiring respiratory support has improved over the last two decades, but unfortunately many suffer morbidity from ventilator related complications.

Aim: To undertake a series of studies using physiological measurements as outcomes in infants with evolving or established bronchopulmonary dysplasia (BPD) to test the following hypotheses and carry out a national survey.

Hypotheses: Proportional assist ventilation (PAV) compared to assist control ventilation (ACV) would improve oxygenation as assessed by the oxygenation index (OI). Neurally adjusted ventilatory assist (NAVA) compared to ACV would improve oxygenation. Use of heated, humidified, high flow nasal cannula (HHFNC) would not have increased given the results of recent randomised trials. Continuous positive airway pressure (CPAP) would reduce the work of breathing (WOB) and thoraco-abdominal asynchrony (TAA) and improve oxygen saturation (SaO_2) compared to HHFNC.

Methods: Four studies were undertaken. The OI was calculated from measurement of blood gases and the level of respiratory support. A survey was undertaken of lead practitioners in all UK neonatal units. The WOB was assessed by measurement of the pressure time product of the diaphragm (PTPdi) and TAA using respiratory inductance plethysmography (RIP).

Results: The OI was lower on PAV compared to ACV ($p = 0.012$) and on NAVA compared to ACV ($p=0.0007$). The survey demonstrated HHFNC was used in 56% of units in 2012 and 87% in 2015 ($p=<0.001$). There were no significant differences in the WOB, TAA or SaO_2 on CPAP versus HHFNC.

Conclusions: PAV and NAVA may be beneficial in infants with evolving or established BPD. Use of HHFNC has significantly increased in UK neonatal units. In infants with evolving or established BPD, CPAP compared to HHFNC offered no significant advantage and in infants who required respiratory support beyond 34 weeks post menstrual age (PMA).

Declaration

The statistical analysis for the RCT described in Chapters 3 and 4 was carried out by Professor Janet Peacock; I thank her for her assistance in this regard. Dr Katie Hunt provided assistance with measurement of three of the nine patients in Chapter 4 and helped with administration of the electronic survey described in Chapter 5. Dr Adesh Sunderesan provided assistance with some of the telephone calls in the survey described in Chapter 5. Otherwise, all the work described in this thesis is my own.

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Publications from this thesis (Appendix A3)

Proportional assist versus assist control ventilation

S Shetty, P Bhat, A Hickey, JL Peacock, AD Milner, A Greenough - Eur J Pediatr (2016) 175:57–61.

Crossover study of assist control ventilation and neutrally adjusted ventilatory assist

S Shetty, K Hunt, J Peacock, K Ali, A Greenough - Eur J Pediatr (2017)176:509-513.

Neurally adjusted ventilatory assist compared to other forms of triggered ventilation for neonatal respiratory support.

Rossor TE, Hunt KA, **Shetty S**, Greenough A - Cochrane Database of Systematic Reviews 2017, Issue 10.

Changes in use of heated humidified high flow nasal cannula oxygen (HHFNC)

S Shetty, Sundaresan A, Hunt K, Desai P, A Greenough - Arch Dis Child Fetal Neonatal Ed 2016; 101:F371-F372.

Work of breathing during CPAP and heated humidified high flow nasal cannula

S Shetty, A Hickey, GF Rafferty, JL Peacock, A Greenough - Arch Dis Child Fetal Neonatal Ed 2016; 101:F404–F407.

Neonatal ventilation strategies and long-term respiratory outcomes

S Shetty, A Greenough. Early Hum Dev. 2014; 90(11):735-9.

Review finds insufficient evidence to support the routine use of heated, humidified high-flow nasal cannula use in neonates.

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Abbreviations used in this thesis

AC	Assist Control
ACV	Assist Control Ventilation
B/min	Beats per minute
BAL	Broncho alveolar Lavage
BAPM	British Association of Perinatal Medicine
BIPAP	Bi-level nasal CPAP
BOOST	Benefits of Oxygen Saturation Trials
BPD	Bronchopulmonary Dysplasia
BW	Birth Weight
CAP	Caffeine for Apnoea of Prematurity
Cdyn	Dynamic Compliance
CGA	Corrected Gestational Age
CI	Confidence Interval
CLD	Chronic Lung Disease
CMV	Continous Mandatory Ventilation
COT	Canadian Oxygen Trial
CP	Cerebral Palsy
CPAP	Continuous Positive Airway Pressure
CPS	Canadian Paediatric Society
Edi	Diaphragm Electrical Activity
EELV	End-Expiratory Lung Volumes
ELBW	Extremely Low Birth Weight
ELGAN	Extremely Low Gestational Age New born
ETT	Endotracheal Tube
FEV1	Forced expiratory volume in one second

FiO_2	Fraction of inspired oxygen
FRC	Functional Residual Capacity
FVC	Forced Vital Capacity
g	grams
GA	Gestational Age
GWAS	Genome wide association studies
H2O	Water
HFOV	High Frequency Oscillatory Ventilation
HFV	High Frequency Ventilation
HHFNC	Heated, Humidified, High Flow Nasal Cannula
HR	Heart rate
Hz	Hertz
i.e.	id est (that is)
ICAM-1	Intercellular Adhesion Molecule-1
IL	Interleukin
IVH	Intraventricular Haemorrhage
Kfc	Capillary Filtration Coefficient
Kg	Kilogram
L	Litre
LOS	Length of Hospital Stay
MAP	Mean Airway Pressure
MD	Mean Difference
μV	Microvolt
min	minute
mls	Millilitres
MV	Mechanical Ventilation

NAVA	Neurally Adjusted Ventilatory Assist
nCPAP	nasal CPAP
NEC	Necrotising Enterocolitis
NHLBI	National Heart, Lung, and Blood Institute
NICHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
NIPPV	Non-invasive positive pressure ventilation
NIV	Non-invasive ventilation
NIV-NAVA	Non-invasive Neurally Adjusted Ventilator Assist
NNAP	National Neonatal Audit Programme
OI	Oxygenation Index
OR	Odds Ratio
ORD	Office of Rare Diseases
PAH	Pulmonary Arterial Hypertension
PAV	Proportional Assist Ventilation
PDA	Patent Ductus Arteriosus
Pdi	Trans-diaphragmatic pressure
PEEP	Positive End-Expiratory Pressure
Pes	Oesophageal Pressure
PFT's	Pulmonary Function Tests
Pgas	Gastric pressure
pH	Power of Hydrogen
PH	Pulmonary Hypertension
Pinf	Inflection Point
PIP	Peak Inflation Pressure

PLV	Pressure-limited ventilation
PMA	Postmenstrual age
PNA	Postnatal age
PS	Pressure Support
PSV	Pressure Support Ventilation
PTP	Pressure Time Product
PTPdi	Trans-diaphragmatic Pressure-Time Product
PTV	Patient triggered ventilation
PVL	Periventricular Leukomalacia
RCT	Randomised Controlled Trial
RDS	Respiratory Distress Syndrome
RIP	Respiratory Inductive Plethysmography
ROP	Retinopathy of prematurity
RR	Relative Risk
RR	Respiratory rate
RV	Residual Volume
SaO_2	Oxygen Saturation
SD	Standard Deviation
SIMV	Synchronised Intermittent Mandatory Ventilation
SIV	Synchronised Intermittent Ventilation
SNP	Single Nucleotide Polymorphisms
SUPPORT	Surfactant, Positive Pressure and Oxygenation Randomisation Trial
TAA	Thoraco-Abdominal Asynchrony
TIPP	Trial of Indomethacin Prophylaxis in Preterm
TLC	Total Lung Capacity

Chapter 1: Introduction

Introduction

1.1 Background

1.1.1 Historical perspective

In the mid-sixteenth century the anatomist and physician, Andreas Vesalius, applied positive pressure ventilation to keep the lungs inflated during dissection of the thorax (Vesalius, 1543). It had become evident to the anatomist that it was only necessary now and then to blow a little air into the lung of an animal with an opened thorax to keep it alive for some time. Robert Hooke went on to describe (Davis, 1665), the prolonged preservation of life in an open-chested dog by artificial ventilation. He showed that a dog could be allowed to 'die' and be revived repeatedly by continually inflating the lungs with bellows attached to the trachea.

In 1889, Alexander Graham Bell designed and built a body-type respirator for use in new born infants (Stern et al., 1970), but this was met with little enthusiasm and the apparatus was probably never used. The tank-type respirator designed by Drinker in 1929 was used successfully in twenty-one of thirty-five new born infants for resuscitation of asphyxia at birth by Murphy and his colleagues in 1931(Shaw et al., 1931). Most of the unsuccessful attempts were in premature babies. In 1950 Alan Bloxsom invented the Bloxsom air-lock for new born resuscitation in which the infant was enclosed and the box filled with oxygen. The pressure inside was slowly cycled (Bloxsom, 1950). There followed 60 years of experimental work with individuals designing their own home-made apparatus to assist in the artificial ventilation of new born infants. Examples include the work of Ian Donald and his collaborators. In a series of articles (Donald and Lord, 1953, Donald, 1954), they described early models of the servo-controlled respirator, designed to augment the ventilation of new born infants both acutely and over a period of time (Donald and Lord, 1953, Donald, 1954). During this era poliomyelitis was epidemic, and the resultant respiratory muscle weakness and bulbar respiratory failure was often successfully treated with tank-type negative pressure ventilators of the Drinker design or by manually delivered continuous positive pressure through an endotracheal tube or tracheostomy. Many polio patients were weaned to a negative pressure chest cuirass or to a foot-tilt rocking bed as they improved (Lassen, 1953). By 1957, Professor Donald reported treatment of 151 new born infants with his successive respirator models, and 50 survived, "A large number of which were under three pounds, and even under two pounds” (Donald et al., 1958).

It was not until 1971 that Gregory (Gregory et al., 1971), an anaesthesiologist, developed a method of delivering constant distending airway pressure to the new born lung through an endotracheal tube. This system had the possibility of maintaining open terminal airways at end expiration, thereby avoiding atelectasis when surfactant was deficient and maximising ventilation-to-perfusion ratios. The risks of prolonged use of high inspired oxygen concentrations and high peak airway pressures were thereby often averted. This concept was added to both positive and negative ventilator use, and was further modified by Bancalari who designed a constant distending negative pressure chest cuirass (Bancalari et al., 1973) and by Kattwinkle who developed nasal prongs to avoid the use of an endotracheal tube when a ventilator was not needed (Kattwinkel et al., 1973). Ventilators have now been successively modified and designed to support even in very prematurely born infants.

1.2 Bronchopulmonary dysplasia (BPD)

1.2.1 Introduction

Recent estimates of preterm birth rates (all live births before 37 completed weeks) for 184 countries in 2010 and a time series for 65 countries with sufficient data suggest that 14.9 million (uncertainty range: 12.3 - 18.1 million) babies were born preterm in 2010 (Blencowe et al., 2012). Bronchopulmonary dysplasia (BPD) is a chronic lung disease (CLD) that most commonly occurs in premature infants who have needed mechanical ventilation (MV) and oxygen therapy for acute respiratory distress (Northway et al., 1967, Jobe and Bancalari, 2001, Bancalari et al., 1979), but can also occur in immature infants who have had few signs of initial lung disease (Jobe, 2011). The clinical, radiological, and pathological features of BPD were first described more than five decades ago (Northway et al., 1967). BPD was then seen in moderately prematurely born infants with severe respiratory distress syndrome who had been treated with high inspired oxygen concentrations (Northway et al., 1967). Despite advances in the prevention and management of respiratory distress syndrome (RDS) (including the widespread use of antenatal steroids and surfactant treatment), BPD is the most common adverse outcome of extreme prematurity and hence the prime focus in my thesis involving preterm infants only.

1.2.2 Prevalence of BPD

BPD in the United States occurs in 10,000 to 15,000 infants annually, including approximately 50% of infants with birth weight less than 1000 g (Stoll et al., 2010, Martin et al., 2013). The Israeli Neonatal Network reported outcomes for all very low birth weight infants (VLBW; birth weight < 1500 g) born in Israel between 2000 and 2010 who survived to 36 weeks PMA (n =12,139) (Klinger et al., 2013). Based on the need for supplemental oxygen at 36 weeks PMA, 13.7% of VLBW and 31% of Extremely low birth weight (ELBW) infants met the diagnostic criteria (Klinger et al., 2013). In the Canadian and Japanese Neonatal Networks, rates of BPD by NICHD criteria for surviving VLBW infants were 12.3% and 14.6% between 2006 and 2008 respectively (Isayama et al., 2012).

In the Vermont Oxford Network (VON), yearly rates of BPD for VLBW infants ranged from 26.2% to 30.4% between 2000 and 2009 (n=305,770) (Horbar et al., 2012). In ten European regions, rates of BPD ranged between 10.5% and 21.5% for infants born less than 32 weeks gestation in 2003 (Zeitlin et al., 2008). While some reports indicate BPD rates are beginning to decline, the majority of studies suggest that rates remained stable or are even increasing, possibly due to increased survival of the highest risk infants (Smith et al., 2005, Fanaroff et al., 2007, Stoll et al., 2010, Stroustrup and Trasande, 2010, Botet et al., 2012, Horbar et al., 2012). Results of the EPICure study indicated no change in rates of BPD between 1995 and 2006 for infants born between 22 and 26 weeks gestation (Costeloe et al., 2012). Hence, this is an important group to study to see if newer strategies have indeed made a difference.

1.2.3 Pathogenesis of BPD

BPD, as it was initially described by Northway in the 1960s, was based on clinical and radiographic evidence of pulmonary disease in moderately to late premature infants with a history of RDS prior to utilisation of surfactant-replacement therapy (Northway et al., 1967). Radiography of these infants showed areas of heterogeneity throughout the lung fields and coarse scattered opacities in the most severely affected of infants (Bancalari and Gerhardt, 1986). Classic BPD was characterised by lung inflammation, airway injury secondary to interstitial and alveolar fluid overload, lung parenchyma fibrosis due to hyperinflation and the development of small airways disease, smooth-muscle hypertrophy, and oxidative stress (Baraldi and Filippone, 2007, Cerny et al., 2008). High ventilator pressures and inspired oxygen levels in addition to lack of antenatal steroids and postnatal surfactant, were largely responsible for the development of classic BPD (Figure1-1).

There is now growing recognition that infants with BPD after premature birth have a different clinical course and pathology than had been recorded before surfactant was used (Charafeddine et al., 1999, Rojas et al., 1995). The classic progressive stages with prominent fibroproliferation that first characterised BPD are generally less striking now and the disease is now predominantly defined by a disruption of distal lung growth, and has been termed the “new BPD”(Jobe, 1999) (Figure1-1). Unlike the original form of the disease, this “new” form often develops in preterm newborns who may have needed little or no ventilatory support, and have had low inspired oxygen concentrations during the early postnatal days (Charafeddine et al., 1999, Rojas et al., 1995). Animal studies suggest that the histology of “new” BPD shows more diffuse disease, fewer areas of hyperinflation, a reduction in alveoli and capillaries, but little fibrosis (Coalson et al., 1995, Jobe, 1999). At autopsy, the lung histology of these infants with the new form has regions of more uniform and milder injury, but impaired alveolar and vascular growth remain prominent (Coalson, 2006) (Figure1-1). The chest radiograph appearance of new BPD, that is small volume, hazy lung fields, is very different from the cystic abnormalities and interstitial fibrosis seen in “old” BPD. As a consequence, lung function abnormalities are likely to differ according to whether an infant is developing old or new BPD.

Although the pathogenesis of the ‘new BPD’ remains unclear, much evidence suggests that this form of chronic respiratory failure reflects abnormal growth and repair of the immature lung exposed to the continuous stress of repetitive inflation with oxygen rich gas in a setting of chronic inflammation, often aggravated by recurrent infection (Pierce and Bancalari, 1995, Zimmerman, 1995). Studies have shown an increase in the number of neutrophils, macrophages and neutrophil-derived elastase activity in liquid suctioned from the airways of infants with acute RDS who later acquire BPD (Ferreira et al., 2000). Studies have also showed that elastase inhibitory capacity and 1-protease inhibitor activity are reduced, as is secretory leukocyte protease inhibitor (Watterberg et al., 1994), in infants with evolving BPD compared to infants without BPD. The reported association of maternal chorioamnionitis and early lung inflammation in infants with subsequent BPD (Watterberg et al., 1996) led to the notion that BPD sometimes may have a prenatal inflammatory origin (Yoon et al., 1997, Gomez et al., 1998, Jobe, 1999).

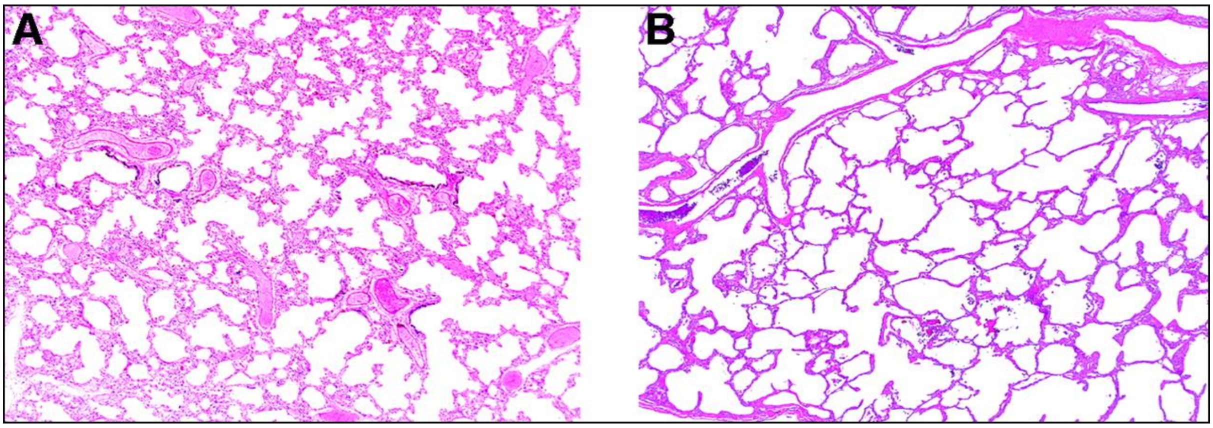

Figure 1-1 Histopathology of Old (A) and New (B) BPD

(Figure adapted from The New BPD: an arrest of lung development, (Jobe, 1999))

1.2.4 Defining BPD

The definition of BPD has continued to evolve since Northway et al. (Northway et al., 1967) reported lung damage as a result of prolonged mechanical ventilation in premature infants with severe RDS. In 1969 (Pusey et al., 1969), Pusey et al described diffuse interstitial fibroplasia associated with mechanical ventilation in newborns including patients without RDS. There was no clear relationship demonstrated between the use of high oxygen concentration and BPD, thus suggesting barotrauma as the primary cause (Pusey et al., 1969). Further definitions of clinical BPD have included supplemental oxygen requirement at 28 days postnatal age (Kraybill et al., 1989, Sinkin et al., 1990) and 36 weeks postmenstrual age (PMA) (Shennan et al., 1988, Marshall et al., 1999).

In 2000, a workshop sponsored by the National Institute of Child Health and Human Development (NICHD), National Heart, Lung, and Blood Institute (NHLBI), and Office of Rare Diseases (ORD) proposed the current National Institutes of Health (NIH) consensus definition of BPD (Jobe and Bancalari, 2001). This definition used supplemental oxygen requirement for 28 days and then identified three grades of severity, dependent on the respiratory support required at either 36 weeks postmenstrual age (PMA) or at discharge for those born at less than 32 weeks gestation or at 56 days of life or discharge for those born at more than 32 weeks gestation (Jobe and Bancalari, 2001) (Table 1-1). This definition was validated preliminarily with the NICHD Neonatal Network database and data from Palta et al. (Palta et al., 2000) and is thought to more accurately identify the risk of adverse outcomes than previous definitions (Jobe and Bancalari, 2001). The definition includes a few additional features. First, a day of treatment with supplemental oxygen was defined as 12 hours or more of supplementary oxygen exposure. Second, infants must require supplemental oxygen for a cumulative of 28 days or more before the assessment at 36 weeks PMA. Finally, respiratory support at the time of assessment should reflect the infant's usual therapy in the days surrounding assessment and not an "acute" event. Studies that rely on a simple "snapshot" of respiratory support at 28 days or 36 weeks PMA may therefore incompletely assess BPD rates based on those criteria (Bancalari et al., 2003). To decrease variability in BPD diagnosis, Walsh et al.(Walsh et al., 2003) proposed a "physiologic" definition which required an oxygen reduction test to determine oxygen dependency. To conduct the test, the fraction of administered oxygen was reduced in a stepwise manner over a defined timed interval. Infants who are unable to maintain saturations ≥ 90% during that time were diagnosed with BPD. Ehrenkranz et al. (Ehrenkranz et al., 2005) attempted to validate the accuracy of the NIH consensus definition of BPD in a cohort of extremely low birth weight (ELBW; birth weight<1000 g) infants followed in the NICHD Neonatal Research Network's very low birth weight registry. The Jobe and Banclari (Jobe and Bancalari, 2001) definition was more accurate in predicting outcome than previous definitions and hence used in this thesis.

Table 1-1: Diagnostic classification of BPD into mild, moderate and severe based on gestational age and respiratory support requirement.

(Adapted from the National Institutes of Health Consensus Definition of Bronchopulmonary Dysplasia (Jobe and Bancalari, 2001))

	BPD classification		
Gestational age	Mild	Moderate	Severe
< 32 weeks	Treatment with > 21% oxygen for 28 days plus no respiratory support at 36 weeks PMA or discharge home	Need for < 30% oxygen at 36weeks PMA or discharge home	Need for ≥ 30% oxygen and/ or positive pressure ventilation or CPAP at 36 weeks PMA or discharge home
≥ 32 weeks	Treatment with > 21% oxygen for 28 days plus no respiratory support at 56 days Postnatal age (PNA) or discharge home	Need for < 30% oxygen at 56 days PNA or discharge home	Need for ≥ 30% oxygen and/or positive pressure ventilation or CPAP at 56 days PNA or discharge home

1.2.5 Risk Factors for BPD

The aetiology of BPD is multifactorial and involves exposure to prenatal and/or postnatal factors, which disrupt pulmonary development, and may cause inflammation and damage to the highly vulnerable premature lung (Jensen and Schmidt, 2014).

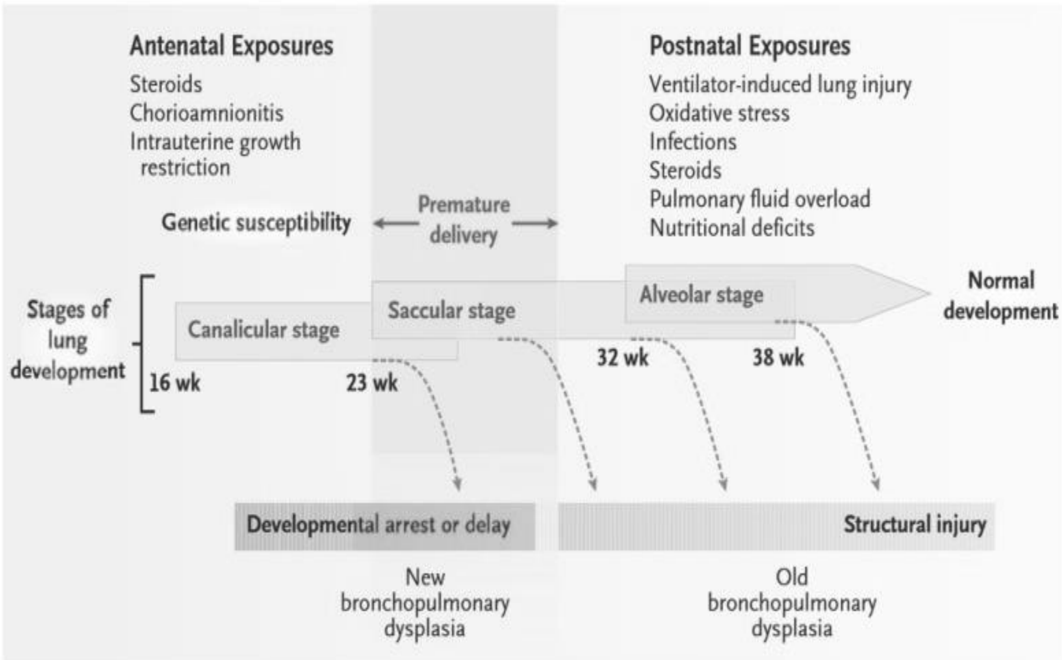

Figure 1-2: Stages of lung development, potentially damaging factors, and types of lung injury.

Adapted from From Eugenio Baraldi, M.D.; Marco Filippone, M.D. Chronic Lung Disease after Premature Birth (Baraldi and Filippone, 2007). *N. Engl. J. Med.* 2007, 357, 1946–1955.

1.2.5.1 Prenatal Risk Factors

1.2.5.1.1 Intrauterine growth restriction

Fetal growth restriction in infants with a gestational age below 28 weeks appears to be an independent risk factor for BPD (Bose et al., 2009, Torchin et al., 2016). The extremely low gestational age newborn (ELGAN) study found a strong association between fetal growth restriction and BPD in infants born less than 29 weeks gestation (Bose et al., 2009). Odds of BPD in that cohort were over threefold higher for infants with birth weight more than one standard deviation below the mean (Bose et al., 2009). In a case-control study that included 2255 infants less than 33 weeks gestation, infants born small for gestational age had more than twice the risk of BPD (Odds ratio (OR) 2.73, 95% Confidence Interval (CI) 2.11-3.55) (Eriksson et al., 2015). Klinger et al. (Klinger et al., 2013) reported the risk-adjusted odds for BPD of 2.65 (95% CI, 2.24–3.12) in VLBW infants with birth weight (BW) less than the 10% for gestational age (GA).

1.2.5.1.2 Chorioamnionitis

Whether maternal chorioamnionitis increases BPD risk remains controversial. A study (Van Marter et al., 2002), reported decreased rates of BPD in VLBW infants exposed to chorioamnionitis, except in those who subsequently developed sepsis. Odds of BPD in those cases were nearly threefold higher (OR, 2.9; 95% CI, 1.1 7.4). Similar decrease in BPD with histologic chorioamnionitis alone was also present in another study but an increase when postnatal sepsis (Lahra et al., 2009). The unreliability of both clinical and histologic diagnoses of chorioamnionitis make the interpretation of available data difficult (Redline et al., 2003, Jobe, 2012). The

ELGAN study which aimed to identify factors that contribute to brain damage, reported that while 51% of placental cultures obtained from 1119 extremely preterm deliveries yielded positive results (Bose et al., 2009). Chorioamnionitis in fetal mice stimulated angiogenesis and produced an inflammatory profile comparable to the inflamed lungs of infants developing BPD (Miller et al., 2010). Infants exposed to severe chorioamnionitis had lower clinical responses to surfactant treatment and those lower responses correlated with longer mechanical ventilation and more BPD (Been et al., 2010). A meta-analysis of studies involving 13,583 infants found that histologically but not clinically diagnosed chorioamnionitis was associated with higher odds (OR 1.89, 95% CI 1.56 to 2.3) of BPD (Hartling et al., 2012).

1.2.5.1.3 Genetics

Several investigators have attempted to identify associations with BPD of molecules or pathways that are known to be associated with lung development, maturation, inflammation, fibrosis, angiogenesis, oxidative stress, or tissue injury and repair. In general, many of these studies have focused on single nucleotide polymorphisms (SNPs) in relatively few genes or pathways, and have had limited sample sizes from one or a few centres (Hallman and Haataja, 2006, Lahti et al., 2004, Sorensen et al., 2014). A limitation of these approaches is that we currently do not have a good understanding of the regulation of the transition from the saccular to the alveolar stage of lung development. Hence, we do not know all the molecules or pathways of critical importance to distal lung development (and therefore to BPD pathogenesis) that can be targeted for analysis. Twin studies provide insight into genetic predispositions as monozygotic twins share 100% of their genetic information while dizygotic twins are 50% concordant (Shaw and O'Brodovich, 2013). A total of 450 twin pairs were analysed using mixed-effects logistic-regression and a latent variable probit model in a multicentre retrospective study. This analysis concluded that 65% of the variances in BPD susceptibility could be accounted for by genetic and shared environmental factors (Bhandari et al., 2006). Subsequent multicentre studies confirmed the heritability of BPD by way of data identifying greater similarity in monozygotic as compared to dizygotic twins. One series of over 300 twins reported that genetics contributed to approximately 80% of the observed variance in rates of BPD (Lavoie et al., 2008). More recently, several genome-wide association studies (GWAS) have been conducted to identify candidate SNP’s associated with BPD. The largest study evaluated over 1700 infants and failed to identify genomic loci or pathways that accounted for the previously described heritability for BPD (Wang et al., 2013). A second, smaller analysis (n=418) concluded that the SPOCK2 gene may represent a possible candidate susceptibility gene and a key regulator of alveolarisation (Hadchouel et al., 2011).

1.2.5.2 Risk Factors At Birth

1.2.5.2.1 Gestational age

GA is inversely proportional to the incidence of BPD, as well as the severity of the disease. Among infants meeting the physiological definition of BPD at 36 weeks postmenstrual age (PMA), 95% were very-low-birth-weight (VLBW) (Walsh et al., 2004). In the NICHD network, the incidence of BPD at 23 weeks PMA (as defined as oxygen at 36 weeks PMA) was 73% with 56% of infants having severe BPD. In comparison, at 28 weeks PMA the incidence of BPD was 23% with only 8% of infants with severe BPD (Stoll et al., 2010). In the NICHD Neonatal Research Network, the incidence of BPD in infants born at 23 weeks gestation was 73%, 56% of whom developed severe disease (Stoll et al., 2010). At 28 weeks gestation, 23% develop BPD, with severe disease found in only 8% (Stoll et al., 2010).

The Canadian Neonatal Network reported that 28.1% of surviving infants born less than 25 weeks gestation developed BPD (defined as oxygen use at 36 weeks PMA following oxygen use on the 28th day after birth) compared with only 4% of infants born at 29 to 32 weeks gestation (Isayama et al., 2012). In an Israeli national cohort, 50.1% of surviving infants born at 24 to 25 weeks gestation developed BPD diagnosed by oxygen requirement at 36 weeks PMA compared with only 4.1% born between 30 and 32 weeks) (Klinger et al., 2013).

1.2.5.2.2 Gender

Male infants are at increased risk of BPD compared with females of similar GA and BW (Palta et al., 1991, Rojas et al., 1995, Ambalavanan et al., 2008, Costeloe et al., 2012). Among VLBW infants enrolled in the NICHD trial of inhaled nitric oxide, the adjusted odds of BPD or death were nearly five times greater for males than females (Ambalavanan et al., 2008). Surviving males in the EPICure studies were over twice more likely to develop BPD than similar females (Costeloe et al., 2012).

1.2.5.3 Postnatal Risk Factors

1.2.5.3.1 Supplementary oxygen

1.2.5.3.1.1 Delivery room resuscitation

Several studies of delivery room resuscitation and early respiratory management evaluated whether interventions aimed at reducing mechanical ventilation and supplemental oxygen exposure result in improved respiratory outcomes. In a small randomised control trial (RCT), (Vento et al., 2009), infants born between 24 to 28 weeks gestation those, resuscitated in the delivery room with 30% (n=37) and compared to those with 90% (n=41) supplemental oxygen had a lower incidence of BPD (31.7% vs 15.4%; $p < 0.05$). The Room Air versus Oxygen Administration During Resuscitation of Preterm Infants (ROAR) study (Rabi et al., 2011), however, found no difference in BPD rates between preterm infants treated with room air (n=34), titrated oxygen (n=34), or 100% supplemental oxygen (n=38) (Rabi et al., 2011). In another study (Kapadia et al., 2013), BPD in infants with gestational age of 24 to 34 weeks were randomised to two different delivery room resuscitation strategies. In one arm (n=44), resuscitation was initiated with room air and supplemental oxygen was titrated to achieve the neonatal resuscitation program (Kattwinkel et al., 2010) recommended saturation levels. The alternate arm (n=44) titrated from 100% supplemental oxygen to achieve a saturation of 85 to 94%. BPD rates were lower in the infants initially resuscitated without supplemental oxygen (7% vs. 25%; p=0.04) (Kapadia et al., 2013).

1.2.5.3.1.2 Target oxygen saturation

Extensive efforts have been made to define optimal saturation targets for premature infants (Manja et al., 2015). A meta-analysis including five separate trials did not identify significant differences in the outcomes of visual disability following retinopathy of prematurity or BPD but raised concerns for increased risk of mortality at 18 – 22 month corrected gestational age (CGA) with lower saturation targets (low 85%-89% versus high 91% – 95%) as well as higher rates of necrotizing enterocolitis (NEC) (Stenson, 2016, Saugstad and Aune, 2014). Specific to the outcome of BPD, the Surfactant, Positive Pressure and Oxygenation Randomization Trial (SUPPORT) found non-significant lower rates of BPD (38% versus 41.7%) in the low-saturation group (Network et al., 2010a). The Canadian Oxygen Trial (COT) identified a similar trend with BPD rates of 31.8% and 33.1% in the low- and high-saturation groups, respectively (Schmidt et al., 2013). Finally, the three trials conducted in New Zealand, the UK and Australia combined as the Benefits of Oxygen Saturation Trials (BOOST II) found similar non-significant trends with rates of 39.5% and 44.7% in the low- and high-saturation groups respectively (Group et al., 2013, Stenson et al., 2011). Use of higher saturation targets will inherently increase documented rates of BPD as infants cannot be weaned until they can maintain these higher goals. Nonetheless, the meta-analysis including all five studies still failed to identify a significant difference in rates of oxygen requirement at 36 weeks (Saugstad and Aune, 2014). Despite the theoretical concerns for increased risk of oxidative lung injury and pulmonary vascular remodelling, many units now use higher saturation limits of 91%-95% based upon the collective finding of improved survival in these five trials. Some suggest that higher targets of 93% – 97% should be considered with established BPD to reduce risks of subsequent pulmonary hypertension (Cummings et al., 2016).

1.2.5.3.2 Permissive Hypercapnia

Permissive hypercapnia is a ventilatory strategy that permits relatively high levels of partial pressure of arterial carbon dioxide ($PaCO_2$) and always used to avoid lung injury and BPD (Miller and Carlo, 2007). Four studies that enrolled a total of 693 participants selected to a meta-analysis (Mariani et al., 1999, Carlo et al., 2002, Thome et al., 2006, Thome et al., 2015), revealed no effect of permissive hypercapnia on decreasing rates of bronchopulmonary dysplasia (BPD). Permissive hypercapnia also had no significant effect on mortality, intraventricular haemorrhage (IVH), IVH (grade 3–4), periventricular leukomalacia (PVL), necrotising enterocolitis (NEC), and retinopathy of prematurity (ROP) or air leaks in extremely low birth weight infants (Ma and Ye, 2016).

1.2.5.3.3 Patent ductus arteriosus

The role of a patent ductus arteriosus (PDA) in the development of BPD is much-debated. There is evidence to support an association but not a causal relationship between persistent PDA and BPD (Benitz, 2010, Benitz, 2012, Trzaski et al., 2012). Studies of prophylactic closure of PDA showed no benefit for prevention of BPD and some suggest that treatment may increase BPD risk (Cooke et al., 2003, Fowlie et al., 2010, Ohlsson et al., 2013). In the Trial of Indomethacin Prophylaxis in Preterm (TIPP) (Schmidt et al., 2001), Indomethacin reduced the incidence of PDA (24% vs. 50% in the placebo group; odds ratio, 0.3; $p<0.001$) and severe Periventricular Haemorrhage (PVH) and IVH (9%, vs. 13% in the placebo group; odds ratio, 0.6; $p = 0.02$). No other outcomes were altered by the prophylactic administration of indomethacin. In a follow-up to the TIPP study, the treatment did not prevent BPD, although it reduced the frequency of PDA (Schmidt et al., 2006). BPD rates were considerably lower (30% vs. 43%) in infants in whom PDAs closed spontaneously without indomethacin compared with those with closure following indomethacin (Schmidt et al., 2006). A recent Cochrane Review found no difference in the incidence of BPD following medical versus surgical closure of PDA in preterm infants, but the analysis contained only a single small RCT (Malviya et al., 2013). In a subsequent systematic review of all RCTs evaluating both surgical and pharmacologic methods of PDA closure, Benitz (Benitz, 2010) found no reduction in BPD or the combined outcome of death or BPD with any therapy.

1.2.5.3.4 Infection and Inflammation

There exists controversy regarding the contribution of postnatal inflammation or nosocomial infection to the increased risk of developing BPD (Oh et al., 2005, Lahra et al., 2009, Klinger et al., 2010). Novitsky et al. identified that premature infants with BPD were more likely to receive prolonged courses of antibiotics in the first week after birth and to have evidence of resistant gram-negative bacilli in their endotracheal tube (Novitsky et al., 2015). Those data raises concerns that the presence of resistant organisms may result in more severe infection, advocating for judicious use of prophylactic or prolonged antibiotics in premature infants at risk. Non-infectious exposures, including oxygen and mechanical ventilation, cause further injury to the preterm lung resulting in secondary insult via inflammatory mediated responses. Increased pro-inflammatory cytokines found in tracheal aspirates and blood samples from premature infants, including tumor necrosis factor alpha (TNFα), IL-8, IL-1β and IL-6, have been shown to correlate with increased risk of BPD (Tullus et al., 1996, Jonsson et al., 1997, D'Angio et al., 2016).

1.2.5.3.5 Postnatal corticosteroids

The potential benefits of systemic steroids are often outweighed by concerns for long-term neurodevelopmental sequelae including increased risk of cerebral palsy (CP) (Halliday, 2002, Halliday et al., 2009). Rates of use of systemic steroids for prevention of BPD have markedly decreased following American Academy of Pediatrics (AAP) and Canadian Pediatric Society (CPS) recommendations in 2002 against routine use (Jarreau et al., 2010, Yoder et al., 2009). Specifically, rates of postnatal corticosteroids use declined from 20% in 1997 – 2000 to only 12% in 2001 – 2002 and then again to 8% in 2004 with no significant change thereafter (Fanaroff et al., 2007, Stoll et al., 2015).

1.2.6 Long-term Outcome

1.2.6.1 Re-hospitalisation

In a study of 238 infants who were born at less than 33 weeks gestation, 49% of infants with BPD required readmission during the first year after birth compared with 23% of non-BPD infants (Smith et al., 2004). The mean number of readmissions and length of stay were also greater for infants with BPD (Smith et al., 2004). During the first two years, Greenough et al. (Greenough et al., 2001) reported that 57% of infants with BPD required re-hospitalisation for respiratory problems. Respiratory syncytial virus infection in particular was associated with higher readmission rates (Greenough et al., 2001, Drysdale et al., 2011). In the NICHD Neonatal Research Network, rates of rehospitalisation and pulmonary medication use at 18 to 22 months increased with increasing severity of BPD (Ehrenkranz et al., 2005). During the second and third year of life, re-hospitalisation rates decline, although BPD survivors may remain at increased risk for respiratory related hospitalisations well into adulthood (Walter et al., 2009).

1.2.6.2 Respiratory symptoms

Many survivors of BPD demonstrate a component of reactive airway disease. Problematic respiratory symptoms, such as wheezing and coughing, can continue into preschool years (2-5 years) (Greenough et al., 2006). In a cohort of 308 extremely preterm infants followed through six years of life, wheezing, coughing, and use of inhaled medications were significantly more common in those with than without BPD (Hennessy et al., 2008). At 11-year follow-up of infants from the same cohort, 28% with a history of BPD were diagnosed with asthma, 24% suffered exercise induced wheezing, and 22% experienced nocturnal cough (Fawke et al., 2010). Cough, wheeze, and dyspnoea are also common in young adult survivors with BPD (Gough et al., 2012). Lung function abnormalities and respiratory symptoms can continue into adulthood. A study of 690 adults who had developed BPD as infants (Vrijlandt et al., 2005) highlighted that compared to controls, wheezing without a cold, asthma diagnosis and shortness of breath on exercise were more common, but only in the female population.

Long-term follow-up of infants born less than 26 weeks of gestation identified that 25% had an asthma diagnosis at 11 years of age while over twice this percentage (56%) had evidence of abnormal spirometry (Fawke et al., 2010). Cohort studies show a significantly greater prevalence of asthma like symptoms and the use of inhaled asthma medication among persons 8 to 19 years old who were born prematurely regardless of whether they had BPD than among persons born at term (Doyle et al., 2006, Anand et al., 2003, Halvorsen et al., 2004). A trend toward clinical improvement is usually seen over time, however; symptoms progressively subside, respiratory exacerbations become uncommon, and most persons lead apparently normal lives (Kinsella et al., 2006).

While children with BPD have asthma-like symptoms, they are also less likely to demonstrate airway hyper-responsiveness or response to bronchodilators as they may suffer a fixed peripheral airway narrowing (Joshi et al., 2013). In addition, co-morbid bronchomalacia or other central airway disease in ex-premature infants can result in exacerbated wheezing with use of bronchodilator therapy (Allen et al., 2003). Benefits from inhaled corticosteroids are also thought to be less consistent for children with BPD as compared to those with asthma (Allen et al., 2003). The reversibility and impact of this asthma - like phenotype on late adult pulmonary morbidity remains unknown.

1.2.6.3 Pulmonary function

In most infants with BPD, lung growth and remodelling during infancy results in progressive improvement of pulmonary function and weaning from oxygen therapy; few BPD patients remain oxygen-dependent beyond two years of age (Greenough et al., 2004). Several studies in infants (aged 6 to 12 months) with BPD have demonstrated evidence of small airway disease and impaired alveolar growth. Lung function is usually in the low-to-normal range by age two to three years, but airflow abnormalities can remain. In another study, sequential measurements during the first two to three years following hospital discharge demonstrated gradual increases in FRC (mL/kg) from initial low levels to more normal levels, but with persistent limitations of maximum flow at FRC

(V_{max}FRC) (Fakhoury et al., 2010). Approximately one-third of those patients responded to bronchodilators (Fakhoury et al., 2010).

Although clinical symptoms in individuals with BPD often improve during childhood, pulmonary function tests (PFTs) often remain abnormal, particularly in those with more severe disease (Baraldi and Filippone, 2007, Ronkainen et al., 2015). One study (Filippone et al., 2003), reported a strong correlation between VmaxFRC at two years of age and FEV_1 at school age (mean 8·8 years), suggesting persistent airflow limitation in some patients with BPD. Another study compared preschool children with healthy controls and found decreased forced expiratory volume in one second (FEV_1), increased FRC, residual volume (RV), and the ratio of RV to total lung capacity (RV/TLC) in the BPD group consistent with obstructive lung disease (Robin et al., 2004). Those findings are consistent with persistent airflow obstruction and gas trapping. A retrospective review of 322 preterm infants with BPD (Landry et al., 2011) demonstrated that lung function as assessed by forced expiratory volume, forced vital capacity and forced expiratory fraction was significantly reduced at seven years of age compared to controls. They also observed that lung function abnormalities and health-care utilisation during childhood was significantly associated with the initial severity of BPD. In many patients, especially those with mild disease, pulmonary function tests (PFTs) gradually improved over time, possibly in conjunction with new alveolar development and improvement in small airway flow limitation (Baraldi et al., 1997, Fakhoury et al., 2010, Gerhardt et al., 1987).

There are few data on the pulmonary function of adult patients with a history of premature birth and old BPD. Long-term respiratory morbidity is not limited to BPD survivors born before routine surfactant use. BPD survivors from the EPICure cohort, 89% of whom received surfactant, suffered significantly decreased lung function at 11 years of age compared with extremely preterm and term controls without BPD (Fawke et al., 2010). Abnormalities in PFTs are commonly found in children and adults with BPD (Doyle et al., 2006, Landry et al., 2011, Doyle and Anderson, 2009). PFTs frequently show decreased FEV_1 and decreased ratios of FEV_1 to forced vital capacity (FEV_1/FVC), consistent with airflow limitation and small airway obstruction (Doyle et al., 2006, Landry et al., 2011).

A recent systematic review of adults born during the pre-surfactant era found higher rates of pulmonary function abnormalities and radiographic evidence of persistent structural changes in the lungs of those with a history of BPD (Gough et al., 2012). Another study compared lung function at eighteen years of age in two cohorts of ELBW infants, one born before and the other after availability of surfactant. Significant airway obstruction was found in preterm survivors from both cohorts, with airflow limitations most pronounced in those with a history of BPD (Vollsaeter et al., 2013).

1.2.6.1 Pulmonary Hypertension

Complications of BPD include pulmonary hypertension (PH), due to anatomical and physiological abnormalities in lung circulation in BPD patients, which contributes significant mortality and morbidity in BPD patients (Kim, 2010). While the true incidence of pulmonary arterial hypertension in infants with BPD is unknown, several small retrospective reports estimate rates at 25% to 37% (An et al., 2010, Slaughter et al., 2011, Kim et al., 2012, Check et al., 2013). Forty-five percent of infants who required supplemental oxygen at 36 weeks PMA were diagnosed with PH. The incidence of PAH increased with increasing BPD severity. Only 2% of infants with mild BPD had evidence of pulmonary arterial hypertension compared with 36% with moderate and 50% with severe BPD (Bhat et al., 2012). In a series of 42 VLBW infants with BPD and PAH, mortality was 38% during a median follow-up period of 10.9 months and only 25% with severe PH and BPD survived to two to three years of age (Khemani et al., 2007). Among all survivors with BPD and pulmonary arterial hypertension, however, 89% demonstrated improvement in pulmonary arterial hypertension during the follow-up period (Khemani et al., 2007).

1.3 Ventilator-induced lung injury (VILI)

Ventilator-induced lung injury (VILI) is a common complication of MV in premature infants and may predispose the infant to abnormal lung growth and development and BPD (Attar and Donn, 2002). Several mechanisms may contribute to the lung injury that is associated with MV. These mechanisms are not mutually exclusive and may act synergistically. Understanding these mechanisms may have therapeutic implications.

1.3.1 Barotrauma

Barotrauma occurs when high pressures are used in ventilation, thus increasing the risk of air leak syndromes, such as interstitial emphysema, pneumothorax, and pneumomediastinum (Morisot et al., 1990), which in turn activate the inflammatory cascade (Carvalho et al., 2013). In a study (Webb and Tierney, 1974), anaesthetised rats were ventilated with room air at peak inspiratory pressures of 14, 30 or 45 cmH_2O without any added PEEP, while other rats were ventilated with the same inspiratory pressures but with an added PEEP of 10 cmH_2O. The results showed that the control group of rats that were not ventilated and the group of rats ventilated with pressures of 14/0 showed no pathological lung changes while the group of rats ventilated on 30/0 and 30/10 had perivascular oedema but no alveolar oedema. Similarly, rats ventilated on 45/10 had no alveolar oedema and survived (Webb and Tierney, 1974). On the contrary, rats ventilated with higher pressures of 45/0 cmH_2O had alveolar and perivascular oedema, severe hypoxemia, and decreased compliance and died within one hour concluding that that interstitial perivascular oedema develops from ventilation with high tidal volumes generated by high distending pressures (Webb and Tierney, 1974).

Several investigators questioned whether VILI was caused by the ventilatory pressures per se (i.e. barotrauma), or the resultant ventilatory volumes (i.e. volume trauma) (Dreyfuss and Saumon, 1993, Hernandez et al., 1989, Carlton et al., 1990, Dreyfuss et al., 1988). Hernandez and coworkers (Hernandez et al., 1989) addressed this question by comparing the effect of ventilation with 15, 30, or 45 cm H_2O PIP on normal rabbits, rabbits encased in plaster casts to limit chest excursions, and excised rabbit lungs. No significant changes in capillary filtration coefficient (Kfc) or any signs of macroscopic lung injury were found in the rabbits encased in plaster. However, significant increases in Kfc were found in the other two groups (i.e. normal rabbits or ex vivo lungs). Therefore, they concluded that it was the large lung volumes (volutrauma), rather than the high airway pressures, which produced lung injury. A similar conclusion was reached by Dreyfuss et al., based on their findings of pulmonary oedema when rats were ventilated with either high tidal volumes and high airway pressures (high pressure conventional mechanical ventilation) or high tidal volumes and low airway pressures (negative pressure ventilation). In contrast, no pulmonary oedema was found with normal tidal volume ventilation at high airway pressures (positive pressure ventilation with thoraco-abdominal strapping) (Dreyfuss et al., 1988).

1.3.2 Volutrauma

Whilst pressure and volume are inextricably linked, over expansion of lung parenchyma, rather than the absolute pressure, leads to lung injury (Dreyfuss and Saumon, 1992). The importance of volutrauma has been demonstrated in animal models. Young rabbits were exposed to peak inspiratory pressures (PIP) of 15, 30, and 45 cmH_2O, in isolated lung preparations, intact rabbits, and rabbits in which the chest and abdomen were encased in plaster of Paris, limiting expansion. The lungs of the restricted expansion rabbits appeared macroscopically normal, and measurements of capillary permeability, increased in lung injury, remained static at each of the pressure intervals. In contrast, the lungs from uncasted rabbits showed progressive macroscopic damage as the pressure to which they were exposed increased, with increasing capillary permeability. The isolated lung preparations, with no restriction to expansion, were worst affected (Hernandez et al., 1989). This study demonstrates that volutrauma was more important than the absolute pressure applied in provoking this aspect of lung injury. This is particularly significant in premature neonates, whose compliant chest walls offer little protection against over-distension.

Another animal study has shown that even a small number of large inflations soon after birth can adversely affect surfactant-deficient lungs (Bjorklund et al., 1997). In this study of new born lambs, one lamb of each of five pairs was randomly assigned to receive six large manual inflations ("bagging") after preterm delivery and before starting MV and receiving artificial surfactant. At four hours, the bagged animals compared with controls had lower inspiratory capacity and maximal deflation, were more difficult to ventilate, and had less well expanded alveoli and more widespread lung injury on histologic examination. Injury caused by mechanical ventilation primarily is due to large tidal volumes (volutrauma) that over distended airways and airspaces, rather than increased airway pressures (Hernandez et al., 1989, Carlton et al., 1990).

1.3.3 Atelectotrauma

Atelectorauma results from regionally or totally reduced lung parenchyma expansion. Pulmonary injury is associated with alveolar instability: the successive collapsing and reopening of the alveolar walls cause the lysis of the structural elements that compose the lung interstitium, triggering local and systemic inflammation. Experimental models of surfactant deficiency showed that low-volume MV induces cytokine release and initiates the inflammatory cascade, which also occurs in volutrauma (Froese et al., 1993). Studies performed during conventional MV of surfactant-depleted lungs with various levels of Peak end expiratory pressure (PEEP) provide support to the concept that the repeated opening and closing of terminal units causes additional injury (Sandhar et al., 1988, Muscedere et al., 1994). Muscedere et al. ventilated isolated, nonperfused, lavaged rat lungs at different end-expiratory pressures above and below the inflection point (Pinf) of the inspiratory pressure-volume curve. In the group ventilated with PEEP below Pinf, compliance fell dramatically after ventilation, and lung injury assessed morphologically was significantly greater (Muscedere et al., 1994). Another benefit of setting PEEP above this inflection point is that it usually results in a very abrupt decrease in shunt fractions and increase in PaO_2 (Falke et al., 1972). It seems likely that unstable lung units may be damaged by repeated opening and closing during tidal ventilation. PEEP may prevent diffuse alveolar damage during prolonged ventilation at high lung volume by stabilising distal units. This may explain in part the preservation of alveolar epithelium integrity and the decrease in oedema during high tidal volume mechanical ventilation in the presence of PEEP in a ventilated rat model (Dreyfuss et al., 1988), and minimisation of injury to ventilated surfactant-deficient rabbit lungs by recruiting lung volumes and then maintaining a higher than normal FRC by high frequency oscillatory ventilation (McCulloch et al., 1988). Keeping end-expiratory lung volumes (EELV) high enough to prevent atelectasis, and using small tidal volumes to prevent over distension improved surfactant efficacy in premature rabbits (Gattinoni et al., 1987). Therefore, the lung apparently also has a low volume injury zone (Jobe and Ikegami, 1998). If both high and low volume lung injury concepts are clinically relevant, the logical inference is that MV of acutely injured lungs should be placed on the linear portion of the pressure-volume curve (Dreyfuss and Saumon, 1994), above the lower inflection point but below the upper inflection (or ‘deflection’ point). This linear portion may be very short. In such case, a tidal volume (Vt) that would not be deleterious in normal lungs may lead to excessive end-inspiratory volume when the PEEP is set high enough to be above the lower inflection point.

1.3.4 Biotrauma

Numerous studies over the past twenty years have demonstrated that there can be release of various mediators into the lung, pulmonary recruitment of leukocytes, and local initiation of inflammatory processes. This biological response to mechanical forces has been called biotrauma (Tremblay and Slutsky, 1998). The biotrauma hypothesis postulates that the circulating mediators can cause local lung injury, and if they translocate into the systemic circulation, they may lead to distal organ dysfunction and death (Slutsky and Tremblay, 1998).

Tremblay et al (Tremblay et al., 1997) found that isolated non-perfused rat lungs ventilated for two hours with large tidal volumes without PEEP had large increases in lavage concentrations of tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, and macrophage inflammatory peptide 2. High Vt ventilation also increased expression of c-fos mRNA, a transcription factor important in the early stress response (Tremblay et al., 1997).

The potential for ventilation-induced inflammation in humans was examined in forty-four patients with ARDS who were randomised to receive traditional or lung-protective ventilation (Ranieri et al., 1999). Broncho-alevolar lavage (BAL) and plasma concentrations of several proinflammatory cytokines were lower in patients receiving protective ventilation, as were other indices of plasma and alveolar fluid inflammation, compared with patients receiving traditional tidal volumes and lower PEEP.

Inflammation is a process that is a vital response to injury that needs to be triggered to bring about recruitment of blood leucocytes, activation of tissue macrophages, and production of a series of mediators. The inflammatory response to injury may include activation of macrophages that generate ‘early response cytokines’ like TNF-α and IL-1. These cytokines stimulate vascular endothelial cells to express vascular adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1), and E-selectin. Blood neutrophils adhere to endothelial cells and transmigrate into the interstitial and alveolar compartments (Ward and Lentsch, 1999). The entry of neutrophils into the alveolar compartment together with tissue-activated macrophages sets the stage for injury of both lung cells and matrix glycoproteins (e.g., collagens, elastin). Injury is related to generation of oxidants by phagocytic cells and the release of proteases. The activation of NF-kB in phagocytic cells is central to the generation of inflammatory mediators. NF- kB has the ability to bind with promoter sequence in DNA and to inaugurate transcription (generation of messenger RNA) for many inflammatory peptides. The NF- kB is held in check by inhibitors, which bind to the NF-kB complex and prevent its entry into the nucleus (translocation) and subsequent binding to DNA. In the rat model of immune complex-induced alveolitis, several interleukins were found to have a strong anti-inflammatory response, with IL-10=IL-13>IL-4>IL-6>IL-12 (Ward and Lentsch, 1999).

MV provokes the release of cytokines, both pro-inflammatory (IL-1, IL-6, IL-8, TNF-α) and anti-inflammatory (IL-10), and other mediators from the cells. In vitro studies suggest that this release is caused by mechanical stretch to the tissue, leading both to disruption of the contact between individual cells and also to transduction of the forces intracellularly via the cytoskeleton (Halbertsma et al., 2005). The pro-inflammatory response, increased in preterm neonates due to reduced anti-inflammatory cytokine release (Oei et al., 2002), attracts neutrophils and other inflammatory cells to the airways, and also increases vascular permeability (Munshi et al., 1997, Groneck et al., 1994). Surfactant dysfunction, either due to a direct cytokine effect or due to increased alveolar capillary leak of proteins, increases the propensity for lung damage. It has been shown that preterm neonates who go on to develop BPD have higher levels of inflammatory cytokines and that these persist longer than those infants who do not develop BPD (Jonsson et al., 1997, Arnon et al., 1993, Tullus et al., 1996). This inflammatory cascade can induce apoptosis in pulmonary epithelial cells and is also implicated in the alteration of gene expression in injured lung tissue, both sustaining inflammatory responses and also modifying pathways involved in tissue repair and remodelling (Denervaud et al., 2015). Animal studies have demonstrated that lung injury induced by MV and associated with increased pro-inflammatory cytokine release leads to delayed alveolarisation and saccular wall fibrosis, similar to the histological changes found in neonates with BPD (Ratner et al., 2013, Coalson et al., 1999).

The mechanical factors that lead to barotrauma, volutrauma and atelectrauma have been associated with inflammatory mediator-related injury which has been termed biotrauma. MV promotes inflammation and direct damage to the lungs in premature infants. For that reason, ventilator strategies which are least harmful are needed for preventing ventilator-induced injuries and in turn prevent BPD.

1.4 Neonatal ventilation strategies

Management strategies are aimed at protecting against lung injury and the development of BPD. As the pathogenesis of disease is multifactorial, diverse approaches have been adopted including both ventilation and medical strategies. Interestingly, both antenatal steroids and surfactant reduce rates of RDS and improve survival; however, neither has been shown to reduce incidence of BPD (Stoll et al., 2015). It is important to determine the impact of different modes of ventilation on respiratory morbidity in order to optimise neonatal ventilation. There are a number of modes of ventilation currently used to support prematurely born infants, including invasive and non-invasive methods.

1.4.1 Invasive ventilation

1.4.1.1 Volume targeted ventilation

During VTV, a constant volume set by the practitioner is delivered to the infant regardless of changes in the infant's lung function. At least eighteen randomised or quasi-randomised trials have been undertaken comparing VTV to pressure-limited ventilation in prematurely born infants. Meta-analysis (Peng et al., 2014) demonstrated that VTV was associated with a reduction in BPD (nine trials) and significant reductions in all IVH, grades 3–4 IVH, PVL and pneumothorax. In addition, the durations of MV and supplementary oxygen were shorter with VTV.

There was, however, no significant reduction in mortality and no long-term outcomes were reported. Difficulties in generalising the results of the meta-analysis are that different ventilators were used in the two arms of some trials and different volume targeting ventilators were used. A variety of mechanisms are used to achieve volume targeting and, as a consequence, there are differences in the airway pressure waveform and mean airway pressure at apparently the same Vt setting according to ventilator type (Sharma et al., 2007). In addition, different levels of volume targeting used in the various trials and the VT level used significantly affects the WOB in infants with acute respiratory distress (Patel et al., 2010b) and in the recovery stage (Patel et al., 2009b).

1.4.1.2 High-Frequency Oscillation

During high-frequency oscillatory ventilation (HFOV), small tidal volumes are delivered at fast rates, usually in the range of 10 – 15 Hz. The performance of high frequency oscillators varies, but for all, the delivered volume is affected primarily by the oscillatory pressure and less by the frequency (Laubscher et al 1996). Volume delivery, however, was reduced as frequency was increased (Laubscher et al 1996). Randomised clinical trials have demonstrated that HFOV have potential to reduce risk of BPD (Sun et al., 2014, Henderson-Smart et al., 2007); however, a Cochrane review of elective HFOV revealed only a small reduction in the incidence of chronic lung disease with notable inconsistency across the nineteen studies included (Cools et al., 2015). As many infants require more sedation with high frequency ventilation (HFV), prophylactic use of HFV remains controversial.

In the United Kingdom Oscillation Study (UKOS) (Johnson et al., 2002), 797 infants born prior to 29 weeks of gestation from 25 centres, were randomised uniquely within an hour of birth to HFOV or conventional ventilation (Johnson et al., 2002); no significant differences in short-term outcomes were demonstrated. There were also no significant differences in lung function results at one year of age (Thomas et al., 2004), but the results were only from a subset who lived close to the London centre and small airway function was only assessed by measurement of gas trapping. In another study (Hofhuis et al., 2002) demonstrated small airway function, as assessed by maximal flow at functional residual capacity (V′ max FRC) at 12 months corrected, was significantly better in infants who had been supported by HFOV rather than CMV. Those results (Hofhuis et al., 2002) were not from a randomised trial, but suggested that HFOV might preserve small airway function. That hypothesis was proven by an assessment of 320 “UKOS” children when aged 11 to 14 years, which demonstrated significant differences in small airway function in favour of HFOV (Zivanovic et al., 2014).

1.4.1.3 Patient triggered ventilation (PTV)

1.4.1.3.1 Assist control and synchronised intermittent ventilation (AC and SIV)

PTV was introduced into neonatal intensive care in the 1980s, initially as assist/control (A/C, inflations triggered by every spontaneous breath that exceeded the critical trigger threshold) and synchronised intermittent mandatory ventilation (SIMV), only the preset number of inflations is triggered regardless of the infant's spontaneous respiratory rate). It was hoped that these ventilation modes would be more likely to promote synchrony between the infant and ventilator inflations and hence reduce air leaks and BPD. The recent Cochrane review (Greenough et al., 2016) of randomised trials comparing AC/SIMV to pressure limited ventilation (PLV) demonstrated that ACV/SIMV compared to CMV was associated with a shorter duration of ventilation (mean difference (MD) 38.3 hours, 95% CI − 53.90 to −22.69). SIMV or SIMV + Pressure Support (PS) was associated with a greater risk of moderate/severe BPD compared to HFO (Relative Risk (RR) 1.33, 95% CI 1.07 to 1.65) and a longer duration of mechanical ventilation compared to HFO (MD 1.89 days, 95% CI 1.04 to 2.74). ACV compared to SIMV was associated with a trend to a shorter duration of weaning (MD − 42.38 hours, 95% CI −94.35 to 9.60). Neither ACV nor SIMV was associated with a significant reduction in the incidence of BPD.

1.4.1.3.2 Pressure support ventilation (PSV)

During pressure support ventilation (PSV), the infant's inspiratory efforts determine both the initiation and termination of ventilator inflation. Ventilator inflation is terminated when the infant's inspiratory flow declines to a predefined level, which varies according to the type of ventilator. A randomised trial (Reyes et al., 2006) showed that the use of PSV in addition to SIMV during the first week after birth facilitated weaning in infants of birth weight ≤1000 g compared to SIMV alone. This was associated with a shorter oxygen dependency in infants of BW 700–1000 g. The likely benefits were explained by the results of a crossover study (Patel et al., 2009a), where one hour periods of SIMV and SIMV with pressure support were compared (n=20 infants, mean GA of 31 weeks). They found that the addition of pressure support to SIMV reduce the WOB in infants being weaned from the ventilator. The likely explanation for the success of PSV with SIMV versus SIMV alone is that, in the former ventilator strategy, all the infant's breaths are supported and this reduces their WOB (Patel et al., 2009a).

1.4.1.3.3 Proportional assist ventilation (PAV)

During proportional assist ventilation (PAV), the applied pressure is servo controlled, based on continuous input from the infant's breathing throughout each spontaneous breath. In addition, the ventilator can provide inflation pressure in phase with the Vt change in order to reduce the compliance load (i.e. the load due to the stiffness of infant's lungs) and in phase with the flow change to reduce the resistance load (i.e. the load due to airflow obstruction), termed elastic and resistive unloading, respectively (Schulze, 2002). Very prematurely born infants developing or with established BPD will have stiff lungs (that is non-compliant) despite a very compliant chest wall, so may be particularly likely to benefit from elastic unloading.

PAV, however, has only been assessed in neonates in a few studies. In prematurely born infants with acute respiratory disease, PAV was associated with maintenance of gas exchange with lower transpulmonary pressure swings compared to continuous mandatory ventilation (CMV) and ACV in a crossover study (Schulze et al., 1999). In evolving CLD in prematurely born infants, PAV was shown to provide satisfactory gas exchange at lower mean airway pressures compared to SIMV and ACV in a crossover study (Schulze et al., 2007), but PAV was demonstrated to reduce TAA and chest wall distortion in preterm infants (Musante et al., 2001).

In a crossover study, infants with evolving or established BPD supported on PAV compared ACV had better oxygenation indices, a lower WOB and better respiratory muscle strength. The infants, however, were only studied on each ventilator mode for one hour (Bhat et al., 2015). The longest infants have been reported to be studied on PAV was four hours (Schulze et al., 2007), but during that study, only changes in pulse oximetry results were assessed. During PAV, a trigger delay of 60 milliseconds was demonstrated using an in vitro model (Patel et al., 2010a); hence, it is important to assess blood gases over a longer period than previously studied.

1.4.1.3.4 Neurally adjusted ventilatory assist (NAVA)

In 1987 Daubenspeck et al. described a new technique to evaluate the diaphragmatic EMG using an array of seven sequential electrode pairs on an oesophageal catheter (Daubenspeck et al., 1989). In the 1990's Sinderby and Beck expanded this concept with the introduction of embedded electrodes in a nasogastric tube that detected a reliable diaphragmatic EMG signal. The signal reflected the patient's neural respiratory drive in real time, and minimised artefacts (Sinderby, 2002, Beck et al., 1998, Beck et al., 1995). The technology was integrated into a commercially available mechanical ventilator (Servo-I and Servo-N; Maquet, Solna, Sweden) that converted the electrical activity into a synchronised breath known as NAVA (Sinderby, 2002, Beck et al., 2015).

NAVA is a mode of ventilation where the patient's neural respiratory drive controls the timing and amount of assist provided (Sinderby et al., 1999, Sinderby C, 2012). The neural respiratory drive is interpreted from the diaphragm electrical activity (Edi), measured with small sensors on the patient's Edi catheter at the level of the gastroesophageal junction. Measuring the Edi in the oesophagus removes potential contamination from changes in lung volume, body position, intra-abdominal pressure, postural and expiratory muscles, the subcutaneous layers, and applied PEEP (Beck et al., 1998, Beck et al., 1995, Sinderby et al., 1999, Barwing et al., 2011, Barwing et al., 2009). Signal integrity also does not seem to be influenced when receiving bolus versus continuous nasogastric feeds (Ng E, 2010) or with milk influx during oral feeding (Stein et al., 2012). Edi has been shown to correlate with transdiaphragmatic pressure (Beck et al., 1998, Beck et al., 2001, Fauroux et al., 2003) and with the pressure generated by the respiratory muscles and inspiratory effort (Bellani et al., 2013).

There are few studies of NAVA and they address short-term outcomes, but available data are encouraging. In a retrospective analysis of the results of fifty-two neonates changed to NAVA from conventional ventilation, peak inflation pressures and supplementary oxygen levels were lower and the partial pressure of carbon dioxide improved during NAVA (Stein and Howard, 2012). Those results were subsequently confirmed in a prospective study of five infants each exposed to four hourly cycles of pressure controlled ventilation and NAVA, despite lower peak inflation pressures the partial pressure of carbon dioxide was lower during NAVA (Stein et al., 2013a). In a four hour crossover comparison between NAVA and SIMV with PS, in twenty-six preterm infants, the WOB was lower on NAVA and blood gases were maintained despite lower peak pressures (Lee et al., 2012). NAVA compared to pressure regulated-volume control has also been associated with less asynchrony and need for sedation (Longhini et al., 2015).

Infants with evolving or established BPD have a high resistance which means flow triggering can be challenging. In addition, the severity of their lung function abnormalities likely means that supporting each breath throughout the inspiratory cycle ie with a small trigger delay would be advantageous. This thesis will test the hypothesis that NAVA compared to ACV would result in a lower oxygenation index (OI) in infants with evolving or established BPD.

1.4.2 Non-invasive respiratory support

Significant efforts have been made to move away from use of invasive ventilation over the past two decades (Stoll et al., 2015). In a secondary analysis from the Caffeine for Apnea of Prematurity (CAP) trial, higher rates of BPD in infants who were intubated at birth compared with those who were stabilised with non-invasive CPAP were found (DeMauro et al., 2011). A recent meta-analysis of four RCTs with a total of 2782 very preterm infants compared early use of CPAP to intubation and MV (Morley et al., 2008, Network et al., 2010b, Sandri et al., 2010, Dunn et al., 2011, Schmolzer et al., 2013). BPD rates were only modestly reduced with early CPAP (32.4% vs.34.0%), and the results failed to meet statistical significance (RR, 0.91; 95% CI, 0.82 – 1.01) (Schmolzer et al., 2013). Use of alternative non-invasive modalities including non-invasive positive pressure ventilation (NIPPV), bi-level nasal CPAP (biPAP) and HHFNC is also increasing with some evidence to suggest these modes may also be effective in managing neonatal respiratory disease (Hutchison and Bignall, 2008, Kugelman et al., 2007, Yoder et al., 2013). Studies have identified that an early attempt at extubation alone may decrease the risk of BPD, regardless of need for reintubation or duration of ventilation (Jensen et al., 2015, Robbins et al., 2015).

The optimal approach, impact on BPD and long-term outcomes with use of non-invasive ventilation (NIV) remain to be defined. Studies above suggest a need for additional prospective trials.

1.4.2.1 Continuous positive airway pressure (CPAP)

CPAP has been used since the 1970's as a modality to prevent alveolar collapse by maintaining mean airway pressure (Gregory et al., 1971). A survey of eight tertiary neonatal centres in the United States of America (USA) (Avery et al., 1987) demonstrated the centre which used CPAP as initial respiratory support had the lowest rate of BPD with similar survival rates; the other centres used intubation and ventilation as their initial ventilatory mode. Other observational studies highlighted that use of early CPAP was associated with significantly less need for intubation and ventilation (Aly et al., 2004, Miksch et al., 2008, Narendran et al., 2003) and BPD (Aly et al., 2004, Miksch et al., 2008, Ammari et al., 2005, Birenbaum et al., 2009). There have subsequently been randomised trials which have yielded differing results. The COIN trial (Continuous Positive Airway Pressure or Intubation at Birth) (Morely et al., 2008) showed that the use of early CPAP in the delivery suite in very preterm infants (25 – 28 weeks) compared to intubation and ventilation was associated with lower risk of the combined outcome of death or need for oxygen therapy at 28 days, but there was no significant difference in oxygen dependency at 36 weeks post menstrual age. The trial however highlighted that the CPAP group had a higher incidence of pneumothorax, which might relate to the CPAP pressure of 8 cm H_2O or the lower use of prophylactic surfactant. In the SUPPORT trial (intubation and early surfactant followed by CPAP versus early CPAP) (Finer et al., 2010), there was no significant difference in the primary outcome of death or BPD, although there was higher postnatal steroid use in the intubation–surfactant group (13.2% vs. 7.2%, $p < 0.001$). The CPAP group required significantly less days of mechanical ventilation ($p = 0.03$) and had a significantly higher rate of survival free of mechanical ventilation at seven days (RR 1.14, 95% CI, 1.03–1.25). A prospective follow up study to SUPPORT, the breathing outcomes study (Stevens et al., 2014), assessed respiratory morbidity at 6-month intervals from hospital discharge to 18 – 22 months corrected age. The study found that infants randomised to early CPAP rather than intubation and early surfactant had fewer episodes of wheezing without a cold, fewer respiratory illnesses diagnosed by a doctor, and fewer physician or emergency room visits for breathing problems. In the CURPAP trial (prophylactic surfactant followed by CPAP versus early CPAP) (Sandri et al., 2010), no significant difference was found in the primary outcome, the need for MV in the first 5 days or in the secondary outcomes including death, BPD, air leaks, grades 3-4 IVH, sepsis, retinopathy of prematurity and pulmonary haemorrhage. A subsequent Randomised controlled trial (RCT) randomised 648 infants to one of three arms: initial management to prophylactic surfactant followed by a period of mechanical ventilation, prophylactic surfactant followed by rapid extubation to bubble CPAP or bubble CPAP and selective surfactant (Dunn et al., 2011). The study was terminated early because of declining recruitment. There were no significant differences between the groups with regard to mortality or other complications of prematurity (Dunn et al., 2011). A meta-analysis of four RCT's, (Morely et al., 2008, Dunn et al., 2011, Network et al., 2010b, Sandri et al., 2010) comparing use of nCPAP to intubation in infants born at less than 32 weeks of gestation demonstrated nCPAP was associated with a significant reduction in BPD or death (Schmolzer et al., 2013). Thus, early CPAP therapy for preterm infants compared to invasive ventilation has been demonstrated to be associated with less respiratory morbidity.

1.4.2.1.1 Methods of CPAP generation

There are a number of methods of CPAP generation and delivery. Devices which generate CPAP can broadly be divided into two categories, continuous flow or variable flow devices. Continuous flow devices include conventional ventilators, jet ventilation systems and bubble CPAP. Conventional ventilators provide a constant flow of gas and the pressure is controlled by the exhalation valve. With a jet system, a small jet is produced either at the nostrils or in a prechamber in front of the nasal prongs. During bubble CPAP, a variable flow device, the pressure is set by immersing the expiratory limb of the CPAP device in an underwater chamber to a depth equal to the desired CPAP level. The gas flows through the system causing bubbling in the chamber; this causes variability in the mean CPAP pressure. Using a variable flow device, the CPAP level is dependent on the flow of gas. There have been few randomised trials comparing methods of CPAP generation, the results of those studies have suggested that variable-flow CPAP has advantages over ventilator-delivered CPAP being associated with lower duration of supplementary oxygen, length of stay (LOS) and WOB and greater stability of flow and tidal volume (Huckstadt et al., 2003, Pandit et al., 2001, Stefanescu et al., 2003). In subgroup analysis of infants ventilated for less than two weeks, bubble CPAP compared to variable-flow CPAP was associated with a significantly lower rate of extubation failure, as well as a significantly reduced duration of CPAP, but overall, there were no significant differences in the rates of successful extubation (Gupta et al., 2009).

1.4.2.1.2 CPAP delivery

Short binasal prongs and nasal masks are two of the most commonly used interfaces for delivering CPAP (Kieran et al., 2011). Other methods include a nasopharyngeal prong, an endotracheal tube and a helmet. In a short-term randomised crossover study, ‘helmet’ CPAP was found to be as effective as nasal CPAP with respect to oxygen requirement, oxygen saturation (SaO_2), heart rate (HR), respiratory rate (RR), mean arterial blood pressure (MAP), and transcutaneous carbon dioxide. In addition, helmet CPAP use was associated with a significant increase in infant comfort assessed by the Neonatal Infant Pain Scale (Trevisanuto et al., 2005). There are, however, concerns that it may adversely affect cerebral blood flow (Zaramella et al., 2006) and it is associated with significantly higher noise levels than nasal CPAP (Trevisanuto et al., 2011).

Short binasal prongs are associated with a lower WOB compared to nasopharyngeal prongs (De Paoli et al., 2002). The results of a meta-analysis highlighted that binasal prongs were more effective in preventing reintubation in prematurely born infants when compared to either single nasal or nasopharyngeal prongs (De Paoli et al., 2008). Nasal injury has been described using short nasal prongs. In a randomised study which included eighty-nine very low-birthweight infants, no significant difference in the incidence of nasal injury was demonstrated between nasal prongs and nasal mask, but the incidence of nasal injury was significantly associated with CPAP duration (Yong et al., 2005). Continuous method of CPAP with nasal mask would be used for studies in this thesis.

1.4.2.2 Heated Humidified High Flow Nasal Cannula (HHFNC)

During humidified, high flow nasal cannula (HHFNC), heated and humidified gas is delivered at flow rates between 2 – 8 L/min via nasal cannulae. It has been suggested that HHFNC may be effective by eliminating the dead space (Dysart et al., 2009), reducing the WOB (Saslow et al., 2006), improving lung compliance at higher flow rates (Saslow et al., 2006) and delivering some degree of continuous positive airway pressure (Dysart et al., 2009, Spence et al., 2007). There are, however, concerns about the unpredictability of the positive airway pressures generated (Kubicka et al., 2008, Lampland et al., 2009, Finer and Mannino, 2009) and the possibility of increased risk of infection, particularly due to Ralstonia species (CDC, 2005) and gram-negative organisms (Shoemaker et al., 2007) resulting from contaminated humidifier cartridges in the Vapotherm 2000i device in 2005 (Jhung et al., 2007). Following the introduction of stricter infection control guidance by the manufacturer, there have been no further infection concerns since. Nevertheless, the technique has become popular, HHFNC has gained popularity in many countries (Ojha et al., 2013, Hochwald O, 2010, Hough et al., 2012, Manley et al., 2013, Roehr et al., 2007, Manley et al., 2012). Sixty three percent of units in Australia and New Zealand were reported to be using HHFNC in 2010 (Manley et al., 2012). A survey of fifty-seven level two or three neonatal units in the UK reported in 2013 that HHFNC was used in 77% of units (Ojha et al., 2013). In addition, infants were perceived to be more comfortable and more easily handled on HHFNC compared to nCPAP (Ojha et al., 2013).

1.4.2.2.1 Distending pressures generated by HHFNC

The distending pressure delivered by HHFNC is dependent on prong size. There have been several attempts to produce a formula to calculate the pressure generation during HHFNC at different flow rates on the basis of infant weight, but inconsistent results have been produced (Dysart et al., 2009, Sreenan et al., 2001). Airway pressure increases with the nasal prong to nares ratio (Sivieri et al., 2013). In an in vitro system (Lampland et al., 2009), and in eighteen infants (Wilkinson et al., 2008), the pressure increased with increased flow (Lampland et al., 2009). In 15 patients with RDS, the presence of a leak as small as 30% reduced the pressure to less than 3 cm H_2O (Lampland et al., 2009). Among infants with a postmenstrual age of between 29 and 44 weeks, and a birth weight of 835–3735 g, no pressure was generated when the infants' mouths were open, regardless of whether flow rates of up to 5 L/min were used (Kubicka et al., 2008). When the infants' mouths were closed, the oral cavity pressure was related to both flow rate and weight. For the subgroup of infants with birth weights ≤1500 g, there was a linear relationship between flow rate and oral cavity pressure (Kubicka et al., 2008). In a model, small, medium and large nares were simulated by holes drilled in a plastic fixture, which was connected to a lung simulator that simulated spontaneous breathing (Volsko et al., 2011). Nasal cannulae were inserted in the nares of the model, ensuring that the occlusion of the nares did not exceed 50%. Flow was adjusted from 2 to 6 L/min in 1 L/min increments. Not surprisingly, the greatest effects on Vt and pressure change as flow was increased, occurred with the smallest cannula. Another study (Collins et al., 2013b), compared pharyngeal pressures using two commonly used HHFNC devices, the Fisher & Paykel Healthcare HHFNC (Auckland, New Zealand) and the Vapotherm 2000 (Vapotherm Inc., Stevensville, MD,USA), in nine infants at flow rates of 2 – 8 L/min. There was no difference in pharyngeal pressures recorded between devices at flow rates of 2 – 6 L/min. At flow rates of 7 L/min, the Vapotherm delivered a mean pharyngeal pressure of 4.7, with a standard deviation (SD) of 2.2 cm H_2O, compared with a mean of 4.23 (SD 2.2) cm H_2O by the Fisher & Paykel device ($p = 0.04$). At a flow of 8 L/min, the mean pharyngeal pressure via the Vapotherm was 4.9 (SD 2.2) cm H_2O, compared with 4.1 (SD 2.3) cm H_2O with the Fisher & Paykel device ($p = 0.05$). Whether such differences are clinically important remains to be determined and further studies are required to assess the relationship between flow and pressure in a variety of patient groups.

Flow rates needed to generate significant positive airway pressure remain unclear. Lampland et al. (2009) found that end-expiratory oesophageal pressure increased linearly with flow rate (1-6L/min), however there was large inter-patient and intra-patient variability, therefore delivered pressure for a given flow rate could not be predicted. Lavizarri et al. (2014) randomised twenty preterm infants with mild-moderate respiratory distress to receive CPAP (at 2, 4 or 6cm H_2O) and HHFNC (at 2, 4 or 6L/min). Retropharyngeal pressure was measured between periods of CPAP and HHFNC. It was found that the retropharyngeal pressures achieved during HHFNC were very variable. Retropharyngeal pressures of 2cm H_2O was achieved in four infants with 2 L/min and in eleven infants with 4L/min, whilst pressures of 4cm H_2O was reached in four infants with 4L/min and in eleven infants with 6L/min. Pressures of 6cm H_2O were only obtained in five of the twenty infants supported with HHFNC, whereas 6cm H_2O of CPAP achieved pressures of 6cm H_2O in all twenty infants. This study highlights the variability in airway pressures achieved during HHFNC, and thus confirms the unpredictability of the pressures generated by HHFNC.

1.4.2.2.2 Work of breathing (WOB) and HHFNC

In a crossover study (Saslow et al., 2006), 18 infants with a birth weight <2 kg and a mean gestational age (GA) of 28 weeks were randomised to 6 cm H_2O nCPAP or HHFNC delivered at 3, 4 and 5 L/min. No significant differences in the WOB on the two respiratory support modes were reported. Measurements of tidal oesophageal pressure were used to approximate pleural pressures using an oesophageal balloon catheter (Viasys Healthcare Inc., Palm Springs, CA). In another study (de Jongh et al., 2014), the WOB was compared in a crossover study involving twenty infants (mean GA 28 weeks and BW 1.5 kg) at two levels of nCPAP settings 5 and 6 cm H_2O and two levels of HFNC settings 3 and 5 L/min. The WOB was assessed using respiratory inductive plethysmography (RIP). They found that infants on nCPAP had significant greater chest and abdomen synchrony on CPAP compared with HHFNC, but there was overlap of the confidence intervals; hence, the authors suggested the results were unlikely to be of clinical significance. In a third study (Lavizzari et al., 2014), twenty infants with mild or moderate RDS less than 96 hour old were studied, no significant differences were found in the WOB and lung mechanics during periods of support on nasal CPAP (nCPAP) (2, 4 cm H_2O) and HHFNC (2, 4 L/min). Tidal volume by RIP, pleural pressure estimated by oesophageal pressure, and gas exchange were evaluated at each setting and used to compute breathing pattern parameters, lung mechanics and WOB.

None of the above studies looked into WOB of infants with evolving or established BPD, and hence the need for the study in the thesis comparing WOB between HHFNC and CPAP in evolving or established BPD.

1.4.2.2.3 The efficacy of HHFNC compared to CPAP

Four studies, including three post-extubation studies, were considered in a Cochrane review, which concluded that, post-extubation, HHFNC may be associated with a higher rate of intubation than nCPAP. In addition, the review highlighted that there was insufficient evidence to establish the safety or efficacy of HHFNC as a form of respiratory support for prematurely born infants ie infants born less than twenty eight weeks gestation (Wilkinson et al., 2011). In a multicentre trial, infants randomised to HHFNC compared with those randomised to nCPAP did not differ significantly with regard to the primary outcome, which was treatment failure within seven days. If HHFNC failed, the infants could then be transferred to nCPAP and if nCPAP failed, infants were reintubated. Almost half of the infants not successfully supported by HHFNC were subsequently successfully treated with CPAP without reintubation. The incidence of nasal trauma was lower in the HHFNC group than in the CPAP group ($p=0.01$). There were no significant differences in the rates of death before discharge, need for oxygen supplementation at 36 weeks of PMA, pneumothorax, PDA, requiring treatment, NEC, retinopathy of prematurity (ROP) or intraventricular haemorrhage (IVH) (Manley et al., 2013).

In a randomised trial of 432 infants of 28–42 weeks of GA, no significant difference was seen in early (<72 h) extubation failure between infants on HHFNC (10.8%) compared with nCPAP (8.2%) (Yoder et al., 2013). There was also no significant difference in the subsequent need for intubation or in adverse outcomes including air leak between the two groups. Infants remained on HHFNC longer than on nCPAP (median 4 versus 2 days, $p = 0.01$). There were no significant differences with regard to days on supplemental oxygen (median: 10 versus 8 days) or the incidence of BPD (20% versus 16%).

Collins et al. (Collins et al., 2013a) randomly assigned 132 infants less than 32 weeks of gestational age to receive either HHFNC or nCPAP post-extubation. The primary outcome of extubation failure in the subsequent seven days was defined as at least one of the following: apnoea (respiratory pause more than 20 seconds), more than six episodes in 6 hours or one requiring intermittent positive pressure ventilation, acidosis, pH<7.25 and arterial carbon dioxide levels more than 66 mmHg and more than a 15% sustained increase in the inspired oxygen concentration. No significant differences were found in the primary outcome or in the number of infants reintubated in the first week. The mean nasal trauma score, however, was lower in the HHFNC group (3.1 versus 7.4, $p < 0.001$).

1.5 Outcome measures

This thesis will utilise physiological measurements and oxygenation indices as outcome measures. The physiological outcome measures will be work of breathing (WOB), thoraco-abdominal asynchrony (TAA) and assessment of oxygenation indices (OI). In addition, time to achieve full oral feeds will be determined for the oral feeding study.

1.5.1 Assessment of work of breathing

Infants with BPD may be compromised by several factors, which include respiratory limitations and increased energy needs. The work of breathing gives an indication as to how much energy the infant is expending to inhale and exhale (Cabello and Mancebo, 2006), and thus a low WOB suggests lower respiratory muscle work. The work of the respiratory muscles may be assessed by either calculating the mechanical work or by evaluating the oxygen cost of breathing (Milic-Emili et al., 1999). A method of quantifying the effort expended by the respiratory muscles is the pressure time product (PTP) (Cabello and Mancebo, 2006).

Work in a two-dimensional system is equal to the force applied to an object multiplied by the distance the object travels. That is,

Work = force × distance, or W = F × D

However, in the three-dimensions that apply in the respiratory system, work now becomes the pressure applied to yield a change in the volume of the system, or

$W = P \times V = \int_0^v P \times dv$

in which $\int_0^v P$ is the integral of the pressure across the respiratory system, as a function of volume, and dv is the change in the volume of the respiratory system.

1.5.2 Assessment of the diaphragmatic pressure time product

Pressure time product (PTP) is defined as the pressure developed by the respiratory muscles integrated to the time taken for the contraction (Cabello and Mancebo, 2006). The pressure time product of the diaphragm (PTPdi) can be calculated from the time integral of the transdiaphragmatic pressure (Pdi) (Brochard, 1991), where Pdi is the difference between pressures in the thoracic (pleural) and abdominal compartments, which are represented by the oesophageal (Poes) and gastric (Pgas) pressures respectively. In this thesis PTPdi will be used as a measure of WOB.

PTPdi = $\int_0^{Ti} Pdi.dt$ Where Pdi = Pgas – Poes

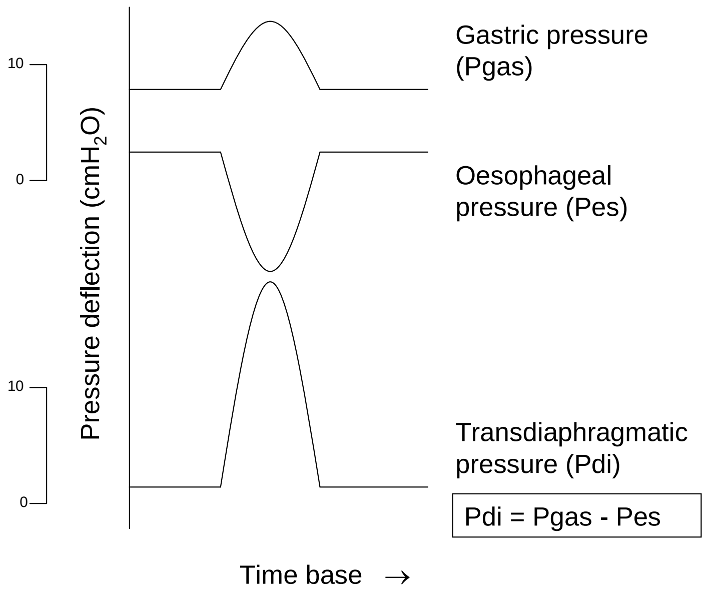

Figure 1-3: Schematic representation of the gastric and oesophageal pressure change

1.5.3 Thoracoabdominal asynchrony

Asynchrony between the motion of the chest wall (ribcage) and abdomen occurs in respiratory distress (Hammer and Newth, 2009). Asynchrony occurs frequently in prematurely born infants as they have a predominantly cartilaginous ribcage that is highly compliant (Gerhardt and Bancalari, 1980). In infants with BPD, the degree of asynchrony has been shown to be directly proportional to airways resistance and inversely proportional to lung compliance (Allen et al., 1991). The increased negative pleural pressure generated during inspiration in infants with a high airways resistance is transmitted to the highly compliant chest wall, uncoupling rib cage and abdominal wall motion (Allen et al., 1990). The degree of asynchrony between the ribcage and abdominal motion is related to the inspiratory load which in turn may lead to fatigue (Tobin et al., 1987).

Thoracoabdominal motion may be assessed using a Respiratory inductance plethysmography (RIP) to map the magnitude and duration of both ribcage and abdominal motion. The two signals are mapped on an XY plot to form a Lissajous figure from which a phase angle can be calculated (Figure 1-4, 1-5 and 1-6). Once the Lissajous figures are constructed, an index of asynchrony was then calculated as described Allen et al (Allen et al., 1990), by dividing the width of the loop at mid ribcage excursion (m) by the width at the extremes of abdominal 90 excursion (s). Degrees of motion (φ) was calculated from the radian, where sin φ (in radians) = m/s, where φ is < 90 and where φ is > 180, then φ =180 –sin (m/s) (Allen et al., 1990, Mayer et al., 2003). This is done using the Excel spreadsheet (Microsoft corporation, USA). Completely synchronous motion has a phase angle of zero degrees (figure 1-4) and paradoxical motion an angle of 180 degrees (figure 1-5)

(Allen et al., 1990) . In this thesis, RIP will be used to measure TAA due to the relative ease of interpretation and non-invasive nature.

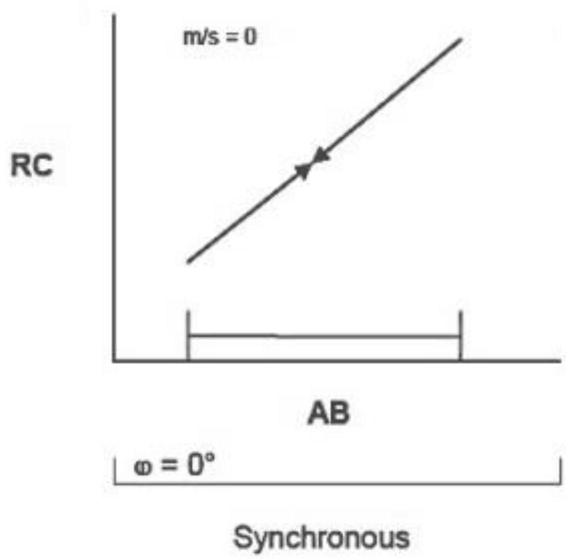

Figure 1-4: Complete synchronous motion of the rib cage and the abdomen

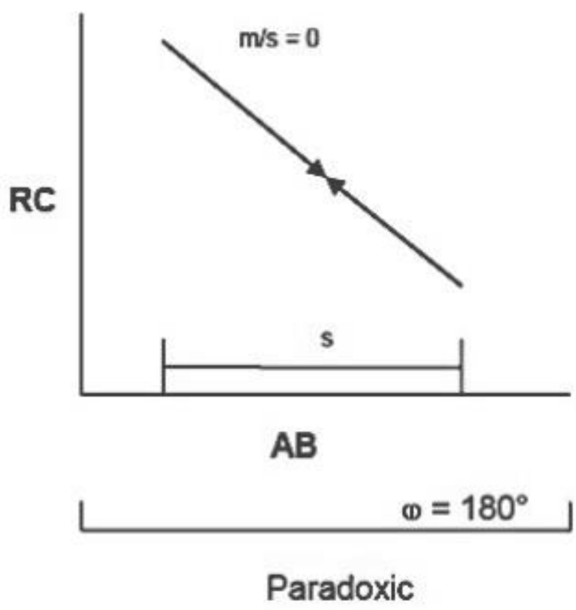

Figure 1-5: Complete asynchronous motion of the rib cage and the abdomen

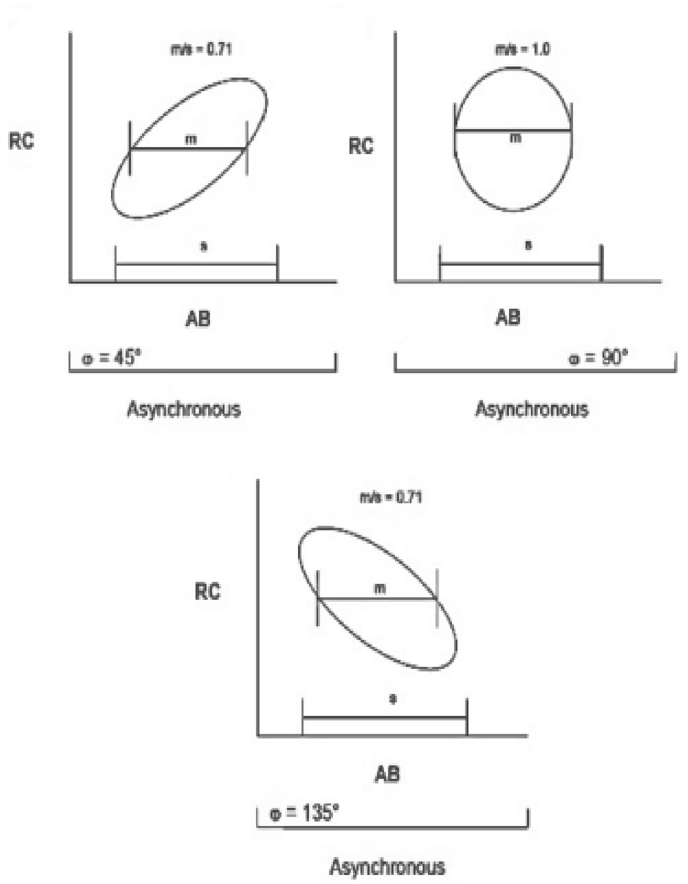

Figure 1-6: Lissajous figures demonstrating various degrees of asynchronous motion of the rib cage and the abdomen.

1.5.4 Blood gases

The oxygenation index will be used to assess the intensity of ventilatory support required to maintain oxygenation. A lower OI is better.

:

$$\text{Oxygen Index (OI)} = \frac{FiO_2 \times MAP \times 100}{PaO_2}$$

FiO_2: Fraction of inspired oxygen in percentage

MAP: Mean Airway Pressure (mmHg)

PaO_2: Partial pressure of arterial oxygen (mmHg)

Weaning of FiO_2 in the clinical studies was done by the bed-side nurse to avoid any potential bias.

1.6 Hypotheses

- PAV compared to ACV will improve oxygenation as assessed by the oxygen index (OI).
- NAVA compared to ACV will improve oxygenation as assessed by the OI.
- Current use of HHFNC will not have increased in view of the results of recent randomised trials.
- HHFNC will reduce the WOB and the degree of TAA compared to CPAP.

1.7 Aim

Overall aim is to undertake series of studies involving invasive and non-invasive ventilation using physiological measurements as outcomes in infants with evolving or established bronchopulmonary dysplasia (BPD), and to carry out a national survey.

- To determine if PAV compared to ACV will improve oxygenation as assessed by the OI.
- To determine if NAVA compared to ACV reduces the WOB and asynchrony with improvements in oxygenation.
- To conduct a survey to evaluate current practice regarding the use of HHFNC in all United Kingdom neonatal units.
- To determine in infants who are chronically CPAP dependent i.e. they are receiving CPAP two weeks after birth, whether HHFNC reduces the WOB and the degree of TAA compared to CPAP.

Chapter 2: Methods

2.1 Overview of protocols and ethical approval

2.1.1 Randomised crossover study comparing PAV with ACV

Recruited infants were randomly assigned to receive either PAV or ACV. Each infant was exposed to each mode for four hours, at the end of which an arterial blood sample was obtained, the ventilator settings were noted and the OI was calculated. The infant was then switched over to receive the other mode. Mean respiratory rate (RR), tidal volume (Vt) and mean airway pressure (MAP) was calculated over the last five minutes of the four hour study period. All the infants had continuous oxygen saturation monitoring. The data were obtained from the nursing chart taken each hour and mean calculated.

The South East London Research Ethics Committee approved the study (REC reference number: 07/H0808/147). Infants were entered into the study if their parents gave informed written consent. The study was undertaken at King’s College Hospital NHS Foundation Trust, London.

2.1.2 Randomised crossover study comparing NAVA with ACV

A randomised crossover study comparing NAVA to ACV was undertaken in prematurely born infants. Infants were studied for one hour each on NAVA and ACV in random order. At the end of each hour the Edi Peak and Edi min, MAP and dynamic compliance (Cdyn) were measured and the oxygenation index (OI) calculated. In addition, the HR, RR and oxygen saturation were noted. Data obtained by the Edi catheter was downloaded from the ventilator into Excel via USB stick.

The study was approved by the West Midlands - Solihull Research Ethics Committee (REC reference number: REC15/WH/0330). Infants were entered into the study if their parents gave informed written consent. The study was undertaken at King's College Hospital NHS Foundation Trust, London.

2.1.3 Survey to evaluate current practice regarding the use of HHFNC in all United Kingdom neonatal units.

In 2015, clinicians in all UK neonatal units, identified from the National Neonatal Audit Programme (NNAP) Report, British Association of Perinatal Medicine (BAPM) directory and a departmental database from previous audits, were sent an email inviting them to complete an electronic web-based survey using Survey Monkey. Non-responders were sent email reminders and then contacted by telephone. In 2012, practitioners from the then 203 UK neonatal units had been contacted.

2.1.4 Comparison of WOB between CPAP and HHFNC in infants with evolving BPD

A randomised crossover study comparing the WOB between CPAP and HHFNC was undertaken in prematurely born infants with evolving BPD. Infants were studied on two consecutive days. On each study day infants received CPAP and HHFNC each for two hours, the order of which was randomised. The order in which the modes were delivered was reversed on the second day. The WOB was assessed by measuring the pressure time product of the diaphragm (PTPdi). PTPdi, TAA and SaO_2 were assessed during the final five minutes of each two hour period and average values calculated.

The study was approved by the London – Westminster Research Ethics Committee (REC reference number: REC 14/LO/0202). Infants were entered into the study if their parents gave informed written consent. The study was undertaken at King's College Hospital NHS Foundation Trust, London.

2.2 Equipment

2.2.1 Blood gas analysis

Measurement of blood pH, pCO_2 and pO_2 and the calculation of OI were performed using the blood gas equipment available on the NICU at King's College Hospital (ABL 700 series, Radiometer, Copenhagen, Denmark). In the randomised crossover studies of PAV versus ACV 0.2 – 0.3 millilitres of blood was withdrawn from an infants' indwelling arterial line, inserted by the clinical team for clinical reasons prior to commencing the study. For NAVA versus ACV study, capillary blood samples were taken via a heel prick. The blood gas machine was automatically calibrated four times in each 24-hour period. In addition, the blood gas analyser underwent a quality control (QC) check with the bioengineer at least once every 24 hours as per the trust and the neonatal unit standard operating procedure.

2.2.2 Comparison of WOB between CPAP and HHFNC in infants with evolving BPD

2.2.2.1 Measurement of airway flow and pressure

Respiratory flow was measured using a pneumotachograph (F10L, GM Instruments, Kilwinning, Scotland) and associated differential pressure transducer (MP45 range +/- 2 cmH_2O, Validyne, Northridge CA, USA). The pneumotachograph was calibrated prior to each study using a rotameter (10 L/min KDG Mobrey®, England). Airway pressure was measured using a differential pressure transducer (MP45 range +/-100 cmH_2O, Validyne, Northridge CA, USA) attached to a side arm on the pneumotachograph via a fine bore catheter. The flow and pressure signals from were amplified (CD 280, Validyne Northridge CA, USA) prior to acquisition.

2.2.2.2 Linearity of the pneumotachograph

The linearity of the pneumotachograph / transducer / amplifier / system was tested by passing air at known flows through the pneumotachograph and plotting the amplified electrical output against actual flow delivered by the rotameter. The pneumotachograph / transducer / amplifier / system were linear across the range ± 8 L/min.

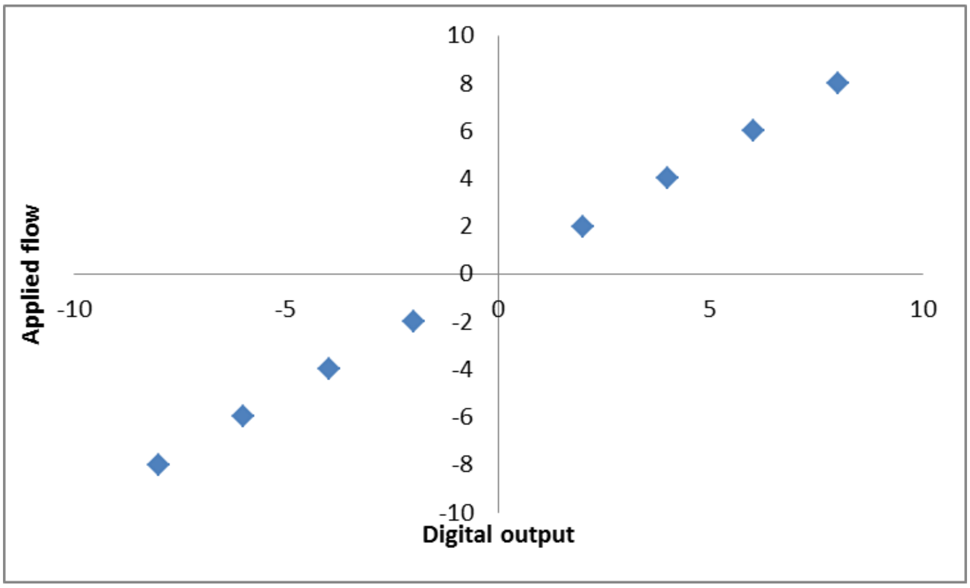

Figure 2-1: Linearity of flow system

2.2.2.3 Linearity of the airway pressure transducer

The linearity of the airway pressure transducer was tested using a digital pressure meter (C950315/IS, Comark Limited, Welwyn Garden City, UK). The transducer was connected to the pressure meter using a three way tap and pressures were applied using a hand held syringe in 10 cmH_2O increments from -150 to 150 cmH_2O. The linearity of the Comark pressure meter was tested against a water manometer (Figure 2-2).The applied pressures measured by the digital pressure meter were plotted against the corresponding amplified output voltage from the transducer converted to digital units by the acquisition system software. The transducer had a linear response over a range ± 150 cmH_2O. The pressures measured and reported in this thesis lie within this range.

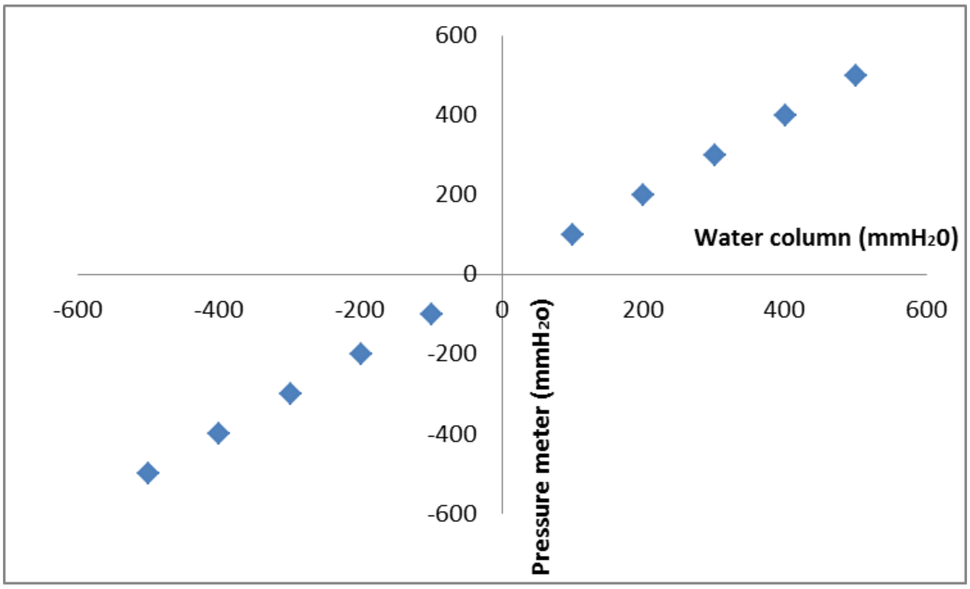

Figure 2-2: Linearity of Comark Pressure meter against a water manometer (mmH_2O)

2.2.2.4 Measurement of intrathoraic, intra-abdominal and transdiaphragmatic pressure

Intrathoracic and intraabdominal pressures were obtained by measuring the pressures in the lower third of the oesophagus (Poes) and stomach (gastric pressure (Pgas)) respectively, using a dual pressure transducer tipped catheter (Gaeltec CTO - 2, Gaeltec Ltd, Isle of Sky, Scotland) and its associated amplifier (model type S7b/2, Gaeltec Ltd, Isle of Skye, Scotland). The catheter was 120 cm in length, and mounted with two miniature strain gauge transducers (5 x 2 mm). The gastric transducer was mounted at the tip of the catheter and the oesphageal transducer was mounted five cm proximal from the gastric transducer. The external diameter of the catheter was 2.1 mm. Prior to insertion, the catheter was lubricated with sterile aqueous gel (Aquagel, Williams Medical Supplies, Gwent, Wales, UK) and either inserted nasally or orally and advanced until the distal transducer was located in the stomach and the proximal transducer in the lower third of the oesophagus which was indicated by a positive deflection in Pgas and a negative deflection in Poes. Correct positioning of the Poes transducer was checked by comparing oesophageal to airway pressure during an occluded breath. Agreement between Poes oesophageal and mouth pressures within 90% and 110% (Beardsmore et al., 1980, Baydur et al., 1982) indicated that the transducer was correctly located in the thoracic oesophagus and hence pleural pressure could be reliably estimated.

2.2.2.5 Calibration

To calibrate the pressure transducer-amplifier system, the catheter was placed inside an airtight calibration tube and the amplifier zeroed at ambient pressure. A known pressure was then applied to the catheter using the digital pressure meter and the gain of the amplifier was set to 50 cmH_20/V. Prior to each study, the dual tipped pressure transducer catheter-amplifier-computer system was calibrated with a two point calibration. The lower, zero point being atmospheric pressure and the upper, either negative or positive pressure, applied using the calibration tube and measured using the digital pressure meter. The linearity of the dual tipped pressure transducer catheter-amplifier-computer system was tested as described above for the differential pressure transducer across the range ± 150cmH_2O using the digital pressure meter.

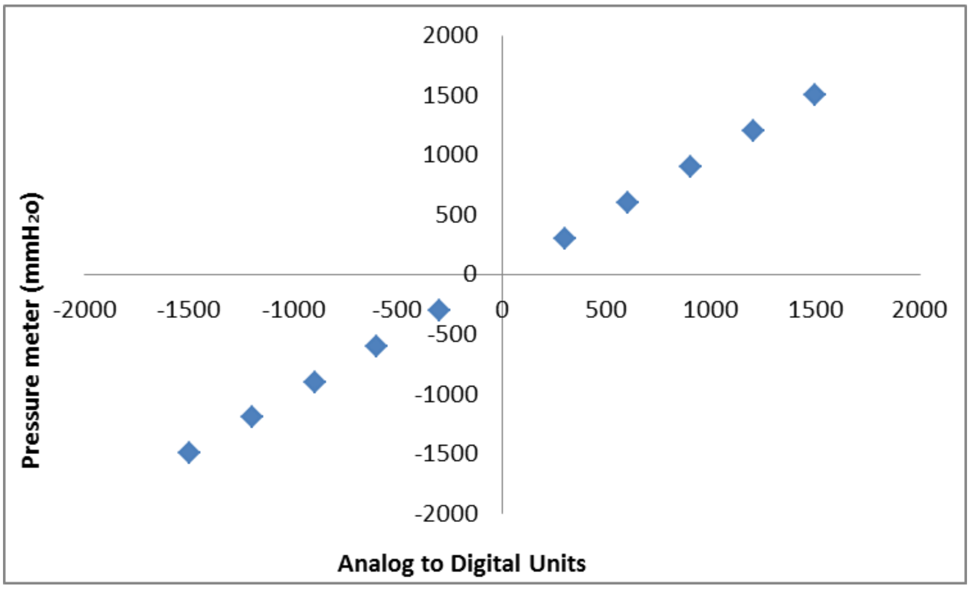

Figure 2-3: Linearity of oesophageal transducer

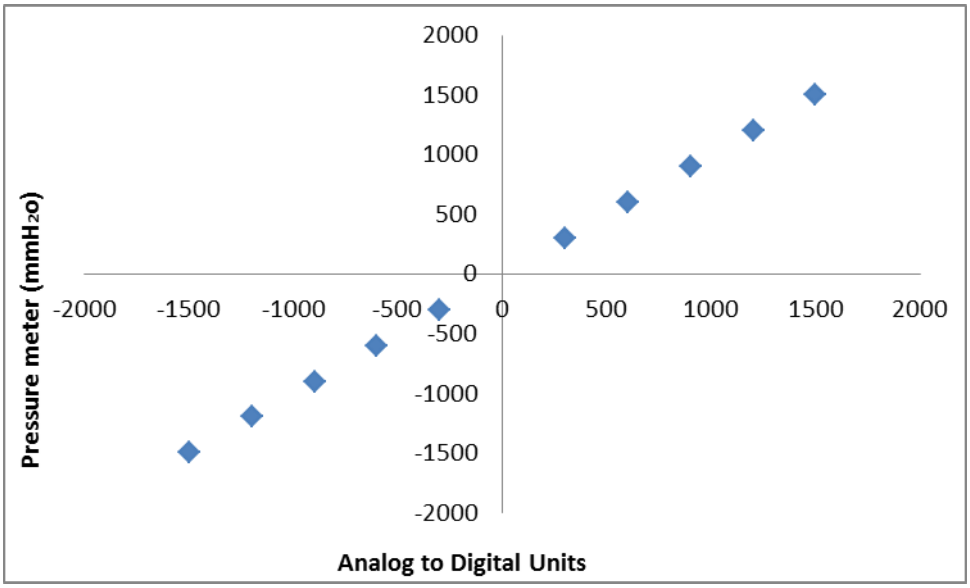

Figure 2-4: Linearity of gastric transducer

2.2.2.6 Frequency response

The respiratory rate of a neonate is between 60 to 120 breaths per minute. The fundamental frequency (the first harmonic) is therefore 1-2 Hz. The first ten harmonics contribute to the pressure waveform. Ideally the frequency response of the measuring system should be at least ten times the frequency of the infant's respiratory efforts, i.e. 20 Hz, to enable it to reproduce the first ten harmonics of the pressure wave without distortion.

The frequency response was determined by creating a quasi-instantaneous change in pressure using a 'pop test' in which an inflated balloon was fitted over the signal input site and then burst, producing an instantaneous negative step input to the system. The frequency response of the system (f3db) was calculated using the equation f3db =1/3 x Tr, where Tr (response time in seconds) is defined as the time taken for pressure to fall from 90% to 10% of the initial pressure (Figure2-5).

The frequency response of each system used was determined using the pop test method, with the change in pressure against time recorded on a computer (MacBook, Apple Computer Corp, Cupertino, California, USA) using Chart software (Version 5.0, ADInstruments Pty Ltd, Bella Vista, NSW Australia) with analogue-to-digital sampling at 40KHz (Powerlab, ADInstruments Pty Ltd, Bella Vista, NSW, Australia).

The frequency response of the airway pressure transducer system (consisting of the pressure transducer, connecting tubing, amplifier and computer) was determined by placing the tubing which connected the transducer to the pneumotachograph sideport inside an inflated balloon which was then burst. The response time was 8 milliseconds (0.008s), giving a calculated frequency response of 41.6 Hz.

The frequency response of the flow measurement system (consisting of the pneumotachograph, connecting tubing, pressure transducer for flow, amplifier and computer) was determined by attaching one end of the pneumotachograph to an inflated balloon. Partial occlusion of the other end of the pneumotachograph, allowed a constant background flow to be produced. Once flow through the pneumotachograph had been established at a constant rate, the balloon was burst resulting in an immediate fall in airflow to zero. The response time was 9 milliseconds (0.009s), giving a calculated frequency response of 37 Hz.

The frequency response of the oesophageal and gastric pressure transducing system (consisting of the dual microtransducer-tipped catheter, amplifier and computer) was tested by placing the catheter inside an inflated balloon which was then burst. The response time was 3.6 milliseconds for the oesophageal pressure transducer and 3 milliseconds for the gastric pressure transducer, giving frequency responses of 92.5 Hz and 111 Hz respectively.

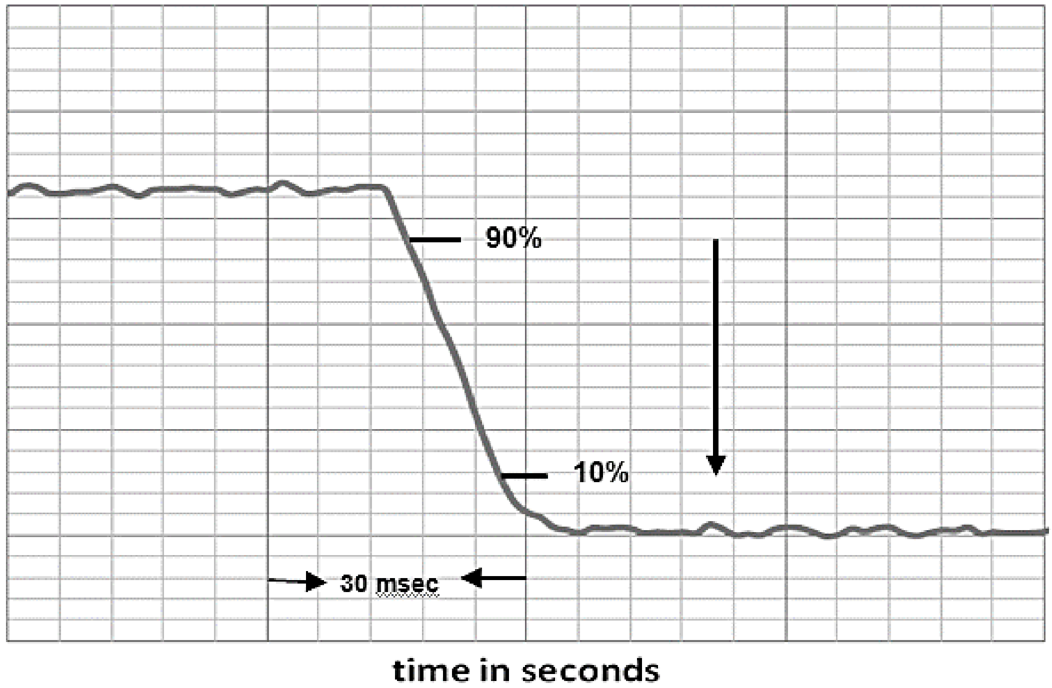

Figure 2-5: The response to a sudden decrease in pressure associated with the bursting of a balloon on the measurement of pressure

2.2.2.7 Data acquisition and storage

Amplified signals from the dual pressure catheter ie oesophageal and gastric pressures were recorded and displayed in real time on a desktop computer with Spectra® software version 3.0.0.9 (Grove Medical Ltd, U.K.) with 100 Hz analogue to digital sampling (PCI-MIO-16XE-50, National Instruments, Austin, USA). Pressure signals were then transferred to laptop computer (Dell Optiplex 170L) running Labchart software (v7.3.7 27, Powerlab 16SP, ADInstruments, Sydney, Australia) with analog to digital sampling at 100Hz (Powerlab 16SP, ADInstruments, Sydney, Australia). The data stored in the desktop computer was encrypted and transferred on to a secure laptop computer in the research office immediately after data acquisition which was secured by a laptop lock. Paper copies containing patient identifiable data were kept in a locked filing cabinet.

2.2.2.8 Measurement of thoraco-abdominal asynchrony

To provide data on thoracoabdominal synchrony, chest and abdominal wall motion was assessed using a non-invasive method of uncalibrated respiratory inductive plethysmography (RIP) (Respitrace Corporation, Ardsley NY, USA) in AC uncoupled mode. Inductance coils embedded in two elastic bandages were placed around the rib cage (RC) under the axillae and at the level of the umbilicus (AB). Output voltages from the RIP were proportional to the changes in band inductance which were in turn proportional to the changes in the underlying cross sectional area or excursions of the chest and abdomen. The voltages from both bands were acquired and recorded.

2.2.2.8.1 Analysis of TAA waveforms

TAA was determined from ten artefact-free breaths during a five minute measurement period. For each breath, the rib cage (RC) and abdomen (ABD) movements were measured and a Lissajous figure plotted (Figure 2-6) with ABD movements on the x axis. Individual breaths were delineated by points of zero voltage (Figure 2-7). Asynchrony between RC and ABD movements were quantified by determining the phase angle by comparing the difference between inspiratory and expiratory abdominal positions at mid-RC excursion (ABdiff) with the maximum abdominal excursion (ABmax). The phase angle φ was calculated as sin φ=ABdiff/ABmax. When RC and ABD move in perfect synchrony, the phase angle is 0˚. As asynchrony appears the loop opens. Complete asynchrony (paradoxical movements) results in a phase angle of 180˚Adapted from (Hammer and Newth, 2009).

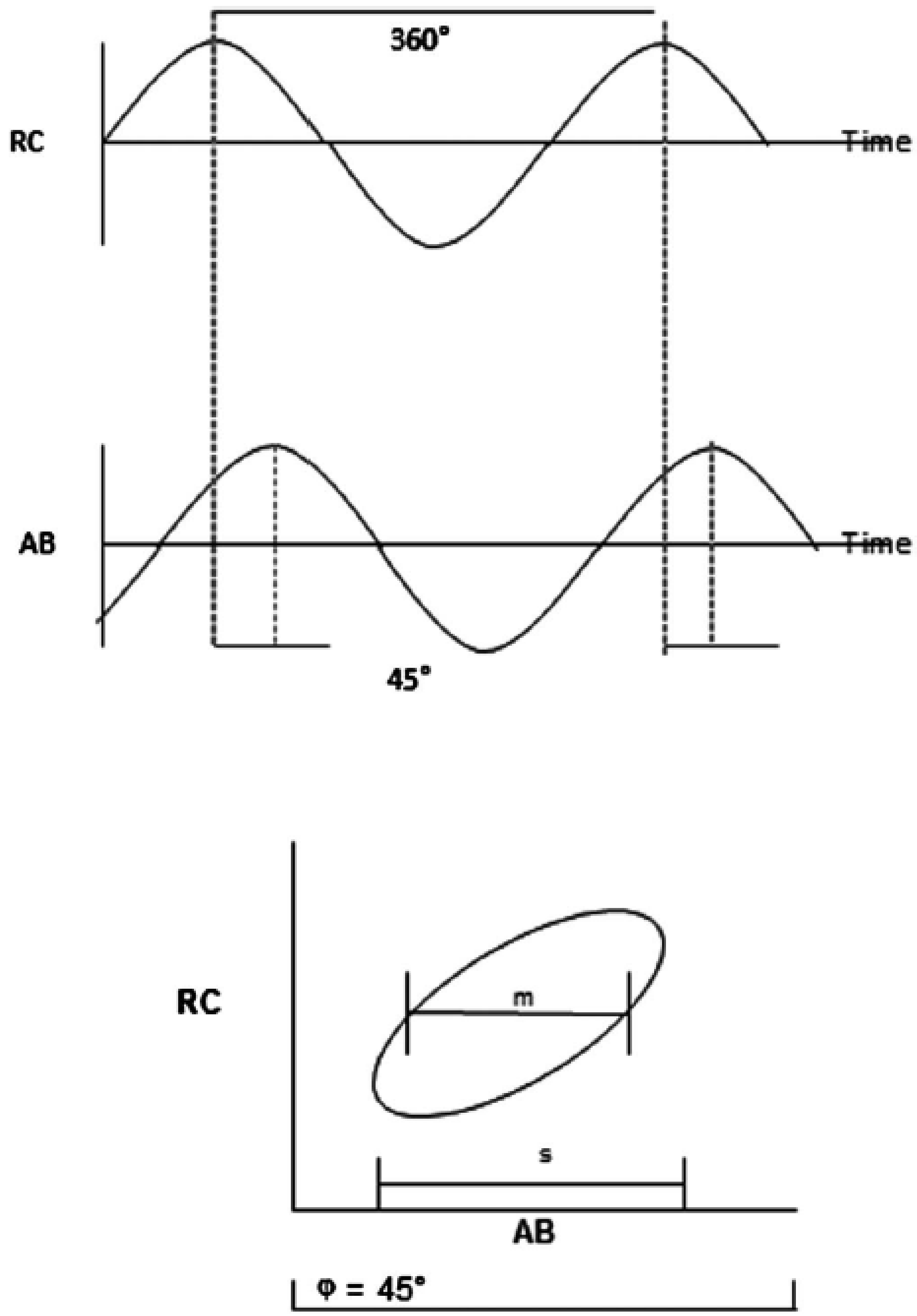

Figure 2-6: A trace demonstrating an asynchronous motion of the rib cage (RC) and the abdomen (AB) wherein the RC and AB motion are out of phase by 45 degrees. ‘m’ is the width of the figure at mid RC excursion, and ‘s’ is the width representing AB excursion.

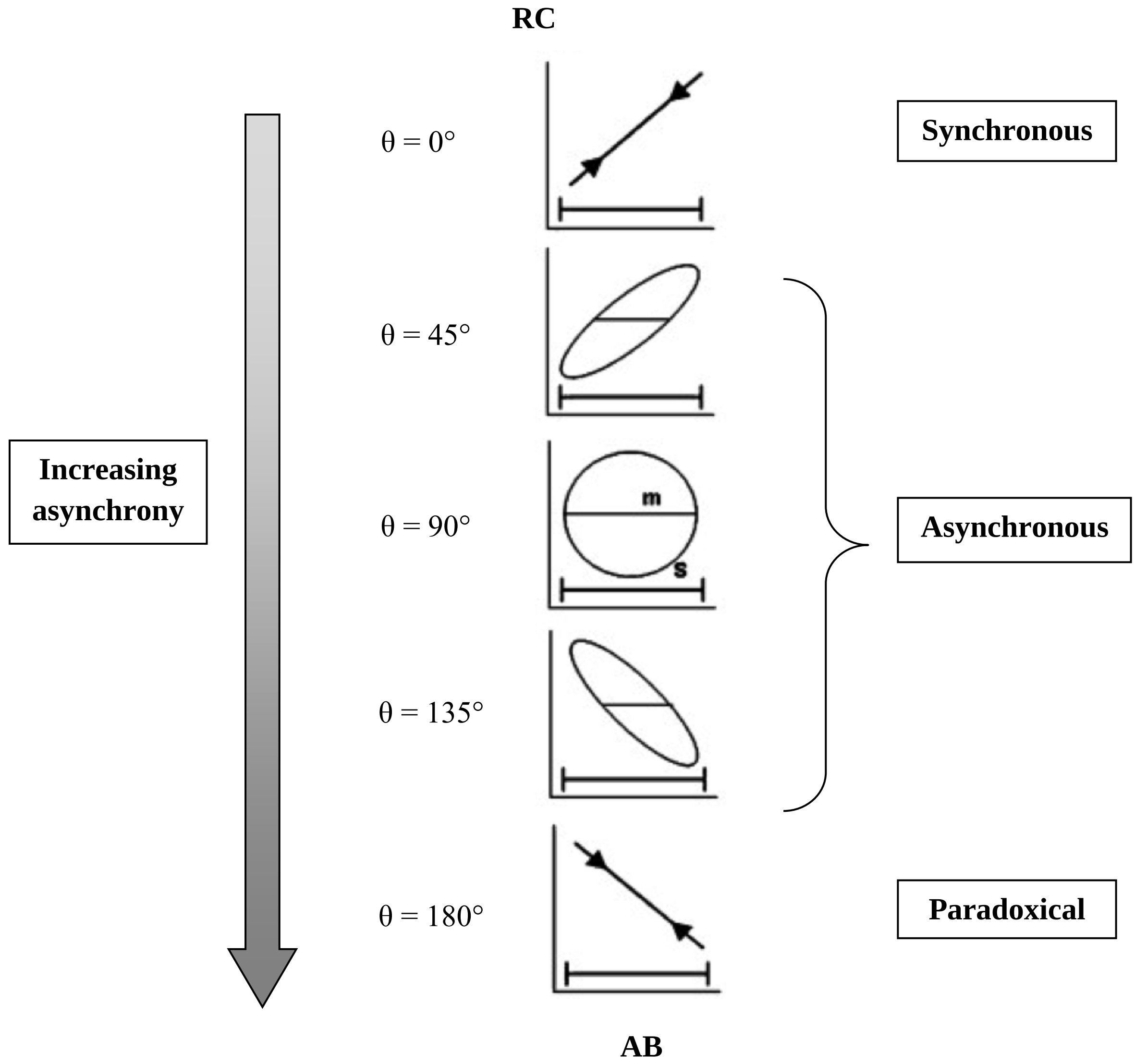

Figure 2-7: Lissajous figures and their respective phase angles (θ) demonstrating various degrees of asynchronous motion of the rib cage and the abdomen.

Adapted from (Hammer and Newth, 2009).

2.2.2.9 Transdiaphragmatic pressure time product (PTPdi)

The transdiaphragmatic pressure time product (PTPdi) was measured as an index of the WOB in the randomised, crossover study comparing CPAP and HHFNC in prematurely born infants with evolving BPD. PTPdi was calculated breath by breath by integrating the area subtended by the transdiaphragmatic pressure during inspiration. Measurement and acquisition of Pdi is described above. The phase transition of respiratory flow is generally used to determine the start and end of inspiration. Because of the use of HHFNC, it was not possible, to measure respiratory flow directly in the study. The beginning of inspiration was determined, therefore, by the rise in Pdi at the start of a breath and end of inspiration was determined from rib cage movement using RIP (Figure 2-8 and 2-9).The mean of 20 consecutive infant respiratory efforts was taken to calculate the PTPdi.

Figure 2-8: Trace obtained from an infant showing Pgas, Pes, chest and abdomen signals obtained when infant was measured on CPAP mode. The shaded area depicts calculation of PTPdi which was obtained from the area subtended by the Pdi trace during inspiration.

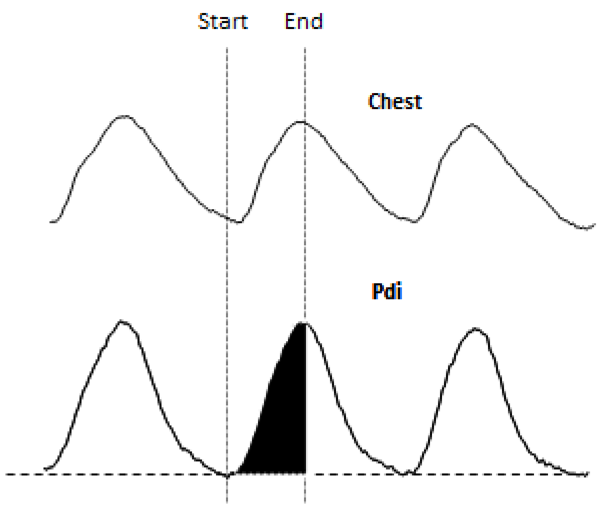

Figure 2-9: A diagram representing the calculation of PTPdi during inspiration

2.2.3 Measurement of diaphragm electrical activity (Edi)

NAVA uses the electrical activity of the diaphragm (Edi), captured by a specialised nasogastric tube with an array of eight bipolar electrodes (Edi catheter), to servo control the applied ventilator pressure. The Edi is used both to trigger each inflation and also to determine the level of support proportional to the infant's neural drive to breathe throughout each inflation (Navalesi and Longhini, 2015). Signals from each electrode pair are differentially amplified, digitised, and processed. The signal is filtered to remove electrical contamination from the heart, esophagus, and environment to give the highest possible signal-to-noise ratio (Sinderby et al., 2007).

Before insertion, the Edi catheter (Figure 2-10) (Maquet Critical Care AB) was dipped in sterile water for a few seconds to both activate the coating which improves electrical conductivity and to aid insertion. Edi catheter size and insertion distance for each patient was determined by the patient weight in kilograms and length in cm. The Edi catheter was inserted either oro or nasogastrically by measuring the "NEX" distance (the distance from nose, ear, and xiphoid) for proper insertion depth. The Edi catheter was inserted and correct positioning confirmed as per manufacturer instructions using the Edi catheter positioning guide function on the ventilator (Magnet Servo-n User Manual Version 1.1). The guide function displayed the retrocardiac echocardiograph. Correct positioning was achieved when the P waves and QRS complexes were visible in the uppermost leads and then decreased in size until the P waves disappeared in the lowest lead. Coloured highlighting of the central two leads appeared once the catheter was in the correct place (Figure 2-11). Once correct positioning was confirmed, the catheter was securely attached to the infant's face using an adhesive dressing. Stein et al (Stein et al., 2013b) evaluated the success or failure (due to complications) of placing the Edi catheter in 17 premature, non-ventilated infants (average birthweight 1220 g, range 628-2520 g). The Edi catheter was placed successfully and correctly in all subjects, as determined by a dedicated "catheter positioning" window on the ventilator and no adverse events were noted (i.e. no pharyngeal, esophageal, or gastric damage or trauma, no apnea or bradycardia, and tracheal placement). There was no deterioration in the Edi signal with different positions, or with feeds.

Before the infant was changed to NAVA mode, the NAVA level was adjusted so that the estimated pressure waveform on NAVA closely matched the actual pressure waveform on the baseline settings, aiming for the peak Edi to be between 5-15μV as per the recommendations of the manufacturer. The baseline ventilator settings were used to determine the back-up settings to be used on NAVA in the absence of an Edi signal. The backup setting was the pressure setting when baby was on the ACV, default Edi trigger was 0.5 mcV and apnoea time set was 2 seconds. The upper pressure limit was at least five cm H_2O higher than the baseline settings, but did not exceed 30 cm H_2O.

The highest Edi value of the waveform (Edi peak) represented neural inspiratory effort, responsible for the size and duration of the breath. The lowest Edi (Edi min) represented spontaneous tonic activity of the diaphragm, which prevents de-recruitment of alveoli during expiration. The Edi trigger (μV; the minimum increase in electrical activity from the previous trough) triggered the ventilator to recognise the increase in electrical activity, thereby resulting in initiation of a breath.

The NAVA level ($cmH_2O/\mu V$; a conversion factor) translated the Edi signal into proportional pressures. Edi multiplied by the NAVA level determined airway pressure delivered by the ventilator for each breath. The NAVA software automatically calculates peak inspiratory pressure (PIP) every seventeen minutes demonstrated by the formula

$$PIP = NAVA\ level \times (Edi\ peak - Edi\ min) + PEEP.$$

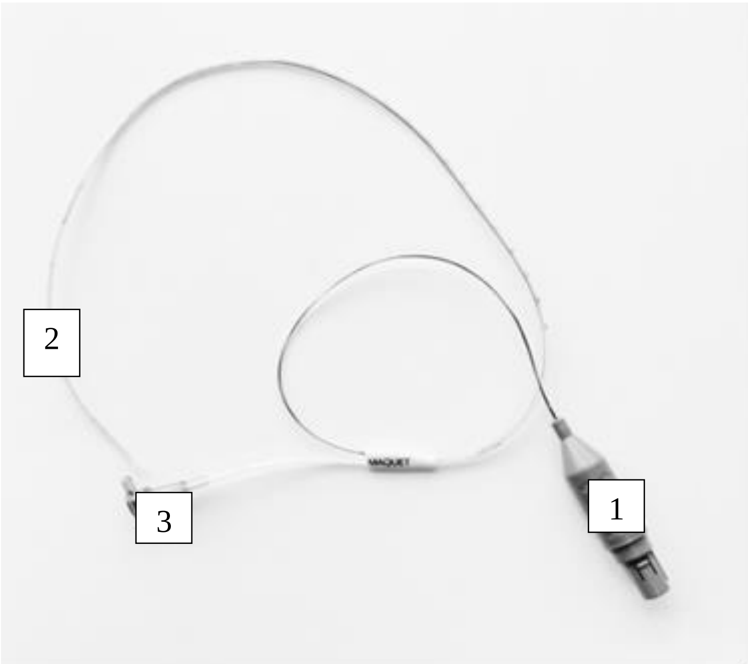

Figure 2-10: NAVA - Edi Catheter

1- Connection to the module used for electrical activity of the diaphragm (EAdi) measurements, 2 - Microsensors, 3- Nutrition feed

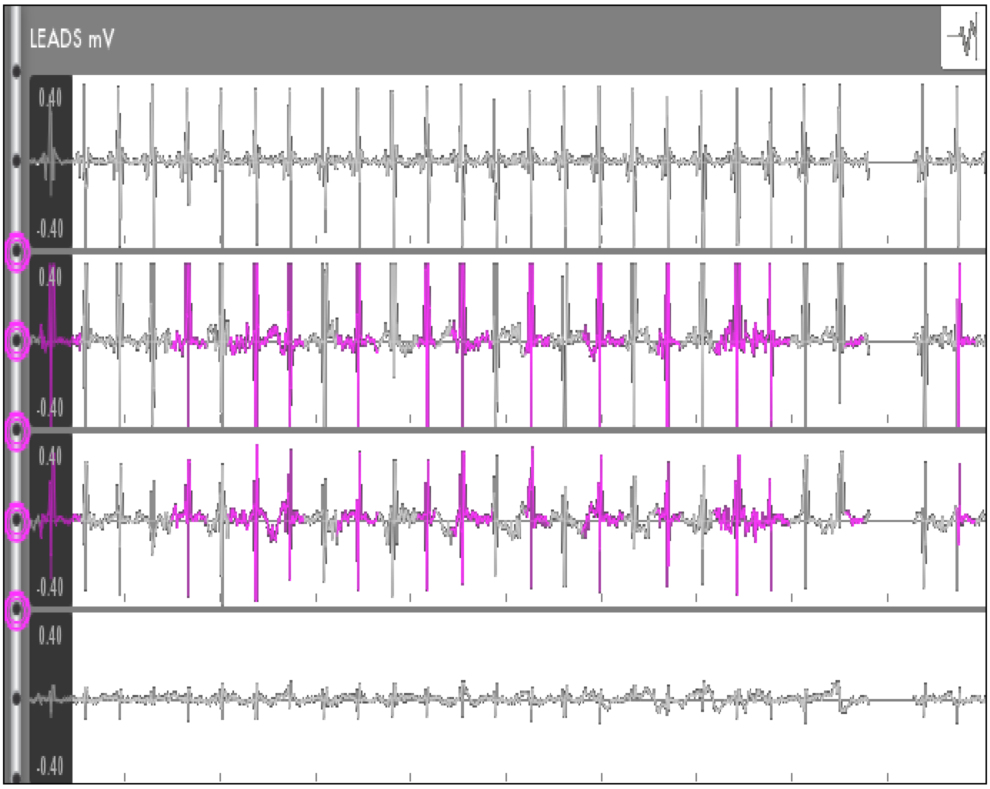

Figure 2-11: Edi catheter positioning screen. Correct placement of the nasogastric tube shows the retro cardiac electrocardiogram (ECG) signal progressing from large p and QRS complexes in the upper leads to small or absent complexes in the lower leads.

2.3 Statistical analysis

Data were analysed for normality using the Kolmogorov-Smirnov, Shapiro-Wilk tests. Student's t-test was used to compare normally distributed groups. Non-parametric data were analysed using the Mann Whitney U test and Wilcoxon signed rank test for paired data. The Chi Squared and Fisher's exact test were used where appropriate. Data were deemed significant if the p value was less than 0.05. SPSS for windows (version 21 or 22 SPSS Inc, Chicago IL, USA) and Stata v 14 were used.

2.4 Randomisation

Randomisation was carried out by random number table generation and selection of a sequential sealed envelope after successful recruitment and meeting of pre-defined entry criteria based upon gestational age. There were no gestational age strata for randomisation. There has been no drop outs in any of the studies.

Chapter 3: Randomised crossover trial of PAV versus ACV

3.1 Introduction

During PAV, the applied pressure is servo controlled, based on continuous input from the infant's breathing throughout each spontaneous breath. In addition, the ventilator can provide inflation pressure in phase with the tidal volume change in order to reduce the compliance load (i.e. the load due to the stiffness of infant's lungs) and in phase with the flow change to reduce the resistance load (i.e. the load due to airflow obstruction), termed elastic and resistive unloading, respectively (Schulze, 2002). Very prematurely born infants developing or with established BPD will have stiff lungs (that is non-compliant) despite a very compliant chest wall, so may be particularly likely to benefit from elastic unloading. PAV has only been assessed in neonates in a few studies. In a previous crossover study, infants with evolving or established BPD on PAV compared to ACV had better oxygenation indices, a lower WOB and better respiratory muscle strength. The infants, however, were only studied on each ventilator mode for one hour (Bhat et al., 2015). The longest infants have been studied on PAV was four hours (Schulze et al., 2007), but during that study, only changes in pulse oximetry results were assessed. During PAV, the applied pressure is servo controlled throughout each breath, whereas during ACV, only the initiation of inflation is synchronised to the start of inspiration; hence, it is likely that oxygenation would be superior on PAV compared to ACV (Bhat et al., 2015). During PAV, however, it has been previously demonstrated that there is a trigger delay of 60 millisecond in an in vitro model (Patel et al., 2010a); hence, it was important to assess blood gases over a longer period than studied previously (Bhat et al., 2015). Hence, in this study the hypothesis that infants with evolving or established BPD would have superior OI results after four hours on PAV compared to after a similar period on ACV, was tested.

3.2 Methods

A randomised, crossover study was undertaken. Infants were entered into the study if their parents gave informed written consent. The study was approved by the South East London Research Ethics Committee (Appendix 1.1).

3.2.1 Protocol

Iinfants who were born prematurely (less than 32 weeks gestation) and who remained ventilated after the first week after birth were eligible for entry into the study if they were being supported by ACV. Evolving BPD was defined as ventilator dependence beyond seven days and established BPD as ventilator dependence beyond twenty-eight days. Infants were ineligible for inclusion in the study if they had a major congenital cardiac abnormality or were receiving a neuromuscular blockade agent.

During the eight hour study period, no other changes were made to the infant care than the changes in ventilator mode. Infants at King's College Hospital NHS Foundation Trust are routinely supported by the SLE 5000. The infants were transferred from the SLE 5000 ventilator to ACV on the Stephanie ventilator using the same ventilator settings (baseline). All infants as per the unit's routine policy were ventilated via shouldered endotracheal tubes which have been shown to have minimal or no leaks (Hird et al., 1990).

One hour was allowed for stabilisation of the infant on the Stephanie ventilator. A blood gas analysis was then performed and the baseline ventilator settings were noted. During the stabilisation period, the ventilator displayed compliance and resistance settings were noted every ten minutes and the six results meaned. The ventilator calculated the compliance from the inflation pressure (PIP - PEEP) and the resultant tidal volume. The value of the reciprocal of the compliance, elastance, was used to set the level of the elastic unloading. Each infant was then randomised to receive first either PAV or ACV mode for four hours and for the second four hours received the alternative mode.

During ACV, the peak inspiratory pressure (PIP), PEEP and the inflation time were kept the same as at baseline. During PAV, the maximum PIP was set at 5 cm H_2O above the PIP on ACV to prevent higher airway pressures. The PEEP level during PAV was the same as at baseline, and the PEEP and the inflation time during back up ventilation were the same as at baseline. Whenever cessation of spontaneous breathing occurred for more than five seconds during PAV, mandatory backup inflations were automatically delivered by the ventilator. The backup rate set at 40 breaths per minute was delivered to the infant for ten seconds with a backup inflation peak pressure of 5 cm H_2O above the PIP used during ACV. Elastic unloading, which was used only during inspiration, was initially set at 75 % of full unloading. If after ten minutes the infant remained stable and no airway pressure waveform abnormalities were observed (Patel et al., 2010a), the unloading was increased to 100 %. Full unloading was the level of unloading which increased the infant's compliance to the expected 'normal', that is, 2.0 mL/cm H_2O/kg. If airway pressure waveform abnormalities were then noted by looking at the pressure display, the unloading was to be reduced back to 75 %. Resistive unloading was not used as, an in vitro model, oscillations in the airway pressure waveforms appeared when the resistive unloading was greater than 100 cm H_2O/L/s (Patel et al., 2010a). The number of desaturations oxygen saturation less than 88 %) on each mode was noted. An arterial blood sample was obtained at the end of each 4 hour period, the ventilator settings were noted and the OI was calculated. RR, Vt and MAP were obtained from the ventilator. The results from the last five minutes of the four hour study period were averaged. All the infants had continuous oxygen saturation monitoring. During the study, the inspired oxygen concentration was adjusted as necessary to maintain the oxygen saturation level in the range 92 – 96 %.

3.2.2 Sample size

In a previous study, the mean OI in the PAV group was 6.0 (SD±2.4) and in the ACV group was 9.8 (SD±3.7) (Bhat et al., 2015). The planned sample size was eighteen infants to allow detection between the two ventilator modes of a within patient difference of 0.7 SD in the oxygenation index results with 80 % power and a two-sided significance of 5 %.

3.2.3 Statistical analysis

Differences were assessed for statistical significance using the paired Wilcoxon signed rank test using IBM SPSS statistical software, V.21 (IBM Corporation, USA).

3.3 Results

Recruitment to the trial was stopped at eight infants as all the OI results were in favour of PAV (Table 3.1). The decision was taken by the clinical team and the study statistician in the knowledge that the probability of all 8/8 results being in the same direction if both modes were in fact equally effective was extremely small ($p=0.0039$).

The median BW of the eight infants was 767 (range 650 –1926) g, GA 25.7 (range 24.4 – 33.5) weeks and postnatal age at measurement 19 (range 10 –105) days; seven of the eight infants were male. All the infants had been exposed to antenatal steroids and received postnatal surfactant and were receiving caffeine at the time of study. None were receiving sedation at the time of study or had received postnatal steroids. Their median baseline compliance was 0.4 (range 0.3–1.1) mL/cm H_2O and resistance was 155 (range 66–252) cmH_2O/L/s. All infants tolerated 100 % elastic unloading the study. The median FiO_2 ($p= 0.049$), the median mean MAP ($p=0.012$) and the median OI ($p=0.012$) were all lower on PAV compared to ACV (Table 3-1). There was no significant difference in the median number of desaturation episodes (Table 3-2) between the two modes.

Table 3-1: Oxygenation index results by ventilator mode

Infant Number	PAV	ACV	Mode used first
1	8.1	15.2	PAV
2	7.0	8.3	PAV
3	17.4	21.6	ACV
4	12.6	20.3	PAV
5	5.2	8.4	ACV
6	10.0	14.1	PAV
7	5.9	11.3	PAV
8	9.9	11.7	ACV
Median	9	12.9	

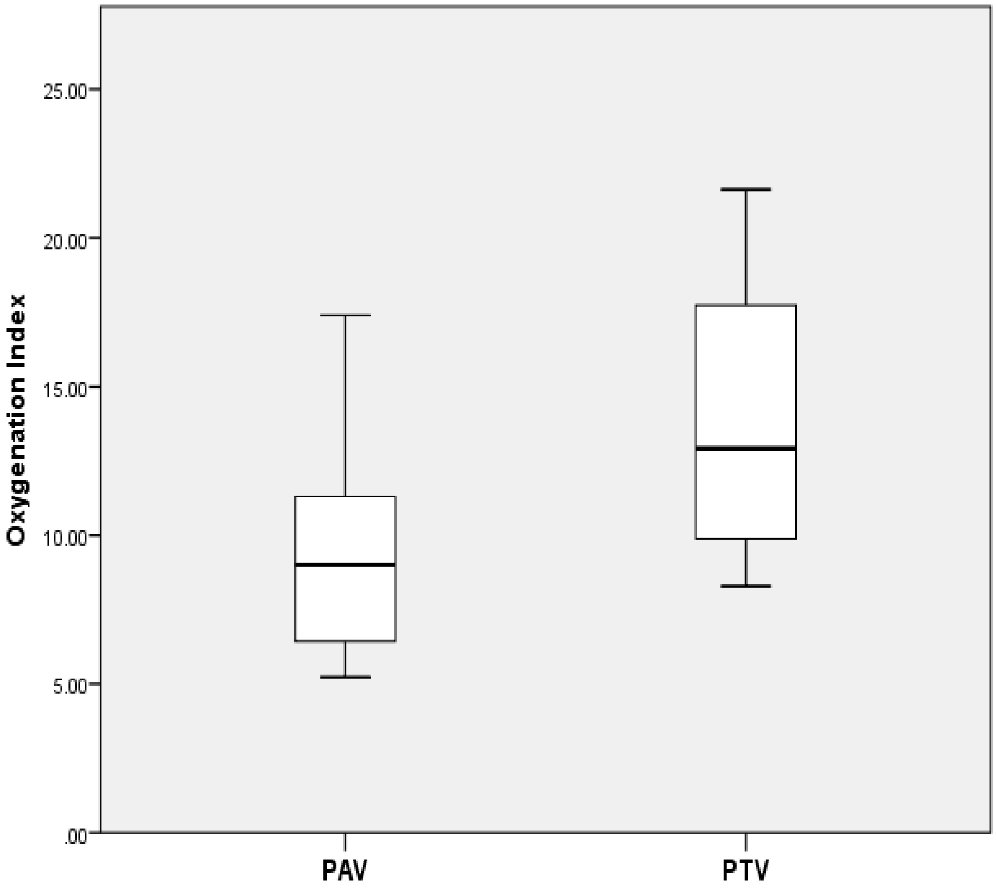

Figure 3-1: Box plot oxygenation index results by ventilator mode

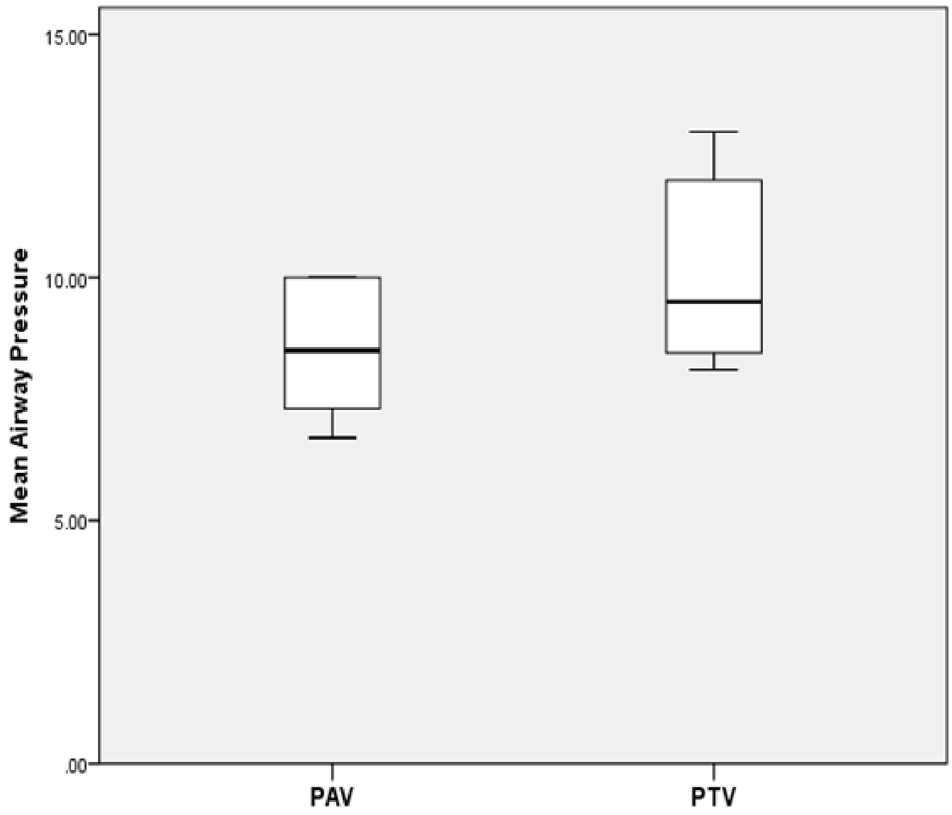

Figure 3-2: Box plot Mean airway pressure results by ventilator mode

Table 3-2: Comparison by ventilator mode (n=8)

The results are expressed as the median (range)

	PAV	ACV	P value
FiO_2	0.48 (0.31-0.65)	0.57 (0.40-0.72)	0.049
PCO_2 (kpa)	8.0 (5.5-9.4)	7.2 (5.5-11)	0.889
OI	9.0 (5.2-17.4)	12.9 (8.3-21.6)	0.012
MAP (cm H_2O)	8.5 (6.7 -10.0)	9.5 (8.1 -13)	0.012
Respiratory rate	56 (47-76)	57 (49-66)	0.401
Tidal Volume (ml/kg)	7.5 (3.70-10.0)	5.8 (3.5-10.3)	0.093
Saturations (Sao2) (%)	95 (92-97)	95(93-98)	0.571
Desaturation episodes (n)	1 (0-2)	0 (0-2)	0.429

Table 3-3: Comparison by PAV ventilator mode used first (n=5)

The results are expressed as the median (range)

	PAV	ACV	p value
FiO_2	0.52 (0.4-0.6)	0.55 (0.46-0.64)	0.343
PCO_2 (kpa)	8.1 (5.5-8.9)	6.9 (5.5-9.3)	0.686
OI	8.1 (5.9-12.7)	14.1 (8.3-20.3)	0.043
MAP (cm H_2O)	7.7 (6.7-10)	8.5 (8.1-12)	0.042
Respiratory rate	55 (48-77)	53 (50-61)	0.225
Tidal Volume (ml/kg)	8.6 (4.1-9.6)	5.5 (3.5-10.3)	0.138
Saturations (Sao2) (%)	96 (93-97)	95 (94-99)	0.480
Desaturation episodes (n)	1 (0-1)	0 (0-2)	0.480

Table 3-4: Comparison by ACV ventilator mode used first (n=3)

The results are expressed as the median (range)

	PAV	ACV	p value
FiO_2	0.45 (0.31-0.65)	0.6 (0.4-0.72)	0.109
PCO_2 (kpa)	7.2 (7.0-9.32)	7.5 (6.4-11)	0.593
OI	9.9 (5.2-17.4)	11.7 (8.5-21.6)	0.109
MAP	9.3 (7.1-10)	10 (9-13)	0.109
Respiratory rate	58 (55-70)	61 (57- 66)	1.00
Tidal Volume (ml/kg)	6.7 (3.7-7.9)	6.3 (3.8-7.5)	0.285
Saturations (Sao2) (%)	94 (94-98)	96 (93-97)	1.00
Desaturation episodes (n)	1 (0-2)	0 (0-2)	0.655

3.4 Discussion

This study has demonstrated that PAV compared with ACV in prematurely born infants ventilated beyond the first week after birth resulted in a reduced WOB and a lower OI. The lower OI is in keeping with the findings of Schulze and colleagues (Schulze et al., 2007), pulse oximetry readings were not significantly different on the two modes in very prematurely born infants (mean GA 25.6 weeks) with evolving CLD. In addition, in prematurely born infants with acute respiratory distress (birth weights between 600 and 1200 g) on 45-minute epochs on PAV compared with 45-minute epochs on ACV or intermittent mandatory ventilation, similar arterial oxygenation was maintained despite lower airway and transpulmonary pressures during PAV (Schulze et al., 1999). The lower mean airway pressure and lower OI that this study has demonstrated on PAV likely reflect that during PAV the applied pressure is servo controlled throughout each spontaneous breath, whereas during ACV, synchronisation of inflation is only at the beginning of inspiration. In addition, the lower OI might also reflect the reduced level of asynchrony during PAV, which was not statistically significant (p=0.05). High airway pressures and airway pressure oscillations have been demonstrated when excessive amounts of elastic and resistive unloading are used (Schulze et al., 1998). Previous study (Bhat et al., 2015) was terminated before the calculated sample size, as all twelve infants in the one hour crossover study had lower OI results on PAV compared to ACV (Bhat et al., 2015). The maximum duration PAV was previously trialled was four hours (Schulze et al., 2007), twenty two infants had a median GA of 25.6 weeks and were studied at a mean PNA of 22.9 days. They found after a four hour period of PAV that despite a lower MAP, the inspired oxygen concentration and pulse oximetry readings were not significantly different between the two groups. Hence, it was important that four hour duration was tested for oxygenation indices when on PAV and compared with ACV. This study has demonstrated that four hour on PAV compared with four hour on ACV resulted in a significant improvement in the OI.

On subgroup analysis, the results remained the same when analysis was done separately depending upon the start mode of ventilation ie PAV first however not when ACV was used first. This indicates that there was no cross over effect of the baseline ventilator mode and that four hour study is adequate to reliably note the differences between the two modes.

There are limitations to this study. The postnatal age of infants studied had a wide range, studying infants at different stages of evolving BPD. Further stratifying based on the postnatal and gestational age would have been ideal however difficult in view of the small sample size.

In conclusion, this short-term cross- over study has demonstrated that PAV compared to ACV was associated with significant superior oxygenation, which likely reflects better synchronisation of the inflation pressure and tidal volume throughout inspiration.

Chapter 4: Neurally adjusted ventilatory assist (NAVA) in very prematurely born infants with evolving BPD

4.1 Introduction

Application of mechanical ventilation in spontaneously breathing children remains a challenge for several reasons: mainly, small tidal volumes and high respiratory rates, especially in the presence of leaks, interfere with patient-ventilator synchrony. Leaks also cause unreliable monitoring of respiratory drive and respiratory rate (Vignaux et al., 2013). Furthermore, ventilator adjustment must take into account that infants have strong vagal reflexes, demonstrate central apnea and periodic breathing, with a high variability in breathing pattern (Beck et al., 2016).

NAVA is a mode of ventilation whereby the timing and amount of ventilatory assist is controlled by the patient's neural respiratory drive. Since NAVA uses the diaphragm electrical activity (Edi) as the controller signal, it is possible to deliver synchronized assist, to follow the variability in breathing pattern, and to monitor patient respiratory drive, independent of leaks (Navalesi and Longhini, 2015).

Infants with evolving or established BPD have a high resistance which means flow triggering can be challenging. In addition, the severity of their lung function abnormalities likely means that supporting each breath throughout the inspiratory cycle would be advantageous. Hence, this study aimed to test the hypothesis that NAVA compared to ACV would result in a lower OI in infants with evolving or established BPD.

4.2 Methods

A randomised, crossover study was undertaken. Infants were entered into the study if their parents gave informed written consent. The study was approved by the West Midlands - Solihull Research Ethics Committee (Appendix 1.2).

4.2.1 Protocol

Infants were eligible for this randomised, crossover study if they were born at less than 32 weeks of gestation and remained ventilated at one week of age on ACV. Those with major congenital abnormalities or receiving neuromuscular blockade were excluded. Infants at King's College Hospital NHS Foundation Trust are routinely supported by the SLE 5000 (software versions 4.3; SLE Ltd., South Croydon, UK). All infants were ventilated with Coles shouldered endotracheal tubes which have been shown to have minimal or no leaks (Hird et al., 1990). Volume targeting was not used. On entry into the study, the infants were transferred from ACV on the SLE 5000 to ACV (named 'Pressure Control' on the Servo-n ventilator, Maquet Critical Care, Solna, Sweden). The same ventilator settings and backup rate were used. In particular, the PEEP was kept at 4–5 cmH_2O as had been used prior to the study and the inflation time was set, as previously, at 0.36 to 0.4 seconds. The back-up setting was set with apnoea time of two seconds and the upper pressure limit at least five cm H_2O higher than the baseline settings, but did not exceed 30 cm H_2O. The default Edi trigger was set at 0.5 mcv. A six French Edi catheter was inserted and correct positioning was confirmed as per the instructions of the manufacturer using the Edi catheter positioning guide function on the ventilator (Magnet Servo-n User Manual Version 1.1).

After one hour of stabilisation on the Servo-n ventilator using the settings described above, blood gas analysis was performed. Infants were then randomised to receive either ACV or NAVA first for one hour and then to receive the alternative mode for a subsequent hour. The order in which the infants received the two modes was randomised between each baby using a sequential opaque sealed envelope system. Before the infant was changed to NAVA mode, the NAVA level was adjusted so that the displayed pressure waveform on NAVA closely matched the actual pressure waveform on the baseline settings, aiming for the peak Edi to be between 5 and 15 μV as per the recommendations of the manufacturer. The baseline ventilator settings were used to determine the backup settings to be used on NAVA in the absence of an Edi signal. The initial ventilator settings were noted, and the number and duration of desaturations (defined as oxygen saturation less than 88%) were noted on each ventilator mode. The inspired oxygen concentration (FiO_2) was adjusted to maintain oxygen saturations between 92 and 96%. At the end of each hour, capillary blood gas analysis was performed and the OI calculated as FiO_2 x MAP × 100/pO_2. The FiO_2, the PIP, MAP, Vt and respiratory system compliance (calculated from the tidal volume divided by the PIP) were recorded from the ventilator displays and averaged from the last five minutes of each one hour period. The data were down-loaded into excel via a USB stick.

4.2.2 Sample size

The planned sample size was eighteen infants, as this allowed detection of a difference in OI between the two modes of one standard deviation (1SD), with 80% power and 5% significance. An interim analysis was planned to take place half way through, i.e. after nine patients, as a previous study with PAV, a ventilation mode which also provides tailored support throughout the infant's inspiratory cycle, demonstrated that the OI on PAV was better in all patients than on ACV (Bhat et al., 2015). In order to preserve the type I error at 5%, the interim analysis was conducted at 0.01 with the final analysis conducted using 0.04. If the interim analysis showed $p < 0.01$, then the trial was to stop and the final analyses was conducted using the nine patients.

4.2.3 Statistical analysis

The results were positively skewed and, therefore, log transformed for analysis so that a paired t test could be used. Using that method, the results including the mean and confidence intervals were on the ratio scale. Results were back-transformed to give geometric means for each mode of ventilation. The ratio of geometric means and the corresponding 95% confidence intervals for the ratio are presented. The ratio of the geometric means was interpreted as the percentage difference between results on NAVA compared to on ACV. The desaturation data were discrete and analysed using the Wilcoxon signed-rank test. Data were analysed using Stata v 14.

4.3 Results

At the interim analysis, the comparison of the OI on NAVA versus ACV was statistically significant using the modified cut-off for significance described above. The OI was lower on NAVA for all infants (Table 4-1). Hence, the clinical and statistics team agreed that the trial was to be stopped and the data analysed. Nine infants had been assessed, seven males and two females. Their median GA was 25 (range 22–27) weeks and median BW 750 (range 545–830) grams. The infants were studied at a median PNA of 20 (range 8–84) days. Three infants with the highest OI's median GA was 25 (range 25-26) weeks, BW 760 (range 760-794) grams and PNA when infants were studied 64 (64-84) days. This when compared with the remaining infants of median GA 25 (range 24-28) weeks, 750 (range 600-830) grams and PNA of 10.5 (range 8-21) days was not statistically significant. All had received at least one dose of antenatal steroids and postnatal surfactant and were on caffeine at the time of the study. Only one infant was receiving sedation and this was at the same dose throughout the study. Five of the infants were studied first on NAVA and four on NAVA then ACV. Neither was there any suggestion that the order (by chance) was related to the size of value, i.e. no suggestion that all those with a high starting OI received the modalities in the same order (p=0.66). The ratio of the geometric means for the OI, the primary outcome, was 0.72 (NAVA/ACV), showing that the mean OI was 28% lower on NAVA compared to ACV with corresponding 95% CIs from 62 to 83% (Table 4-1). Infants who had the highest OI's on ACV tended to have a larger reduction in OI when studied on NAVA (Table 4-1). The mean PIP (p=0.017) and mean MAP (p =0.004) were significantly lower on NAVA, as was the mean FiO_2 (p = 0.007). The mean compliance (p=0.005) and oxygen saturation (p=0.016) were significantly higher on NAVA. The OI results remained statistically significant even without including the infants with highest OI's ($p=0.003$). The means for the Vt, RR and peak Edi and the number of desaturations were not significantly different between the two modes (Table 4-2).

Table 4-1: Results by ventilatory mode

Individual baseline PIP and FiO_2 at the start of the study and individual OI data at the end of each study mode is given below. The mode which was used first in each infant is given in the fifth column.

IP (cm H_2O)	FiO_2	ACV (OI)	NAVA (OI)	Mode first	GA at measurement (wks)	PNA at measurement (days)
27	1	30.3	17.4	ACV	36.3	84
16	0.44	9.2	8	NAVA	26.1	9
18	0.63	7.6	5.7	NAVA	26.6	9
18	0.27	6.7	4.6	ACV	26.4	8
24	0.87	26.8	16	ACV	29.6	30
19	0.41	7.4	6.6	NAVA	29.6	12
19	0.7	24.1	13.4	NAVA	32.6	64
18	0.45	6.4	5.4	NAVA	27.9	21
23	0.4	5.7	4.5	ACV	27.1	20

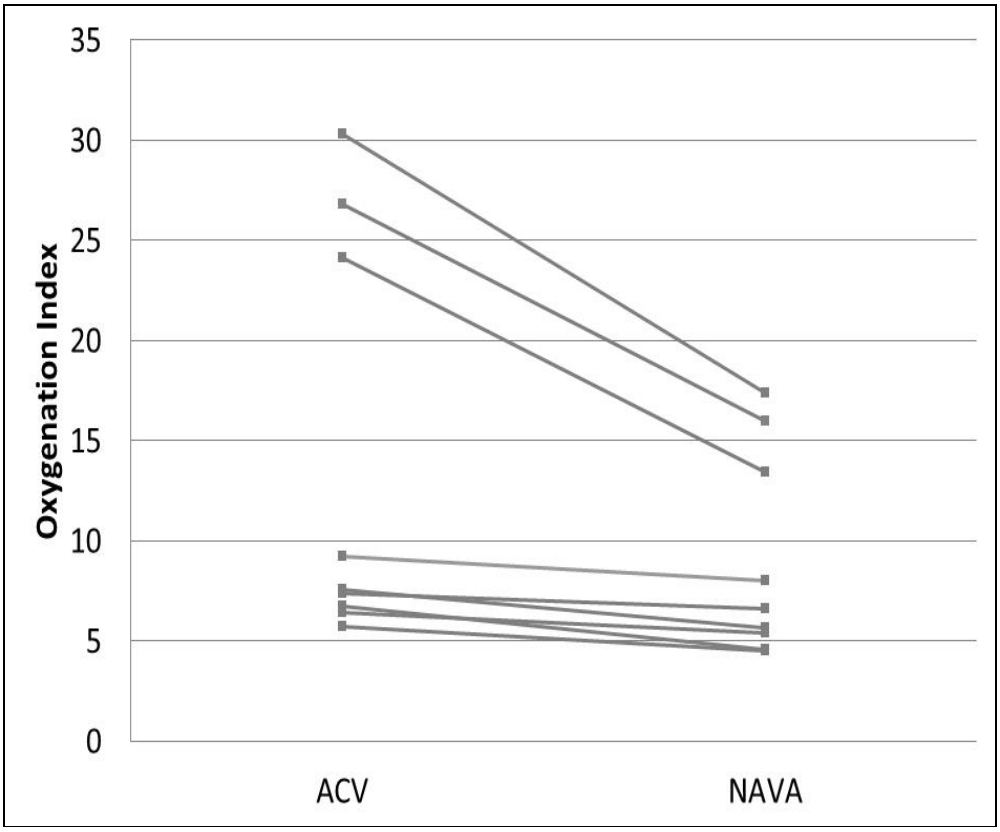

Figure 4-1: Individual OI data at the end of each mode

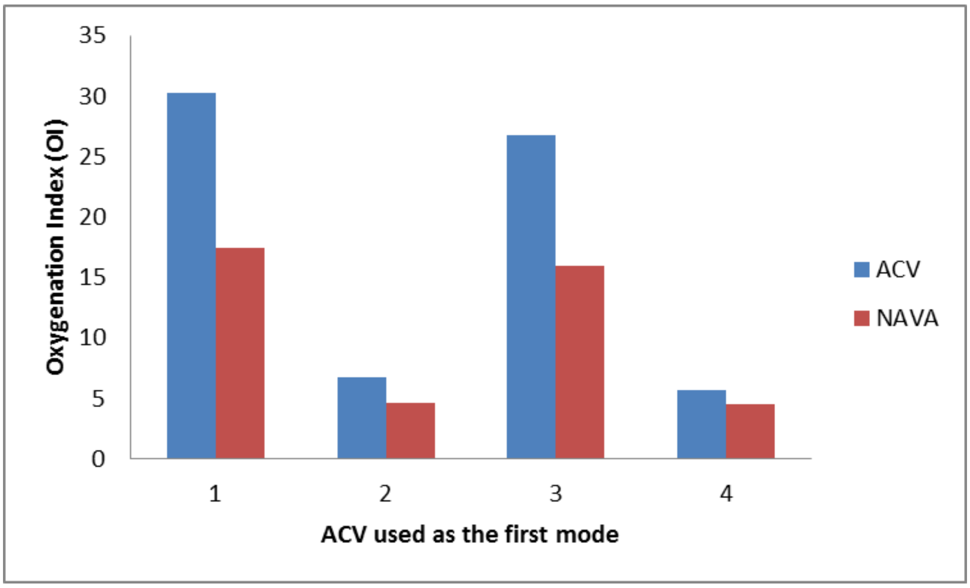

Figure 4-2 OI data when infants randomised to ACV mode first

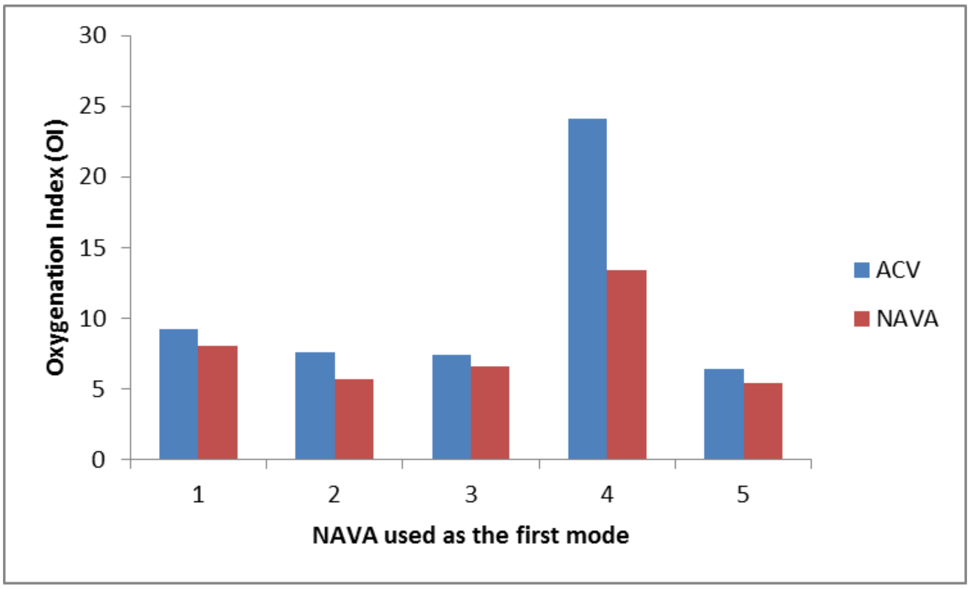

Figure 4-3 OI data when infants randomised to NAVA mode first

Table 4-2: Results by ventilatory mode

The results are presented as the geometric mean (range) for each mode, the ratio of geometric means between the two modes and the corresponding 95% CI

	Mean ACV	Mean NAVA	Ratio of geometric means (NAVA/ACV)	95% confidence interval for ratio	P value
Oxygenation index	11.06 (5.7-30.3)	7.92 (4.7-17.4)	0.72	0.62 – 0.83	0.0007
Peak airway pressure (cmH_2O)	20.13 (14.8 -27.1)	16.72 (12.7-28.6)	0.83	0.72 – 0.96	0.017
Mean airway pressure) (cmH_2O)	10.53 (8.8-14.2)	9.20 (7.8-12.7)	0.87	0.81 – 0.94	0.004
FiO_2	0.45 (29.2-91.0)	0.36 (23-54.9)	0.81	0.71 – 0.93	0.007
Peak Edi (μV)	14.04 (6.1-47.0)	11.10 (7.4-22.0)	0.79	0.60 – 1.05	0.089
Expiratory tidal volume (ml/kg)	7.06 (5.1-8.6)	6.24 (3.9-10)	0.88	0.76 – 1.02	0.87
Compliance (ml/cmH_2O)	0.50 (0.30-0.68)	0.62 (0.34-0.91)	1.24	1.09 – 1.41	0.005
Respiratory rate (breaths/min)	51 (40-65)	50 (38-67)	0.98	0.89 – 1.08	0.616
Oxygen saturations (%)	94 (90-98)	98 (95-100)	1.03	1.01 – 1.05	0.016

4.4 Discussion

This pilot study demonstrated that in infants born very prematurely and with evolving or established BPD, NAVA compared to ACV resulted in a significantly lower OI. This was associated with significantly lower PIPs and MAPs, likely reflecting that during NAVA the applied pressure is servo controlled throughout each inflation. On ACV, although inflation is triggered by the beginning of the infant's inspiratory effort, the start of inflation may have been delayed as a flow trigger was used. Furthermore, after the inflation is triggered during ACV, neither the inflation pressure nor time is tailored to the infant's inspiratory efforts. The higher compliance on NAVA compared to ACV reflects the lower PIPs with similar tidal volumes. A higher compliance on NAVA has been previously reported in neonatal and paediatric patients (Beck et al., 2009, Breatnach et al., 2010, de la Oliva et al., 2012). The study results suggest that infants with the highest OIs, i.e. the most severe lung disease, had the greatest reduction in OI during NAVA. This may reflect, as above, the shorter trigger delay on NAVA which means more of the infant's breath is pressure supported.

There are strengths and some limitations to this study. As the same ventilator was used for each mode, the significant differences demonstrated are due to the differences in the modes, rather than differences in the ventilator performance. Although infants were only studied for an hour on each mode, this study has demonstrated significant differences between the two modes. The infants included had a wide range of severity of respiratory disease as suggested by their PIP and FiO_2, yet a positive effect of NAVA in all infants was noted. The infants had also had a wide range of postnatal ages, but previous audits of 100 consecutive prematurely born infants demonstrated, 95% of those who remained ventilator dependent at one week developed BPD. Thus results demonstrate that compared to ACV, NAVA use was associated with superior results in infants with evolving or established BPD. Capillary blood samples were used to calculate the OIs. This method was used at the end of each of the two periods in all infants, thus the use of capillary blood sampling would not bias the results. The infants were all clinically stable when assessed and none were seriously ill, had shock, hypotension or peripheral vasoconstriction at the time of assessment (McLain et al., 1988). Thus, it was appropriate to calculate the OIs from the capillary blood samples. Only one infant was receiving sedation and this was at the same dose throughout the study, so this did not influence the results. A crossover study design was used as this removes the variability between patients by looking at effects within them. As no order effect was demonstrated, the design gives more precision. The trial was stopped at the planned interim analysis as in all infants the OI was lower on NAVA. There was no significant difference in the peak Edi between the two modes, although there was a trend for it to be lower on NAVA. This may have been due to insufficient redistribution of work from the patient to the ventilator, as the NAVA level was only adjusted so that the estimated pressure waveform closely matched the pressure waveform on the baseline settings. As yet, there are no randomised controlled trials with long-term outcomes assessing NAVA and therefore, any potential long term benefit remains unknown.

In conclusion, this study has demonstrated in a randomised crossover study that NAVA, compared to ACV, resulted in improved (lower) OI and this was associated with lower peak and mean airway pressures. There was no suggestion that the size of difference in OI was greater with order i.e. with either ACV then NAVA and therefore, any potential long term benefit remains unknown.

Chapter 5: Changes in use of heated humidified high flow nasal cannula oxygen (HHFNC)

5.1 Introduction

HHFNC has gained popularity in many countries (Ojha et al., 2013, Hochwald O, 2010, Hough et al., 2012, Manley et al., 2012, Roehr et al., 2007). Recent RCTs, however have not demonstrated any superiority of HHFNC (Collins et al., 2013a, Manley et al., 2013). Hence a survey was conducted with aim to determine whether use of HHFNC had changed since a previous survey in 2012 (Desai P et al, 2012). In addition, the survey aimed to also identify if and why practitioners preferred HHFNC or CPAP.

5.2 Methods

In 2015, lead clinicians of all 194 neonatal units in the UK were identified from the NNAP report, the BAPM directory and a departmental database from previous audits. Clinicians were sent an email inviting them to complete an electronic web-based survey using Survey Monkey (Appendix 1.3). Non-responders were sent email reminders and then contacted by telephone. In the 2012 survey, practitioners from the then 203 UK neonatal units had been contacted (Desai P et al, 2012). Both surveys included questions on the level of neonatal care, the indications for use of HHFNC and the flow rates used. In addition, the 2015 survey also contained questions on nasal prong size, weaning policies and reasons for HHFNC or CPAP preference (practitioners were given a list of reasons to choose from (Table 5-2)).

5.2.1 Statistical analysis

Differences in the results of the two surveys were assessed for statistical significance using the chi-square test. IBM SPSS statistical software, V.22 (IBM Corporation, USA) was used.

5.3 Results

There was a 100% percent response rate to both surveys. Use of HHFNC had significantly increased in 2015 compared to 2012 ($p<0.001$) (Table 5.1). Almost all local neonatal and neonatal intensive care units were using HHFNC in 2015. Although fewer units were using HHFNC as an alternative to CPAP or weaning from CPAP ($p=0.001$), a greater proportion were using it as the primary support mode post extubation ($p=0.001$). The highest and lowest flow rates used varied in both surveys, but the magnitude of change of flow when weaning from HHFNC did not differ significantly in the two surveys. The flow rate tended to be weaned 24 hourly. The 2015 survey highlighted that in 25% of units prong size was chosen to fit snugly and occlude the nostril and 36% of units had no HHFNC guideline. The majority of practitioners preferred HHFNC to CPAP (Table 5.2).

Table 5-1: HHFNC practice in 2012 and 2015

Data are displayed as the n (%)

	2012	2015	P value
HHFNC			
Total number of units	203	194	
Using HHFNC	113 (56%)	169 (87%)	<0.001
Unit Level			
Special Care Unit	12/53 (23%)	22/42 (52%)	0.003
Local Neonatal Unit	60/92 (64%)	84/88 (95%)	<0.001
Neonatal Intensive Care Unit	41/58 (70%)	63/64 (98%)	<0.001
Data are subsequently displayed only for units using HHFNC			
Indication of Use			
Alternative to CPAP/ Weaning from CPAP	66 (58%)	65 (38%)	0.001
Primary mode of respiratory support post extubation	47 (42%)	104 (62%)	0.001
Highest Flow Rate			
8	36 (32%)	78 (46%)	0.011
7	12 (11%)	6 (4%)	0.017
6	38 (34%)	77 (46%)	0.030
5	27 (23%)	8 (4%)	<0.001
Lowest Flow Rate			
4	11 (10%)	18 (11%)	0.485
3	40 (35%)	40 (24%)	0.023
2	45 (40%)	97 (57%)	0.003
1	17 (15%)	14 (8%)	0.058
Size of change in flow when weaning			
0.5 L/min	30 (27%)	51 (30%)	0.301
1 L/min	38 (34%)	58 (35%)	0.504
0.5 - 1 L/min	45 (40%)	60 (36%)	0.271
Time between changes in flow rates			
24 hourly		79 (47%)	
24-48 hourly		21 (12%)	
48 hourly		17 (10%)	
Depends on the infant’s condition		52 (31%)	
Prong size			
Snug fit to occlude the nostril		42 (25%)	
Prong size selected to allow air leak		127 (75%)	
Guideline/Policy			
Yes		108 (64%)	

Table 5-2: Preference for CPAP or HHFNC

Data are displayed as n (%)*

	CPAP	**HHFNC**	**P value**
Which is better	18 (11%)	109 (64%)	<0.001
Better access to the infant	1 (1%)	145 (86%)	<0.001
Easier to set up	13 (8%)	138 (82%)	<0.001
Better access for skin to skin care	0 (0%)	162 (96%)	<0.001
Quicker to achieve full bottle feeding	0 (0%)	166 (98%)	<0.001
Quicker to achieve full breast feeding	0 (0%)	168 (99%)	<0.001
Less nasal trauma	0 (0%)	162 (96%)	<0.001
More comfortable for the infant	1 (1%)	165 (98%)	<0.001
Parental preference	0 (0%)	162 (96%)	<0.001

*Not all practitioners responded to every question

5.4 Discussion

Comparison of the results of surveys has demonstrated that there has been a significant increase in the use of HHFNC between 2012 and 2015. Units are now significantly more likely to use HHFNC rather than CPAP as the primary support mode post extubation. This is despite a lack of evidence that HHFNC provides more efficacious respiratory support (Shetty and Greenough, 2014). This change in practice then reflects practitioners' views on other advantages to the infant that may occur during HHFNC support.

The most commonly used devices were Vapotherm 2000i and the Optiflow TM (Fischer and Paykel). Similar observations were made in a survey in the United States (Hough et al., 2012). HHFNC was used as primary treatment post-extubation from MV in sixty-two percent of the neonatal units in Australia and New Zealand (Hough et al., 2012). Survey done by Ojha et al (Ojha et al., 2013) showed fifty-three percent of the neonatal units used HHFNC post-extubation . In a randomised trial of 432 infants of 28–42 weeks of gestational age, no significant difference was seen in early extubation failure (less than 72 hours) between infants on HHFNC (10.8%) and nCPAP (8.2%) (Yoder et al., 2013). Collins et al. (Collins et al., 2013a), randomly assigned 132 infants less than 32 weeks of gestational age to receive either HHFNC or nCPAP post extubation. No significant differences were found in the primary outcome or in the number of infant's reintubation in the first week.

During HHFNC, airway pressure increases with the nasal prong to nares ratio. As a consequence it has been recommended that the prong diameter should be about half that of the nostril (Hochwald O, 2010). Yet, 25% of units were using prongs of a size to occlude the nostril. Weaning flow in increments of between 0.5 -1 L/min and 24 hourly were most popular, but there was no consensus. This likely reflects that there is currently no evidence to determine the best weaning strategy from HHFNC. As a consequence, infants may stay on HHFNC longer than on CPAP (Gupta A, 2014).

HHFNC was thought to be better than nCPAP by the majority (64%) of responders. Similarly a survey of nursing staff demonstrated 76.9 % of nurses preferred HHFNC over NCPAP in infants equal to or older than 28 weeks of gestational age (Roberts et al., 2014). Practitioners reported that the majority of parents favoured HHFNC over CPAP. A likely influence on parental preference is that almost all practitioners who responded to our survey thought that HHFNC facilitated easier access to skin to skin care, was more comfortable for the infant, caused less nasal trauma and facilitated earlier achievement of full enteral feeds. The evidence for those beliefs, however, is mixed. A randomised, crossover comparison of 24 hours of nCPAP or HHFNC then 24 hours of the alternative support in infants with mild respiratory illness demonstrated that, although parents preferred HHFNC, there were no significant differences in the results of a patient comfort score (Klingenberg et al., 2014). Injury to the nasal mucosa or external nares has been frequently reported in prematurely born infants supported by nCPAP (Newnam et al., 2013, Fischer et al., 2010), and several studies have demonstrated a lower incidence of nasal trauma with HHFNC compared to HHFNC (Manley et al., 2013, Yoder et al., 2013, Kugelman et al., 2015). Infants born extremely prematurely may remain on respiratory support for many months, including the age when they should be able to take oral feeds, that is usually at 34 weeks PMA (Mizuno and Ueda, 2003, Gewolb et al., 2001, Lau et al., 2000). The likelihood of a trial of breast or bottle feeding may be higher if the infant is supported by HHFNC rather than CPAP, but that evidence is only from a retrospective review (Yoon SH, 2011) .

This study has a number of strengths and some limitations. Unlike previous surveys of HHFNC, this survey had a 100% response rate in 2015 as did the comparator survey in 2012. In addition, all levels of units completed the survey. As with all such surveys, the responses may reflect the views of the practitioner answering the survey rather than the unit's policy. Sixty-four percent of units, however, did have an HHFNC policy/guideline so it does feel that our results are likely to reflect UK practice in 2015.

In conclusion, use of HHFNC has significantly increased in UK neonatal units, in particular as the primary support mode post extubation. Those data and the lack of consensus on weaning strategies highlights research is urgently needed to optimise weaning from HHFNC.

Chapter 6: Work of breathing during CPAP and heated humidified high flow nasal cannula

6.1 Introduction:

Non-invasive respiratory management of infants with evolving or established BPD is particularly challenging as such infants often tolerate CPAP poorly. Whether CPAP or HHFNC provides more effective respiratory support has not been assessed in such a population. Hence, the aim of this study was to determine in infants with evolving or established BPD whether CPAP compared to HHFNC reduced the WOB and TAA and improved oxygen saturation (SaO_2).

6.2 Methods

A randomised, crossover study was undertaken. Infants whose parents gave informed written consent were entered into the study. The study was approved by the London – Westminster Research Ethics Committee (Appendix 1.4).

6.2.1 Protocol

Infants born at less than 32 weeks of gestation between April 2014 and February 2015 at King's College Hospital NHS Foundation Trust, London, UK and required CPAP and more than 40% of oxygen at or beyond two weeks of age were eligible for entry into this study. Those infants with a postnatal age greater than 14 days but less than 28 days were diagnosed as having evolving BPD and those aged 28 days or older established BPD. Infants whose parents gave informed written consent were entered into the study.

Infants were studied on two days for two hours each on CPAP (SLE 2000 or 5000 infant ventilator) and HHFNC (Fisher and Paykel using optiflow TM neonatal and infant nasal prongs). Infants were randomised on the first day to be supported on either CPAP or HHFNC for two hours and then by HHFNC or CPAP for two hours, on the second day the modes were delivered in the reverse order. The CPAP level was 6 cm H_2O and during HHFNC a flow rate of 8 L/min was used for infants with a weight more than 1 kg and 6 L/min for infants with a weight less than 1kg. WOB, as the PTPdi was assessed and TAA determined.

6.2.2 Sample size

Recruitment of twenty infants allowed us to detect a difference of twenty-five percent in the WOB between the groups and differences in the results of the other physiological measurements equivalent to one standard deviation with 80 % power at the 5 % level.

6.2.3 Statistical Analysis

The data were tested for normality and found to have a normal distribution, hence a paired t-test was used to assess whether differences were statistically significant. There was no evidence for any effect of the order or of the day in the results, hence the results for each of the two respiratory support modes were averaged over the two days. Regression models were used to examine the effect of the order of modes of respiratory support (CPAP/HHFNC or HHFNC/CPAP). The residuals from the regression model were checked for their fit to a normal distribution. Because of the relatively small sample size and the difficulty in ensuring a normal distribution, the analysis examining mode was also run using a rank test (Wilcoxon matched pairs) which gave similar results. IBM SPPS statistical software, V.22 (IBM Corporation, USA) was used. Analyses were conducted using Stat v12.

6.2.4 Results

Parents of thirty eligible infants were approached and twenty agreed to recruitment. The infants who were recruited compared to those who were not did not differ significantly with regard to their GA (27 (range 25–29) weeks versus 28 (range 25-32) weeks) (p=0.47) or BW (median 834 (664–1020) grams versus 880 (range 512-1500) grams) (p=0.94). When studied the infants required a median FiO_2 of 0.42 (range 0.4-0.58) (Table 6-1). There were no significant differences in the results of any of the physiological measurements between the two groups (Table 6-2).

Table 6-1: Demographic data

The data are presented as median (range) or n (%)

Number of infants recruited (n)	20
Gestational age (weeks)	28 (24-32)
Gestational age $\geq$ 28 weeks	7 (35%)
Birth weight (grams)	888 (512-1500)
Antenatal steroids	18/20 (90%)
Surfactant	20/20 (100%)
Caffeine	20/20 (100%)
Post conceptional age (weeks) at assessment	31 (28-39)
Postnatal age (days)	23 (15-96)
Male (%)	11/20 (55%)
Ethnicity:	
Caucasian	8 (40%)
Afro-Caribbean	5 (25%)
Asian	5 (25%)
Other	2 (10%)

Table 6-2: Physiological assessment results by respiratory support mode

The results are expressed as the median (range)

	CPAP	HHFNC	P value
PTP $cmH_20/s/min$	244 (126-294)	220 (169.5-318)	0.852
TAA (degrees)	12.6 (4.5-23.3)	13.1 (4.2 -23.8)	0.763
HR (bpm)	153 (130-172)	152 (140-175)	0.93
RR (bpm)	55 (35-79)	55 (38-74)	0.78
Oxygenation Saturation (%)	95 (93-100)	96 (94-99)	0.485

6.3 Discussion

This study has demonstrated that in prematurely born infants with evolving or established BPD, there were no significant differences in the WOB, TAA or SaO_2 when the infants were supported by CPAP or HHFNC. Infants with evolving or established BPD were studied exclusively, unlike in previous studies (Lavizzari et al., 2014, Saslow et al., 2006, de Jongh et al., 2014). Interestingly, in the one study which did include infants with BPD, but also other pathologies, no significant difference was found in the WOB between CPAP and HHFNC (Saslow et al., 2006).

This study has a number of strengths and some limitations. A dual pressure tip transducer was used to assess the WOB as assessed by measurement of the transdiaphragmatic pressure time product. Changes in oesophageal pressure may not accurately reflect change in pleural pressures when chest wall distortion results in an uneven distribution of pleural pressure changes. In this study, there were no differences in the TAA between the two respiratory support modes; hence the comparison of the WOB results is valid. A crossover design was used, hence we cannot comment on long term outcomes. Previous studies investigating the WOB were also of a crossover design (Saslow et al., 2006, Lavizzari et al., 2014, de Jongh et al., 2014), but were of single crossover design and did not analyse the effect of the order in which the infants were studied on a particular respiratory mode. This study examined infants on two successive days with the order of respiratory support mode being reversed on the subsequent day and then the results of two days were meaned. It is possible had the infants been exposed to longer periods of HHFNC and CPAP different results may have been obtained. Assessment of ten very low birth weight infants in a crossover design study of two hours on HHFNC (mean flow rate of 4.8

or 5.4 l/min) or CPAP (5 cm H_2O) demonstrated greater diaphragmatic activity on HHFNC suggesting that nCPAP was providing more effective respiratory support. Of note, however, there was no significant difference in the oxygen saturation levels between the two modes (Nasef et al., 2015).

In conclusion, this study has demonstrated that CPAP did not provide superior respiratory support as determined by physiological assessments compared to HHFNC in infants with evolving or established BPD.

Chapter 7: Discussion

7.1 Summary and current literature

7.1.1 Invasive ventilation studies (PAV and NAVA)

In Chapter 3, the randomised crossover study of PAV versus ACV demonstrated that PAV compared to ACV in prematurely born infants with evolving or established BPD, was associated with significant superior oxygenation which likely reflects the better synchronisation of the inflation pressure and tidal volume throughout inspiration. There have been no recent studies examining PAV in premature infants that have been published. The findings from the studies undertaken by our research group (Bhat et al., 2015, Shetty et al., 2016) and by Schulze et.al.(Schulze et al., 2007) in premature infants have shown promising results but a randomised controlled trial with infants on PAV for a duration longer than four hours with long-term outcomes is needed to evaluate if any benefit is appreciable in the long term before routine clinical use. Ventilation strategies designed to improve patient-ventilator 'interaction' have continued to evolve, of which NAVA is an example. Some authors believe that NAVA is more suitable for a wider range of infants than PAV including the most premature infants, due to more accurate triggering and delivery of ventilator support regardless of leak around the endotracheal tube (Kacmarek, 2011).

In Chapter 4, a randomised crossover study demonstrated that NAVA compared to ACV, resulted in improved (lower) OI and reduced peak and mean airway pressures. In the neonatal population NAVA has been compared in a number of crossover trials to date to modes such as PSV and ACV (Lee et al., 2012, Stein et al., 2013a, Longhini et al., 2015). Data from these studies suggest an improved patient ventilator synchrony, lower peak pressures with a lower work of breathing. In a retrospective single centre study (Jung et al., 2016), where twenty-nine preterm infants with a median gestational age of 25.4 weeks (range, 23.4-30.3 wk) and a median birth weight of 680 grams (range, 370 - 1,230 grams) and who were supported with a mechanical ventilator for more than four weeks were converted to NAVA. During NAVA, the peak inspiratory pressure (20.12 ± 2.93 vs 14.15 ± 3.55 cm H_2O; $p < 0.05$), mean airway pressure (11.15 ± 1.29 vs 9.57 ± 1.27 cm H_2O; $p < 0.05$), and work of breathing (0.86 ± 0.22 vs 0.46 ± 0.12 J/L; $p < 0.05$) were significantly decreased, and the blood gas values were significantly improved. In an another study (Lee et al., 2017) of fourteen prematurely born patients who received prolonged ventilation, NAVA reduced cyanotic episodes and the need for sedatives and dexamethasone. NAVA has also been used in improving patient-ventilator synchrony, reducing endotracheal secretion and gastric over distention in a rare skeletal dysplasia (Jeune syndrome -asphyxiating thoracic dystrophy) (Cosi et al., 2016) and also there are case reports of use in unilateral diaphragmatic paralysis (Roosens et al., 2016). However, larger RCTs are needed to determine if these findings are generalisable.

7.1.2 Non-invasive ventilation studies

In chapter 5, I have shown that use of HHFNC has significantly increased in UK neonatal units, in particular as the primary support mode post extubation but concluded that the lack of consensus on weaning strategies highlighted that research is urgently needed. The recent Cochrane review (Farley et al., 2015) also concluded that there is currently no evidence available to suggest the best strategy for weaning and withdrawing HHFNC as a respiratory support in preterm infants.

In Chapter 6, I have demonstrated that CPAP did not provide superior respiratory support compared to HHFNC in infants with evolving or established BPD. HHFNC was not significantly different in efficacy from nCPAP or NIPPV in respiratory support after extubation in a Cochrane meta-analysis (Wilkinson et al., 2016). In another systematic review (Fleeman et al., 2016) concluded that there was lack of convincing evidence suggesting that HHFNC is superior or non-inferior to usual care, in particular NCPAP. Both of these studies, however, looked at non-invasive forms of respiratory support in preterm infants immediately after birth or following extubation. There have been no further studies examining WOB in BPD and hence a larger randomised study would be beneficial in the future.

A pilot study to determine the feasibility of using HHFNC in stabilisation of babies born less than 30 weeks gestation in delivery suite in a single-centre (Reynolds et al., 2016), concluded HHFNC for stabilisation of premature infants in the delivery room and subsequent transfer to NICU is feasible. Whether this would prevent the number of BPD infants is yet to be determined.

Non-invasive Neurally Adjusted Ventilator Assist (NIV-NAVA) has been introduced via a pilot and a randomised observational study to assess its safety, feasibility, and short term physiological effects (Gibu et al., 2017). The pilot protocol applied NIV-NAVA to eleven infants on nasal CPAP, HHFNC, or nasal IMV (NIMV), in multiple two to four hour periods of NIV-NAVA for comparison. The NAVA catheter was used for eighty one patient day's without complications. NIV-NAVA produced significant reductions (as a percentage of measurements on NIMV) in: PIP, 13%, FiO_2, 13%, frequency of desaturations, 42%, length of desaturations, 32%, and phasic Edi, 19%. NIV-NAVA is projected as a safe, alternative mode of non-support that produced beneficial short-term physiological effects, especially compared to NIMV. If NIV-NAVA was the future of NIV is yet to be determined.

In a retrospective analysis (Colaizy et al., 2016) of a cohort of twenty-four VLBW (<1.5 kg) ventilation improved after an increase in NIV NAVA level in 83% of the premature infants studied (20/24) with a decrease in median pCO_2 by 5 mm Hg ($p = 0.0001$). They concluded that NIV NAVA can provide synchronised post-extubation ventilatory support as measured by decreased pCO_2 in premature infants. Our patient group have been infants with evolving or established BPD and to translate above effects to BPD infants would be a challenge.

7.2 Strengths and weaknesses of the studies

7.2.1 Invasive ventilation studies (PAV and NAVA)

We stopped the trial at the planned interim analysis in both the studies in Chapter 3 and 4, as all infants in both these studies had OI's that were lower on NAVA and PAV compared to ACV. Hence our sample size is comparatively low. In the NAVA study, we used capillary blood samples to calculate the OIs. We used this method at the end of each of the two periods in all infants. The infants were all clinically stable when assessed and none were seriously ill, had shock, hypotension or peripheral vasoconstriction at the time of assessment (McLain et al., 1988). Thus, it was appropriate to calculate the OIs from the capillary blood samples, however arterial blood gas analysis would have been ideal.

Ages of infants studied in above studies were wide ranged ie 10 -105 days in Chapter 3 study and 8-84 days in Chapter 4. As per inclusion criteria we have included all infants who required ventilation beyond first week of life. However, in view of the small sample size it would be would be difficult to tease out evolving and established BPD as per definition.

7.2.2 Non-invasive ventilation studies

One of the main strengths of our study in Chapter 6, comparing WOB between CPAP and HHFNC in evolving and established BPD is that infants were studied on two successive days with the order of respiratory support studied being reversed on the subsequent day and the results were then meaned, hence the results are robust. The measure of WOB, PTPdi was calculated by breath by breath integration of the area subtended by the transdiaphragmatic pressure during inspiration. The phase transition of respiratory flow is generally used to determine the start and end of inspiration. Because of the use of HHFNC, it was not possible, to measure respiratory flow directly in the study. The beginning of inspiration was determined, therefore, by the rise in Pdi at the start of a breath and end of inspiration was determined from rib cage movement using RIP. The same method was used for both modes of ventilation and no statistical differences were noted in both the groups.

7.3 Future work

Both PAV and NAVA, respiratory support is servo-controlled based on continuous input from the infant's respiratory effort. Both aim to improve synchronisation of the timing of the respiratory cycle and also to vary the level of support offered breath-to-breath in proportion to the respiratory effort of the patient. In this thesis, both PAV and NAVA have been shown to have advantageous in neonates, but they have not been compared to each other and should be. Studies evaluating NAVA with other modes of ventilation have been small. Since VTV has been shown to improve both short term and long term outcomes in prematurely born infants, randomised trials comparing NAVA with VTV in newborns to see if NAVA is superior to VTV would be useful. As most previous studies and trials were small and did not include long-term patient oriented outcomes, randomised controlled trials are needed to determine whether NAVA is effective in decreasing the duration of ventilation, reducing the incidence of BPD and decreasing LOS, rate of pneumothorax and IVH.

Non-invasive Neurally Adjusted Ventilator Assist (NIV-NAVA) has been introduced into clinical practice via a pilot and a randomised observational study to assess its safety, feasibility, and short term physiological effects (Gibu et al., 2017). The improvements in oxygenation and the reduction in the frequency and severity of episodes of desaturation, if sustained on NIV-NAVA, could make a difference in the long-term outcomes of BPD or retinopathy of prematurity. Well-designed feasibility studies are needed to assess the safety of NIV-NAVA and its possible longer term physiological benefits, which make it a feasible alternate therapy to all current modalities of non-invasive ventilation.

A pilot study to determine the feasibility of using HHFNC in stabilisation of babies born less than 30 weeks gestation in delivery suite in a single-centre (Reynolds et al., 2016), concluded HHFNC for stabilisation of premature infants in the delivery room and subsequent transfer to NICU is feasible. If these finding are generalisable is yet to be found out by well-designed RCTs.

7.4 Conclusions

PAV and NAVA may be beneficial in infants with evolving or established BPD. Use of HHFNC has significantly increased in UK neonatal units. In infants with evolving or established BPD, CPAP compared to HHFNC offered no significant advantage and in infants who required respiratory support beyond 34 weeks PMA.

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Appendices

A1.1 Patient information sheet and Consent form for Chapter 3

King's College Hospital NHS
NHS Trust

INFORMATION SHEET
(19/10/2013, Version 6)

Optimisation of neonatal ventilation – proportional assist ventilation (PAV)

We are inviting you to consider allowing your baby to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Take time to decide whether or not you wish your baby to take part.

Why are we doing it?
A significant proportion of babies admitted to the neonatal unit require help via a machine (ventilator) for their breathing. The survival of such babies has improved dramatically over the years, but complications such as chronic oxygen dependency and other breathing problems at follow-up remain unchanged. New types of ventilation have been developed in the hope their use may reduce the breathing problems. It is important these new types of ventilation are used in the best possible way. One is called proportional assist ventilation (PAV), which delivers support in proportion to the infant's breathing efforts. Our aim is to determine whether PAV offers any advantages for the baby over assist controlled ventilation (patient triggered ventilation), a form of pressure-limited ventilation, during which ventilator breaths are delivered at a pre-set pressure.

How will we do it?
We will assess babies that are still requiring support from the breathing machine at over a week of age who are receiving assist controlled ventilation. Babies will be randomly assigned to either assist controlled ventilation or PAV and they will spend four hours each on PAV and assist controlled ventilation. At the end of each four hour period we will measure your baby's muscle strength and the work associated with breathing (work of breathing). To measure the work of breathing we will use a tube similar to your baby's nasogastric (feeding) tube. Once the measurements are made on both the ventilator modes, your baby will go back to the same mode he/she was on before the study.

Are there any disadvantages of taking part in the study?
There are no known risks to your baby from taking part in this study.

How will the information be shared?
All information that is collected will be kept strictly confidential. We will, with your consent, inform your GP of your child's involvement in this study.

Giving Consent
It is important you understand that this study is voluntary and for research purposes. You may choose not to allow your child to participate in this study and you may withdraw your child at any time without their medical care or legal rights being affected. If you require any further information please ask. There are no harmful side effects associated with this study. No indemnity is available, although, normal NHS procedures apply in the unlikely event of any adverse outcome of the study.

If you decide to allow your child to take part in the study, you will be given a copy of the information sheet and consent form to keep. All information that is collected during the course of the research will be kept strictly confidential and if the results are published then anonymity will be maintained. This study was reviewed and approved by the Research Ethics Committee of King's College Hospital NHS Trust.

Thank you very much for considering your child for enrolment into this project. If you are happy to participate please sign below. If you have any further questions or would like to meet with a member of the research team to discuss this further, please do not hesitate to contact us on the telephone number below.

CONSENT FORM

(19/10/2013, Version 6)

King's College Hospital NHS
NHS Trust

Patient Identifier number
for this trial: ………………… *(1) patient, (2) researcher, (3) hospital notes*

Title of Project: <u>Optimisation of neonatal ventilation</u>

Please initial box

1. I confirm that I have read and understand the information sheet dated 19/10/2013 for the above study and have had the opportunity to ask questions. ☐

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

3. I understand that sections of any of my child's medical notes may be looked at by responsible individuals or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my child's records. ☐

4. I agree to allow my child to take part in the above study. ☐

______________________ ______________

Name of Child Date

______________________ ______________ ______________________

Name of Person giving consent Date Signature

______________________ ______________ ______________________

Researcher Date Signature

A 1.2 Patient information sheet and Consent form for Chapter 4

King's College Hospital NHS
NHS Trust

INFORMATION SHEET
(01/10/2015, Version 3)

Neurally Adjusted Ventilator Assist (NAVA) versus Assist control ventilation

We are inviting you to consider allowing your baby to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Take time to decide whether or not you wish your baby to take part.

Why are we doing it?
Many babies admitted to the neonatal unit require help via a breathing machine (ventilator). The survival of such babies has improved over the last twenty years, but long-term complications such as chronic oxygen dependency and chronic breathing problems remain unchanged.

Modern ventilators attempt to match the patient's needs as much as possible but are not capable of knowing exactly when a patient wants a breath. The ventilator may give breaths even when the patient is not ready and this may cause some discomfort.

A new monitoring tool called NAVA is now available that measures exactly how much "breath" a baby needs to be comfortable. This is a special computerised module that attaches to the ventilator that can work out exactly how much power the diaphragm is generating or needs (the diaphragm is the main respiratory muscle that does all the breathing). The tool is very simple in that it is a special nasogastric tube (one that we ordinarily use to feed babies) that has electrodes in it that measure the power of the diaphragm. It is very much like an ECG for the heart, but only for the breathing muscles. This special nasogastric tube provides an instant feedback to the ventilator of how much breath is required and the ventilator then delivers every breath as demanded by the patient every second. NAVA has been used in adults and children including premature babies and has proven very useful in optimising patient comfort on ventilators.

Our aim is to determine whether NAVA offers any advantages over standard pressure limited ventilation.

How will we do it?
We wish to assess babies who are born prematurely and remain supported by a breathing machine one week after birth because of their breathing problems. Babies will be randomly assigned to either assist controlled ventilation or NAVA and they will spend one hour each on NAVA and assist controlled ventilation. At the end of each one hour period we will measure the baby's muscle strength and the work associated with breathing (work of breathing). To measure the work of breathing we will use an additional tube similar to the baby's nasogastric (feeding) tube. A small blood sample will be taken at the end of each hour from the baby's indwelling catheter, that is there are no extra pricks, to assess the levels of oxygen and carbon dioxide (the waste gas). Once the measurements are made on both the ventilator modes, your baby will go back to the same mode he/she was on before the study.

Are there any disadvantages of taking part in the study?
There are no known risks to your baby taking part in this study. The procedure may cause some disturbance when changing the breathing apparatus, but every effort will be taken to minimise this. If at any point during the study, researcher feels that your child is not ready for the study, and then your child will be put back onto the original ventilator.

What happens if something goes wrong?
Your baby will be closely monitored throughout the study in case any issues do arise. If you do have any concerns about any aspect of this study, you should speak to the researchers, using the contact details below, who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this by contacting the Patient Advice and Liaison Service (PALS) via phone (0203 299 3601) or email (kch-tr.PALS@nhs.net).

How will the information be shared?
All information that is collected will be kept strictly confidential. We will, with your consent, inform your GP of your child's involvement in this study, by stating it in your baby's discharge summary.

Who has reviewed the study?

This study was reviewed and received favourable opinion by the West Midlands – Solihull Research Ethics Committee.

Giving Consent
It is important you understand that this study is voluntary and for research purposes. You may choose not to allow your child to participate in this study and you may withdraw your child at any time without their medical care or legal rights being affected. If you require any further information please ask. There are no harmful side effects associated with this study. In the event that something does go wrong and your baby is harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against King's College London or King's College Hospital NHS Trust, but you may have to pay your legal costs.

If you decide to allow your child to take part in the study you will be given a copy of the information sheet and consent form to keep. All information that is collected during the course of the research will be kept strictly confidential and if the results are published then anonymity will be maintained. This study was reviewed and approved by the West Midlands – Solihull Research Ethics Committee.

Thank you very much for considering your child for enrolment into this project. If you are happy to participate please sign below. If you have any further questions, or would like to meet with a member of the research team to discuss this further, please do not hesitate to contact us on the telephone number below.

King's College Hospital NHS

NHS Trust

CONSENT FORM

(01/10/2015, Version 3)

Patient Identifier number
for this trial: …………………

NB Three copies should be made, for (1) patient, (2) researcher, (3) hospital notes

Title of Project: **<u>Neurally Adjusted Ventilator Assist (NAVA) versus Assist control ventilation</u>**

Please initial box

2. I confirm that I have read and understand the information sheet dated 01/10/2015 for the above study and have had the opportunity to ask questions.

3. I understand that my baby's participation is voluntary and that I am free to withdraw at my baby at any time, without giving any reason, without my baby's medical care or legal rights being affected.

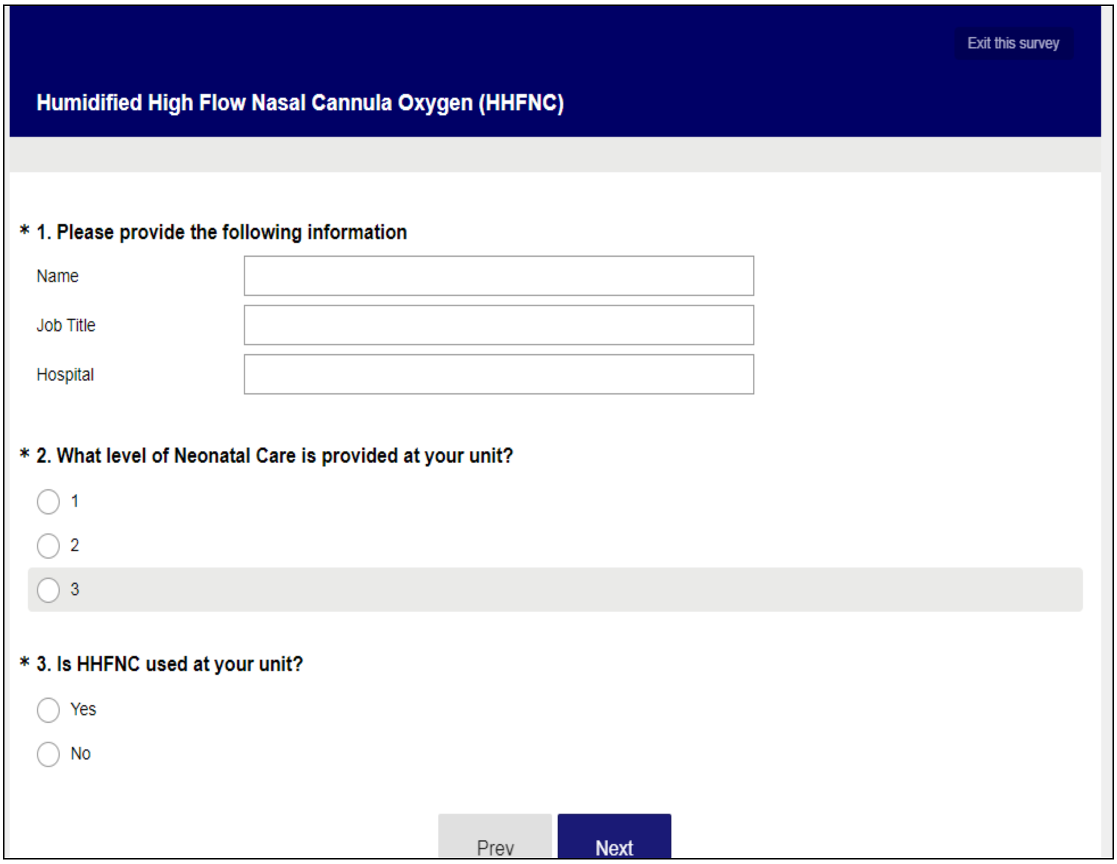
4. I understand that sections of any of my baby's medical notes may be looked at by responsible individuals or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my baby's records.

5. I consent for my GP to be informed of my baby's inclusion into the study

6. I agree to allow my baby to take part in the above study.

Name of Baby	Date	
Name of person giving consent	Date	Signature
Researcher	Date	

A 1.3 Survey Questionnaire in Chapter 5



Exit this survey

Humidified High Flow Nasal Cannula Oxygen (HHFNC)

* 1. Please provide the following information

Name

Job Title

Hospital

* 2. What level of Neonatal Care is provided at your unit?

- 1
- 2
- 3

* 3. Is HHFNC used at your unit?

- Yes
- No

Prev Next

Exit this survey

Humidified High Flow Nasal Cannula Oxygen (HHFNC)

*** 4. What equipment is used at your unit?**

- ☐ Vapotherm
- ☐ Optiflow
- ☐ Other (please specify)

*** 5. Do you have a guideline/policy for HHFNC use at your unit?**

- ○ Yes
- ○ No

*** 6. For which indications is HHFNC used at your unit? Please select all that apply.**

- ☐ Initial respiratory support- alternative to CPAP
- ☐ Weaning from CPAP
- ☐ Post-extubation

*** 7. What starting flow rate is used at your unit?**

- 8l/min
- 6l/min
- Other (please specify)

*** 8. What is the lowest flow rate used at your unit?**

- 4l/min
- 3l/min
- 2l/min
- 1l/min
- Other (please specify)

*** 9. For babies with decreasing requirements, what increment of flow is typically used when weaning?**

- 0.5l/min
- 1l/min
- Other (please specify)

*** 10. When weaning, what would typically be the duration of each step at your unit?**

- ◯ 12 hourly
- ◯ 24 hourly
- ◯ 48 hourly
- ◯ Other (please specify)

*** 11. How are the nasal cannulae sized to fit when using HHFNC at your unit?**

- ◯ Snug fit
- ◯ Cover >50% of nostril but not snug to nostril
- ◯ Cover <50% of nostril

*** 12. Is HHFNC used for particular gestations of babies at your unit?**

- ◯ Preterm babies only
- ◯ Term babies only
- ◯ All gestations

*** 13. Please describe any weight criteria for the use of HHFNC on your unit**

A 1.4 Patient information sheet and Consent form for Chapter 6

INFORMATION SHEET
(11/03/2014, Version 2)

King's College Hospital NHS
NHS Trust

Comparison of the work of breathing during humidified high flow nasal cannula oxygen (HHFNC) and continuous positive airways pressure (CPAP).

We are inviting you to consider allowing your baby to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Take time to decide whether or not you wish your baby to take part.

Why are we doing it?

This study is being carried out to determine whether babies have to work less hard to breathe (work of breathing) on HHFNC or CPAP. Both forms of breathing support are used as a step down when babies no longer need help from the breathing machine (extubated), but still need some support for their breathing. During HHFNC, the breathing gas is delivered at high flows, during CPAP lower flows are used and higher pressures can be given. Both techniques are delivered via nasal cannulae, that is small tubes inserted just inside the nostrils. When babies are taken off the ventilator they have to work harder to breathe and it is not clear whether HHFNC or CPAP better supports babies, that is they have a lower work of breathing. The work of breathing is particularly important in babies who are chronically dependent on breathing support, that is they require breathing support beyond two weeks after birth, if the baby is working hard to breathe this can slow down their weight gain. We, therefore wish to determine whether HHFNC or CPAP better supports in babies who are chronically dependent on respiratory support and which is associated with the lower work of breathing.

How will we do it?

Much of the information we need for this study can be obtained from the medical and nursing teams caring for your baby, but we do need to make some additional measurements. On two successive days, babies will be studied for two hour periods on the two types of breathing support, CPAP and HHFNC. The order in which they will be studied will be chosen by random, that is as tossing a coin. The order in which the breathing support modes will be studied will be reversed on the next day. For the last five minutes at the end of each two hour period we will measure the work associated with breathing (work of breathing) and how well the chest and abdomen move up and down together as your baby breathes. To measure the work of breathing we place a tube similar to your baby's nasogastric (feeding) tube through his/her mouth into the stomach. This allows us to measure the main breathing muscle, the diaphragm. To measure how well the chest and the abdomen move together as your baby breathes, we will put elasticated bands around his/her chest and the abdomen. You are welcome to be present during the procedure.

Why has my baby been invited?

Your baby is still requiring support for their breathing and is over two weeks old.

Are there any disadvantages of taking part in the study?

There are no known risks to your baby taking part in this study, indeed it will help us see which of the two methods of supporting your baby's breathing is more helpful to your baby. The procedure may cause some discomfort and there may be some disturbance when changing the breathing apparatus, but every effort will be taken to minimise this.

How will the information be shared?

The results of the study will be given to the clinical staff looking after your baby and this will be one of the ways they to decide which method of breathing support will be better for your baby. We will, with your consent, inform your GP of your baby's involvement in this study by stating it in your baby's discharge summary.

What will happen to the results of the study?

The results of the research from all the babies that have been taken part will be analysed and the results made available to practitioners such as doctors, nurses and physiotherapists and may be used to guide the management of babies in the future. The results may be presented at national and international meetings and in peer reviewed medical journals for wider distribution. At no point will any information revealing your baby's identity be made available to anyone outside the research team or the clinical team caring for him/her.

What if there is a problem?

There are no harmful side effects associated with this study. In the unlikely event that there is a problem King's College, London and King's College Hospital indemnity will apply.

What happens when the research stops?

Once the required information has been collected from your baby, there is nothing further that you or your baby is required to do. Your baby would continue to receive their medical care as usual

Who has reviewed the study?

A regional Ethics committee (NRES London - Westminster Research Ethics Committee) has reviewed and approved the study.

Giving Consent:

It is important you understand that this study is voluntary and for research purposes. You may choose not to allow your baby to participate in this study and you may withdraw your baby at any time without their medical care or legal rights being affected. If you require any further information, please ask.

If you decide to allow your baby to take part in the study, you will be given a copy of the information sheet and consent form to keep. All information that is collected during the course of the research will be kept strictly confidential and if the results are published then anonymity will be maintained. This study was reviewed and approved by the Research Ethics Committee of King's College Hospital NHS Trust.

Thank you very much for considering your baby for enrolment into this project. If you are happy to participate please sign below. If you have any further questions or would like to meet with a member of the research team to discuss this further, please do not hesitate to contact us on the telephone number below.

CONSENT FORM

(15/01/2014, Version 1)

Patient Identifier number
for this trial: …………………

NB Three copies should be made, for
(1) patient, (2) researcher, (3) hospital notes

Title of Project: **Work of breathing during HHFNC and CPAP**

Please initial box

3. I confirm that I have read and understand the information sheet dated 11/03/2014 for the above study and have had the opportunity to ask questions. ☐

4. I understand that my baby's participation is voluntary and that I am free to withdraw at my baby at any time, without giving any reason, without my baby's medical care or legal rights being affected. ☐

5. I understand that sections of any of my baby's medical notes may be looked at by responsible individuals or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my baby's records. ☐

☐

7. I consent for my GP to be informed of my baby's inclusion into the study

8. I agree to allow my baby to take part in the above study. ☐

Name of Baby	Date

Name of person giving consent	Date	Signature
Researcher	Date	Sign

A3 Publications arising from this thesis

Eur J Pediatr
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ORIGINAL ARTICLE

Proportional assist versus assist control ventilation in premature infants

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Abstract During proportional assist ventilation (PAV), the applied pressure is servo-controlled based on continuous input from the infant's breathing. In addition, elastic and resistive unloading can be employed to compensate for the abnormalities in the infant's lung mechanics. The aim of this study was to test the hypothesis that in very prematurely born infants remaining ventilated beyond the first week, PAV compared to assist control ventilation (ACV) would be associated with superior oxygenation. A randomised crossover study was undertaken. Infants were studied for 4 hours each on PAV and ACV in random order; at the end of each 4-h period, the oxygenation index (OI) was calculated. Eight infants, median gestational age of 25 (range 24–33) weeks, were studied at a median of 19 (range 10–105) days. It had been intended to study 18 infants but as all the infants had superior oxygenation on PAV (p=0.0039), the study was terminated after recruitment of eight infants. The median inspired oxygen concentration (p=0.049), mean airway pressure (p=0.012) and OI (p=0.012) were all lower on PAV.

Conclusion: These results suggest that PAV compared to ACV is advantageous in improving oxygenation for prematurely born infants with evolving or established BPD.

What is known:
- During proportional assist ventilation (PAV), the applied pressure is servo controlled throughout each spontaneous breath.
- Elastic and resistive unloading can compensate for the infant's abnormalities in lung mechanics.

What is new:
- In a randomised crossover study, infants with evolving/established BPD were studied on PAV and ACV each for 4 h.
- The oxygenation index was significantly lower on PAV in all infants studied.

Keywords Proportional assist ventilation · Assist control ventilation · Oxygenation

Communicated by Patrick Van Reempts

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Abbreviations

ACV	Assist control ventilation
BPD	Bronchopulmonary dysplasia
FiO2	Fraction of inspired oxygen concentration
MAP	Mean airway pressure
OI	Oxygenation index
PAV	Proportional assist ventilation
PCV	Patient controlled ventilation
PEEP	Positive end expiratory pressure
PIP	Peak inspiratory pressure
SIMV	Synchronised intermittent mandatory ventilation

Introduction

During proportional assist ventilation (PAV), the applied pressure is servo controlled, based on continuous input from the infant's breathing throughout each spontaneous breath. In addition, the ventilator can provide inflation pressure in phase with the tidal volume change in order to reduce the compliance load (i.e. the load due to the stiffness of infant's lungs) and in phase with the flow change to reduce the resistance load (i.e. the load due to airflow obstruction), termed elastic and resistive unloading, respectively [6]. Very prematurely born infants developing or with established bronchopulmonary dysplasia (BPD) will have stiff lungs (that is non-compliant) despite a very compliant chest wall, so may be particularly likely to benefit from elastic unloading. PAV has only been assessed in neonates in a few studies. In a previous crossover study, we demonstrated that infants with evolving or established bronchopulmonary dysplasia (BPD) on PAV compared to assist control ventilation (ACV) had better oxygenation indices, a lower work of breathing and better respiratory muscle strength. The infants, however, were only studied on each ventilator mode for 1 h [1]. The longest infants have been studied on PAV is 4 h [7], but during that study, only changes in pulse oximetry results were assessed. During PAV, the applied pressure is servo controlled throughout each breath, whereas during ACV, only the initiation of inflation is sycnchronised to the start of inspiration; hence, we hypothesised that oxygenation would be superior on PAV compared to ACV. During PAV, however, we have demonstrated a trigger delay of 60 ms using an in vitro model [4]; hence, it was important to assess blood gases over a longer period that studied previously [1]. The aim of this study, therefore, was to test the hypothesis that infants with evolving or established BPD would have superior oxygenation index results after 4 h on PAV compared to after a similar period on ACV.

Methods

A randomised, crossover study was undertaken. Prematurely born infants remaining ventilated after the first week after birth were eligible for entry into the study if they were being supported by ACV. Evolving BPD was defined as ventilator dependence beyond 14 days and established BPD as ventilator dependence beyond 28 days. Infants were ineligible for inclusion in the study if they had a major congenital cardiac abnormality or were receiving a neuromuscular blockade agent. Infants were entered into the study if their parents gave informed written consent. The study was approved by the South East London Research Ethics Committee and King's College Hospital Research Ethics Committee. During the 8-h study period, no other changes were made to the infant care than the changes in ventilator mode.

Infants at King's College Hospital NHS Foundation Trust are routinely supported by the SLE 5000. The infants were transferred from the SLE 5000 ventilator to ACV on the Stephanie ventilator using the same ventilator settings (baseline). All infants as per the unit's routine policy were ventilated via shouldered endotracheal tubes which have been shown to have minimal or no leaks [2]. One hour was allowed for stabilisation of the infant on the Stephanie ventilator. A blood gas analysis was then performed and the baseline ventilator settings were noted. During the stabilisation period, the ventilator displayed compliance and resistance settings were noted every 10 min and the six results meaned. The ventilator calculated the compliance from the inflation pressure (PIP-PEEP) and the resultant tidal volume. The value of the reciprocal of the compliance, elastance, was used to set the level of the elastic unloading. Each infant was then randomised to receive first either PAV or ACV mode for 4 h and for the second 4 h received the alternative mode. During ACV, the peak inspiratory pressure (PIP), positive end expiratory pressure (PEEP) and the inflation time were kept the same as at baseline. During PAV, the maximum PIP was set at 5 cm H_2O above the PIP on ACV. The PEEP level during PAV was the same as at baseline, and the PEEP and the inflation time during back up ventilation were the same as at baseline. Whenever cessation of spontaneous breathing occurred for more than 5 s during PAV, mandatory backup inflations were automatically delivered by the ventilator. The backup rate set at 40 breaths per minute was delivered to the infant for 10 s with a backup inflation peak pressure of 5 cm H_2O above the PIP used during ACV. Elastic unloading, which was used only during inspiration, was initially set at 75 % of full unloading. Full unloading was the level of unloading which increased the infant's compliance to the expected 'normal', that is, 2.0 mL/cm H_2O/kg. If after 10 min the infant remained stable and no airway pressure waveform abnormalities were observed [4], the unloading was increased to 100 %. If airway pressure waveform abnormalities were then noted by looking at the pressure display, the unloading was to be reduced back to 75 %. Resistive unloading was not used as, an in vitro model, oscillations in the airway pressure waveforms appeared when the resistive unloading was greater than 100 cm H_2O/L/s [4].

The number of desaturations (an oxygen saturation less than 88 %) on each mode was noted. An arterial blood sample was obtained at the end of each 4-h period, the ventilatory settings were noted and the oxygenation index (OI) was calculated. Respiratory rate, tidal volume and mean airway pressure were obtained from the ventilator. The results from the last 5 min of the 4-h study period were averaged. All the infants had continuous oxygen saturation monitoring. During the study, the inspired oxygen concentration was adjusted as necessary to maintain the oxygen saturation level in the range 92–96 %.

Sample size

In our previous study, the mean OI in the PAV group was 6.0 (SD±2.4) and in the ACV group was 9.8 (SD±3.7) [1]. The planned sample size was 18 infants to allow detection between the two ventilator modes of a within patient difference of 0.7 SD in the oxygenation index results with 80 % power and a two-sided significance of 5 %.

Analysis

Differences were assessed for statistical significance using the paired Wilcoxon signed rank test using IBM SPPS statistical software, V.21 (IBM Corporation, USA).

Results

Recruitment to the trial was stopped at eight infants as all the OI results were in favour of PAV (Table 1). The decision was taken by the clinical team and the study statistician in the knowledge that the probability of all 8/8 results in the same direction (hence favouring PAV) if both modes were in fact equally effective was extremely small (0.5^8=0.0039).

Table 1 Oxygenation index results by ventilatory mode. Individual data are given

INFANT	PAV	ACV
1	8.1	15.2
2	7.0	8.3
3	17.4	21.6
4	12.6	20.3
5	5.2	8.4
6	10.0	14.1
7	5.9	11.3
8	9.9	11.7

The median birth weight of the infants was 767 (range 650–1926) g, gestational age 25.7 (range 24.4–33.5) weeks and postnatal age at measurement 19 (range 10–105) days; seven of the eight infants were male. All the infants had been exposed to antenatal steroids, received postnatal surfactant and were receiving caffeine at the time of study. None were receiving sedation at the time of study or had received postnatal steroids. Their median baseline compliance was 0.4 (range 0.3–1.1) mL/cmH_2O and resistance was 155 (range 66–252) cmH_2O/L/s. All infants tolerated 100 % elastic unloading throughout the study. The median FiO_2 (p= 0.049), the median mean airway pressure (p=0.012) and the median oxygenation index (p=0.012) were all lower on PAV compared to ACV (Table 2). There was no significant difference in the median number of desaturation episodes between the two modes.

Discussion

We have demonstrated that PAV compared to ACV in prematurely born infants ventilated beyond the first week after birth resulted in superior oxygenation index results. Those results are in keeping with those of Schulze et al. [7] who compared PAV to SIMV or ACV in infants with evolving BPD. The 22 infants had a median gestational age of 25.6 weeks and were studied at a mean postnatal age of 22.9 days. They found after a 4-h period of PAV that despite a lower MAP, the inspired oxygen concentration and pulse oximetry readings were not significantly different between the two groups. All the infants in our study had arterial blood gas measurements, and hence, we were able to calculate their oxygenation index. We compared PAV to ACV as both modes provide respiratory support for all the infant's breaths. During SIMV, only a preset number of the infant's breaths are supported by the ventilator and hence this might at least partially explain why PAV was superior to SIMV/ACV in the earlier study [7]. We have previously demonstrated that during PAV [1], the inspiratory tidal volume and inflation pressures are closely phase-matched and the oesophageal pressure is out of phase as a result of the proportionality. This does not occur in ACV and likely leads to more efficient support during PAV. We did not record whether compliance was improved on PAV compared to ACV, but in our previous paper [1] demonstrated there was an almost significant (p=0.05) reduction in thoraco-abdominal asynchrony which could improve oxygenation. In our previous study [1], the respiratory rate was significantly lower during PAV, but the medians were 54 bpm on PAV and 57 bpm on ACV, so unlikely to be of clinical significance. In this study, we did not demonstrate any significant differences in the respiratory rates or delivered tidal volumes. PAV compared to ACV support was not associated with any significant reduction in $PaCO_2$ but the mean airway pressure was significantly lower during

Table 2 Comparison of airway pressures and blood gas exchange by ventilator mode. The results are expressed as the median (range)

	PAV	ACV	*p* value
FiO_2	0.48 (0.31–0.65)	0.57 (0.40–0.72)	0.049
PaO_2 (kpa)	5.6 (5.4–8.6)	5.6 (5.0–6.8)	0.327
PCO_2 (kpa)	8.0 (5.5–9.3)	7.2 (5.5–11)	0.889
Oxygenation index	9.0 (5.2–17.4)	12.9 (8.3–21.6)	0.012
Mean airway pressure (cm H_2O)	8.5 (6.7–10.0)	9.5 (8.1–13)	0.012
Respiratory rate (bpm)	56.6 (47.5–76.7)	57.4 (49.5–66)	0.401
Tidal volume (mL/kg)	7.5 (3.7–10.0)	5.8 (3.5–10.3)	0.234
Desaturation episodes (*n*)	1 (0–2)	0 (0–2)	0.429

PAV, suggesting the PIP was lower and hence that PAV might have resulted in greater CO_2 clearance.

In a previous 4-h cross-over study [7], although the incidence of arterial oxygen desaturations was not significantly different, the desaturations lasted longer when infants were supported by PAV. In that study, however, the infants had a history of frequent apnoeas and arterial oxygen desaturations. None of the infants in this study had been ventilated because of a history of apnoea. In addition, in the previous study [7], a time of 10 s was used during which the ventilator software identified cessation of breathing, whereas we used an updated version of the Stephanie software in which a 5-s period was used during which the ventilator software identified the cessation of breathing. It is likely then that this updated version enabled better support during PAV when the infant was apnoeic. We did not demonstrate any significant difference in the number of desaturations; indeed, the infants in both groups experienced very few desaturations.

Our study was terminated before our calculated sample size. We were mindful that all 12 infants in our 1-h cross-over study had lower OI results on PAV compared to ACV [1]. Hence, we wished to stop this study as early as possible if all the PAV results were again superior to the ACV results.

In our previous study [1], we also reported that on PAV, the median pressure time product level was significantly lower than on ACV indicating a lower work of breathing, which may reflect more synchronised support by the ventilator throughout inspiration. Neurally adjusted ventilatory assist (NAVA) also applies airway pressure throughout inspiration. During NAVA, the pressure applied is proportional to the electrical activity of the diaphragm. In a cross-over study of 14 preterm infants [3], asynchrony was significantly lower during 12 h on NAVA than during 12 h on pressure regulated, volume controlled ventilation. In addition, amongst ten infants recovering from severe acute respiratory distress syndrome, oxygenation was superior after 8 h of NAVA compared to after 8 h of pressure support ventilation (PSV) [5]. These data [1, 3, 5] and the results currently reported suggest ventilation modes which apply airway pressure in proportion to the infant's respiratory effort throughout inspiration may be superior to those modes in which synchronisation is only at the start of inspiration (ACV) or the start and end of inspiration (pressure support ventilation).

Conclusion

In conclusion, we have demonstrated in a short-term cross-over study, PAV compared to ACV was associated with significantly superior oxygenation which likely reflects the better synchronisation of the inflation pressure and tidal volume throughout inspiration. We, therefore, feel these data emphasise the need now for a randomised controlled trial.

Acknowledgements AG, ADM and PB designed the study. SS undertook all the assessments. JLP advised on the analysis. All authors were involved in the production of the manuscript.

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Competing interests AG has held grants from various ventilator manufacturers; AG and ADM have received honoraria for giving lectures and advising various ventilator manufactures.

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ORIGINAL ARTICLE

Crossover study of assist control ventilation and neurally adjusted ventilatory assist

Sandeep Shetty[1] · Katie Hunt[1] · Janet Peacock[2,3] · Kamal Ali[4] · Anne Greenough[1,3,5]

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Abstract Some studies of infants with acute respiratory distress have demonstrated that neurally adjusted ventilator assist (NAVA) had better short-term results compared to non-triggered or other triggered models. We determined if very prematurely born infants with evolving or established bronchopulmonary dysplasia (BPD) had a lower oxygenation index (OI) on NAVA compared to assist control ventilation (ACV). Infants were studied for 1 h each on each mode. At the end of each hour, blood gas analysis was performed and the OI calculated. The inspired oxygen concentration (FiO_2), the peak inflation (PIP) and mean airway pressures (MAP) and compliance were averaged from the last 5 min on each mode. Nine infants, median gestational age of 25 (range 22–27) weeks, were studied at a median postnatal age of 20 (range 8–84) days. The mean OI after 1 h on NAVA was 7.9 compared to 11.1 on ACV (p = 0.0007). The FiO_2 (0.36 versus 0.45, p = 0.007), PIP (16.7 versus 20.1 cm H_2O, p = 0.017) and MAP (9.2 versus 10.5 cm H_2O, p = 0.004) were lower on NAVA. Compliance was higher on NAVA (0.62 versus 0.50 ml/cmH_2O/kg, p = 0.005).

Conclusion: NAVA compared to ACV improved oxygenation in prematurely born infants with evolving or established BPD.

What is Known:
- *Neurally assist ventilator adjust (NAVA) uses the electrical activity of the diaphragm to servo control the applied pressure.*
- *In infants with acute RDS, use of NAVA was associated with lower peak inflation pressures and higher tidal volumes.*

What is New:
- *This study uniquely reports infants with evolving or established BPD, and their results were compared on 1 h each of NAVA and assist controlled ventilation.*
- *On NAVA, infants had superior (lower) oxygen indices, lower inspired oxygen concentrations and peak and mean airway pressures and higher compliance.*

Keywords Assist control ventilation · Neurally adjusted ventilatory assist · Prematurity

Abbreviations

ACV	Assist control ventilation
BPD	Bronchopulmonary dysplasia
Edi	Electrical activity of the diaphragm

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FiO_2	Inspired oxygen concentration
MAP	Mean airway pressures
NAVA	Neurally assist ventilator adjust
OI	Oxygenation index
PEEP	Positive end expiratory pressure
PIP	Peak inflation pressure
RDS	Respiratory distress syndrome

Introduction

Whilst the survival of babies born very prematurely has improved, many will develop bronchopulmonary dysplasia (BPD) and chronic respiratory morbidity. New modes of ventilation have been developed with the aim of reducing lung injury and improving respiratory outcomes. One such mode is neurally adjusted ventilatory assist (NAVA). NAVA uses the electrical activity of the diaphragm (Edi), captured by a specialised nasogastric tube with an array of electrodes (the Edi catheter), to servo control the applied ventilator pressure. The Edi is used both to trigger each inflation and also to determine the level of support proportional to the infant's neural drive to breathe throughout each inflation [11]. Inflations are off-cycled when the Edi falls by a prespecified amount. The clinician sets the NAVA level or gain factor by which the Edi signal at each point in time is "translated" into airway pressure provided. The change in electrical activity of the diaphragm that triggers inflation is earlier in the respiratory cycle than the change in flow which is used in other trigger modes; hence, the trigger delay is shorter on NAVA [4]. Edi may be a more accurate method to detect the infant's inspiratory efforts and hence, there would be less ineffective or wasted effort and auto or double triggering.

In infants with acute respiratory distress, in randomised and non-randomised crossover studies, NAVA has been shown to have superior results compared to non-triggered and other triggered modes, but only with regard to pressure levels and lung function. Studies have not addressed clinically important outcomes such as the length of intubation or mortality. In a randomised crossover study of 4-h periods comparing synchronised intermittent mandatory ventilation (SIMV) with pressure support, NAVA was shown to have a lower peak airway pressure in preterm infants born between 24 and 36 weeks [8]. In a non-randomised study, five premature infants with a mean gestational age of 26 weeks were studied at a median postnatal age of 7 days [13]. They were ventilated for consecutive 4-h periods on NAVA followed by pressure controlled ventilation, and the sequence was repeated three times. The peak inflation pressure (PIP) was lower and the tidal volumes and compliance were higher on NAVA [13]. A non-randomised, crossover study of two 12h periods of pressure-regulated volume control ventilation followed by NAVA was performed on 19 infants with a median gestational age of 31.8 weeks. NAVA resulted in lower peak inspiratory pressures and the tidal volumes of the infants were lower on NAVA [9]. In addition, on NAVA, the asynchrony index was lower and there were no neural apnoeas. [9].

Infants with evolving or established bronchopulmonary dysplasia (BPD) have a high resistance of the respiratory system which means flow triggering can be challenging. During NAVA, flow triggering is not used [4]. Previous studies have assessed infants with acute respiratory distress who have very different lung function to those with evolving or established BPD. Hence, it cannot be assumed that similar results from those with acute respiratory distress would be achieved in those with established or evolving BPD. Hence, the aim of our study was to uniquely test the hypothesis that NAVA compared to assist control ventilation (ACV) would result in a lower OI in infants with evolving or established BPD.

Methods

The study was undertaken at King's College Hospital NHS Foundation Trust between December 2015 and June 2016. Infants were eligible for this randomised, crossover study if they were born at less than 32 weeks of gestation and remained ventilated at 1 week of age on assist control ventilation (ACV). Eligible infants were identified on a daily basis by a researcher by discussion with the clinical team. A local audit of 100 consecutive infants born at less than 32 weeks of gestation had demonstrated 95% of those who remained ventilator dependent at 1 week of age developed BPD, that is oxygen dependency beyond 28 days. Those with major congenital abnormalities (that is requiring surgical correction) or receiving neuromuscular blockade were excluded. All infants were clinically stable with assessed. The study was approved by the West Midlands - Solihull Research Ethics Committee. Written, informed parental consent was obtained.

Infants at King's College Hospital NHS Foundation Trust are routinely supported by the SLE 5000 (software versions 4.3; SLE Ltd., South Croydon, UK). All infants were ventilated with Coles shouldered endotracheal tubes which have been shown to have minimal or no leaks [7]. Volume targeting was not used. On entry into the study, the infants were transferred from ACV on the SLE 5000 to ACV (named 'Pressure Control' on the Servo-n ventilator, Maquet Critical Care, Solna, Sweden). The same ventilator settings and backup rate were used. In particular, the positive end expiratory pressure (PEEP) was kept at 4–5 cm H_2O as had been used prior to the study and the inflation time was set, as previously, at 0.36 to 0.4 s. The apnoea time was set to 2 s and the upper pressure limit at least 5 cm H_2O higher than the baseline settings, but did not exceed 30 cm H_2O. A six French Edi catheter was inserted and correct positioning confirmed as per the instructions of the manufacturer using the Edi catheter positioning waveform closely matched the pressure waveform on the baseline settings.

We have previously demonstrated that proportional assist ventilation (PAV), when compared to ACV, resulted in improved oxygenation [2, 12] and a reduced work of breathing [2] in infants with evolving or established bronchopulmonary dysplasia. Both PAV and NAVA provide support in proportion to the respiratory effort throughout each breath. Our results suggest that such modes are superior to ACV. As yet, there are no randomised controlled trials with long-term outcomes assessing either NAVA or PAV and therefore, any potential long term benefit remains unknown.

In conclusion, we have demonstrated in a randomised crossover study that NAVA, compared to ACV, resulted in improved (lower) oxygenation index and this was associated with lower peak and mean airway pressures.

Authors' contributions Professor Greenough and Dr. Ali designed the study and approved the final manuscript as submitted. Dr. Shetty and Dr. Hunt collected the data and approved the final manuscript as submitted. Professor Peacock designed the statistical analysis and analysed the data and approved the final manuscript as submitted. All authors were involved in the preparation of the manuscript and approved the final manuscript as submitted.

Compliance with ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Conflict of interest AG has held grants from various ventilator manufactures and has received honoraria for giving lectures and advising various ventilator manufactures. The Servo-n ventilator was loaned to us by Marquet Critical Care, Solna, Sweden. They were not involved in the study design, data collection, data analysis or production of the manuscript.

Informed consent Infants whose parents gave informed written consent were recruited.

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guide function on the ventilator (Magnet Servo-n User Manual Version 1.1). The guide function displays the retrocardiac echocardiograph. Correct positioning was when the P waves and QRS complexes were visible in the uppermost leads and then decreased in size until the P waves disappeared in the lowest lead. Coloured highlighting of the central two leads appeared once the catheter was in the correct place. Once correct positioning was confirmed, the catheter was securely attached to the infant's face using an adhesive dressing. After 1 h of stabilisation on the Servo-n ventilator using the settings described above, blood gas analysis was performed. Infants were then randomised to receive either ACV or NAVA first for 1 h and then to receive the alternative mode for a subsequent hour. The order in which the infants received the two modes was randomised between each baby using a sequential opaque sealed envelope system. Before the infant was changed to NAVA mode, the NAVA level was adjusted so that the displayed pressure waveform on NAVA closely matched the actual pressure waveform on the baseline settings, aiming for the peak Edi to be between 5 and 15 μVas per the recommendations of the manufacturer. The baseline ventilator settings were used to determine the backup settings to be used on NAVA in the absence of an Edi signal.

The initial ventilator settings were noted, and the number and duration of desaturations (defined as oxygen saturation less than 88%) were noted on each ventilator mode. The FiO_2 was adjusted with the aim of maintaining oxygen saturations between 92 and 96%. At the end of each hour, capillary blood gas analysis was performed and the oxygenation index (OI) calculated as the inspired oxygen concentration (FiO_2) x mean airway pressure (MAP) × 100/pO_2. The FiO_2, the PIP, MAP, tidal volume and respiratory system compliance (calculated from the tidal volume divided by the PIP) were recorded from the ventilator displays and averaged from the last 5 min of each 1-h period. The data were down-loaded into excel via a USB stick.

Sample size

The planned sample size was 18 infants, as this would allow detection of a difference in oxygenation index between the two modes of one standard deviation, with 80% power and 5% significance. An interim analysis was planned to take place half way through, i.e. after nine patients, as our studies with proportional assist ventilation (PAV), a ventilation mode which also provides tailored support throughout the infant's inspiratory cycle, demonstrated the OI on PAV was better in all patients than on ACV [2, 12]. In order to preserve the type I error at 5%, the interim analysis was conducted at 0.01 with the final analysis conducted using 0.04. This gave an overall type 1 error rate (significance level) of 5% [(1–0.01) × (1–0.04) = 0.95 = 1–0.05]. If the interim analysis showed $p < 0.01$, then the trial was to stop and the final analyses conducted using the nine patients treated to that point.

Analysis

The results were positively skewed and, therefore, log-transformed for analysis so that a paired t test could be used. Using that method, the results including the mean and confidence intervals are on the ratio scale [3]. Results were back-transformed to give geometric means for each mode of ventilation. The ratio of geometric means and the corresponding 95% confidence intervals for the ratio are presented. The ratio of the geometric means can be interpreted as the percentage difference between a result on NAVA compared to on ACV. The desaturation data were discrete and analysed using the Wilcoxon signed-rank test. Data were analysed using Stata v 14.

Results

At the interim analysis, the comparison of the OI on NAVA versus ACV was statistically significant using the modified cut-off for significance described above. The OI was lower on NAVA for all infants (Table 1). Hence, the clinical and statistics team agreed that the trial be stopped at that point and the data analysed.

Nine infants had been assessed, seven males and two females. Their median gestational age was 25 (range 22–27) weeks and median birthweight 750 (range 545–830) grammes. The infants were studied at a median postnatal age of 20 (range 8–84) days. All had received at least one dose of antenatal steroids and postnatal surfactant and were on caffeine at the time of the study. Only one infant was receiving sedation and this was at the same dose throughout the study. Five of the infants were studied first on NAVA and four on ACV. There was no suggestion that the size of difference in OI was greater with order (i.e. with either ACV then NAVA or

Table 1 Individual baseline PIP and FiO_2 at the start of the study and individual OI data at the end of each mode. The mode which was used first in each infant is given in the fifth column

PIP (cm H_2O)	FiO_2	ACV	NAVA	Mode first
27	1	30.3	17.4	ACV
16	0.44	9.2	8	NAVA
18	0.63	7.6	5.7	NAVA
18	0.27	6.7	4.6	ACV
24	0.87	26.8	16.0	ACV
19	0.41	7.4	6.6	NAVA
19	0.7	24.1	13.4	NAVA
18	0.45	6.4	5.4	NAVA
23	0.4	5.7	4.5	ACV

Table 2 Results by ventilatory mode. The results are presented as the geometric mean (range) for each mode, the ratio of geometric means between the two modes and the corresponding 95% CI

	Mean ACV	Mean NAVA	Ratio of geometric means (NAVA/ACV)	95% confidence interval for ratio	P value
OI	11.06 (5.7–30.3)	7.92 (4.7–17.4)	0.72	0.62–0.83	0.0007
Peak airway pressure (cmH_2O)	20.13 (14.8–27.1)	16.72 (12.7–28.6)	0.83	0.72–0.96	0.017
Mean airway pressure) (cmH_2O)	10.53 (8.8–14.2)	9.20 (7.8–12.7)	0.87	0.81–0.94	0.004
FiO_2	0.45 (29.2–91.0)	0.36 (23–54.9)	0.81	(0.71–0.93)	0.007
Peak Edi (μV)	14.04 (6.1–47.0)	11.10 (7.4–22.0)	0.79	0.60–1.05	0.089
Expiratory tidal volume (ml/kg)	7.06 (5.1–8.6)	6.24 (3.9–10)	0.88	0.76–1.02	0.87
Compliance (mls/cmH_2O/kg)	0.50 (0.30–0.68)	0.62 (0.34–0.91)	1.24	1.09–1.41	0.005
Respiratory rate (breaths/min)	51.63 (40–65)	50.51 (38–67)	0.98	0.89–1.08	0.616
Oxygen saturation (%)	94.8 (90–98)	97.9 (95–100)	1.03	1.01 – 1.05	0.016
Desaturations[a] (n)	3 (0–12)	1 (0–5)	N/A	N/A	0.70

[a] Medians presented as the data were discrete and assessed using the Wilcoxon signed-rank test; hence, the ratio and 95% CI were not available

NAVA then ACV). Neither was there any suggestion that the order (by chance) was related to the size of value, i.e. no suggestion that all those with a high starting OI received the modalities in the same order ($p = 0.66$).

The ratio of the geometric means for the OI, the primary outcome, was 0.72 (NAVA/ACV), showing that the mean OI was 28% lower on NAVA compared to ACV with corresponding 95% CIs from 62 to 83% (Table 1). Infants who had the highest OIs on ACV tended to have a larger reduction in OI when studied on NAVA (Table 1). The mean PIP ($p = 0.017$) and mean MAP ($p = 0.004$) were significantly lower on NAVA, as was the mean FiO_2 ($p = 0.007$). The mean compliance ($p = 0.005$) and oxygen saturation ($p = 0.016$) were significantly higher on NAVA. The means for the tidal volume, respiratory rate and peak Edi and the number of desaturations were not significantly different between the two modes (Table 2).

Discussion

We have demonstrated that in infants born very prematurely and with evolving or established BPD, NAVA compared to ACV resulted in a significantly lower oxygenation index. This was associated with significantly lower PIPs and MAPs, likely reflecting that during NAVA the applied pressure is servo-controlled throughout each inflation. On ACV, although inflation is triggered by the beginning of the infant's inspiratory effort, the start of inflation may have been delayed as a flow trigger was used. Furthermore, after the inflation is triggered during ACV, neither the inflation pressure nor time is tailored to the infant's inspiratory efforts. The higher compliance on NAVA compared to ACV reflects the lower PIPs with similar tidal volumes. A higher compliance on NAVA has been previously reported in neonatal and paediatric patients [1, 5, 6]. Our results suggest that infants with the highest OIs, i.e. the most severe lung disease, had the greatest reduction in OI during NAVA. This may reflect, as above, the shorter trigger delay on NAVA which means more of the infant's breath is pressure supported.

There are strengths and some limitations to our study. As the same ventilator was used for each mode, the significant differences demonstrated are due to the differences in the modes, rather than differences in the ventilator performance. Although infants were only studied for an hour on each mode, we have demonstrated significant differences between the two modes. The infants included had a wide range of severity of respiratory disease as suggested by their PIP and FiO_2, yet we saw a positive effect of NAVA in all infants. The infants had also had a wide range of postnatal ages, but we have shown in an audit of 100 consecutive prematurely born infants, 95% of those who remained ventilator dependent at 1 week developed BPD. Thus, we feel our results demonstrate that compared to ACV, NAVA use was associated with superior results in infants with evolving or established BPD. We used capillary blood samples to calculate the OIs. We used this method at the end of each of the two periods in all infants, thus the use of capillary blood sampling did not bias our results. The infants were all clinically stable when assessed and none were seriously ill, had shock, hypotension or peripheral vasoconstriction at the time of assessment [10]. Thus, we feel it was appropriate to calculate the OIs from the capillary blood samples. Only one infant was receiving sedation and this was at the same dose throughout the study, so this did not influence the results. We used a crossover design as this removes the variability between patients by looking at effects within them. As we have demonstrated no order effect, the design gives more precision. We stopped the trial at the planned interim analysis as in all infants the OI was lower on NAVA. We did not demonstrate a significant difference in the peak Edi between the two modes, although there was a trend for it to be lower on NAVA. This may have been due to insufficient redistribution of work from the patient to the ventilator, as the NAVA level was only adjusted so that the estimated pressure

LETTER

Changes in the use of humidified high flow nasal cannula oxygen

Humidified high flow nasal cannula (HHFNC) has gained popularity in neonatal care. A systematic review[1] of the results of nine trials, which included a total of 1112 infants, however, demonstrated that HHFNC was not superior to other modes of non-invasive ventilation in infants of >28 weeks gestational age. We, therefore, sought to determine whether clinical practice regarding HHFNC had changed since 2012 when all UK units were surveyed[2] and also to identify why practitioners preferred HHFNC or continuous positive airway pressure (CPAP).

In 2015, lead clinicians of all 194 UK neonatal units were identified from the National Neonatal Audit Programme, British Association of Perinatal Medicine directory and a departmental database from previous audits. In 2012, practitioners from the then 203 UK neonatal units had been contacted.[2] Both surveys included questions on the level of neonatal care, the indications for use of HHFNC and the flow rates used. The 2015 survey also contained questions regarding nasal prong size, weaning policies and HHFNC or CPAP preference (practitioners were given a list of possible reasons to choose from).

There was 100% response rate to both surveys. Use of HHFNC was significantly increased in 2015 compared with 2012 (p<0.001) (table 1). Almost all local neonatal and neonatal intensive care units were using HHFNC in 2015. Fewer units were using HHFNC as an alternative to CPAP or weaning from CPAP (p=0.001), but a greater proportion were using it as the primary support mode post extubation (p=0.001). The 2015 survey highlighted that in 25% of units, the prong size was chosen to fit snugly and occlude the nostril, whereas it is recommended that the fit should be <50% of the nares.[3] Thirty-six per cent of units were using HHFNC without guidelines. The highest and lowest flow rates used varied in both surveys, but the magnitude of change of flow when weaning from HHFNC did not differ significantly in the two surveys. In the 2015 survey, weaning the flow in increments of between 0.5 and 1 L/min and 24 hourly was most popular, but there was no consensus. This likely reflects that there is currently no evidence to determine the best weaning strategy from HHFNC.[4]

The majority of practitioners preferred HHFNC (table 2). In particular, almost all thought babies achieved full oral feeds by breast or bottle quicker on HHFNC and that it was more comfortable for the baby than CPAP.

Table 1 HHFNC practice in 2012 and 2015, data are displayed as the n (%)

	2012	2015	p Value
HHFNC			
Total number of units	203	194	
Using HHFNC	113 (56%)	169 (87%)	<0.001
Unit level			
Special care unit	12/53 (23%)	22/42 (52%)	0.003
Local neonatal unit	60/94 (64%)	84/88 (95%)	<0.001
Neonatal intensive care unit	41/58 (70%)	63/64 (98%)	<0.001
Data are subsequently displayed only for units using HHFNC			
Indication of use			
Alternative to CPAP/weaning from CPAP	66 (58%)	65 (38%)	0.001
Primary mode of respiratory support post extubation	47 (42%)	104 (62%)	0.001
Highest flow rate			
8	36 (32%)	78 (46%)	0.011
7	12 (11%)	6 (4%)	0.017
6	38 (34%)	77 (46%)	0.080
5	27 (23%)	8 (5%)	<0.001
Lowest flow rate			
4	11 (10%)	18 (11%)	0.485
3	40 (35%)	40 (24%)	0.023
2	45 (40%)	97 (57%)	0.003
1	17 (15%)	14 (8%)	0.058
Size of change in flow when weaning (L/min)			
0.5	30 (27%)	51 (30%)	0.301
1	38 (34%)	58 (35%)	0.504
0.5–1	45 (40%)	60 (36%)	0.271
Time between changes in flow rates			
24 hourly		79 (47%)	
24–48 hourly		21 (12%)	
48 hourly		17 (10%)	
Depends on the infant's condition		52 (31%)	
Prong size			
Snug fit to occlude the nostril		42 (25%)	
Prong size selected to allow air leak		127 (75%)	
Guideline/policy			
Yes		108 (64%)	

CPAP, continuous positive airway pressure; HHFNC, humidified high flow nasal cannula.

Table 2 Preference for CPAP or HHFNC, data are displayed as n (%)*

	CPAP	HHFNC	p Value
Which is better	18 (11%)	109 (64%)	<0.001
Better access to the infant	1 (1%)	145 (86%)	<0.001
Easier to set up	13 (8%)	138 (82%)	<0.001
Better access for skin to skin care	0 (0%)	162 (96%)	<0.001
Quicker to achieve full bottle feeding	0 (0%)	166 (98%)	<0.001
Quicker to achieve full breast feeding	0 (0%)	168 (99%)	<0.001
Less nasal trauma	0 (0%)	162 (96%)	<0.001
More comfortable for the infant	1 (1%)	165 (98%)	<0.001
Parental preference	0 (0%)	162 (96%)	<0.001

*Not all practitioners responded to every question.
CPAP, continuous positive airway pressure; HHFNC, humidified high flow nasal cannula.

PostScript

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Contributors AG and SS designed the study. SS, AS and KH collected the data for 2015 survey. SS and PD collected data for the 2012 survey. All the authors were involved in the production of the final manuscript.

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Work of breathing during CPAP and heated humidified high-flow nasal cannula

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ABSTRACT

Objective To determine whether continuous positive airway pressure (CPAP) compared with heated humidified, high-flow nasal cannula (HHFNC) in infants with evolving or established bronchopulmonary dysplasia (BPD) reduced the work of breathing (WOB) and thoracoabdominal asynchrony (TAA) and improved oxygen saturation (SaO_2).

Design Randomised crossover study.

Setting Tertiary neonatal unit.

Patients 20 infants (median gestational age of 27.6 weeks (range 24.6–31.9 weeks)) were studied at a median postnatal age of 30.9 weeks (range 28.1–39.1 weeks).

Interventions Infants were studied on 2 consecutive days. On the first study day, they were randomised to either CPAP or HHFNC each for 2 h, the order being reversed on the second day.

Main outcome measures The WOB was assessed by measuring the pressure time product of the diaphragm (PTPdi). PTPdi, TAA and SaO_2 were assessed during the final 5 min of each 2 h period and the results on the two study days were meaned.

Results There were no significant differences in the results on CPAP versus HHFNC: mean PTPdi 226 (range 126–294) versus 224 cm H_2O/s/min (95% CI for difference: −27 to 22; p=0.85) (range 170–318) (p=0.82), mean TAA 13.4° (range 4.51°–23.32°) versus 14.01° (range 4.25°–23.86°) (95% CI for difference: −3.9 to 2.8: p=0.73) (p=0.63) and mean SaO_2 95% (range 93%–100%) versus 95% (94%–99%), (95% CI for difference −1.8 to 0.5; p=0.25) (p=0.45).

Conclusion In infants with evolving or established BPD, CPAP compared with HHFNC offered no significant advantage with regard to the WOB, degree of asynchrony or oxygen saturation.

What is already known on this topic

- Humidified, high flow nasal cannula (HHFNC) is increasingly being used as an alternative to nasal continuous positive airway pressure (nCPAP).
- The distending pressure during HHFNC is dependent on prong size, nasal prong to nares ratio, flow rate and whether the infant's mouth is open.
- Studies comparing the work of breathing (WOB) on HHFNC or nCPAP have given conflicting results.

What this study adds

- In infants with evolving or established bronchopulmonary dysplasia, we have compared WOB on HHFNC and CPAP.
- In this randomised crossover trial we demonstrated no significant differences in the WOB between the two modes.
- In addition, we highlight that there were no significant differences in the degree of asynchrony or oxygen saturation levels.

INTRODUCTION

Heated and humidified gas delivered at flow rates between 2 and 8 L/min via nasal cannulae (humidified, high-flow nasal cannula (HHFNC)) is increasingly being used as an alternative to continuous positive airway pressure (CPAP). About 63% of Australian/New Zealand units were reported to be using HHFNC in 2010[1] and a survey of 57 level 2 or level 3 UK neonatal units in 2013 highlighted that HHFNC was used in 77% of units.[2] This is despite the distending pressure delivered by HHFNC being dependent on prong size, nasal prong-to-nares ratio, flow rate and whether the infant's mouth is open.[3 4] In addition, it has been reported that even when flows of up to 6 L/min were used during HHFNC, pressures over 5 cm H_2O were rarely achieved.[5] A lower distending pressure would seem likely to result in an increase in the work of breathing (WOB); however, three studies in which the infant's WOB during HHFNC and CPAP was compared have given conflicting results.[5–7] In a crossover study of 18 preterm infants with a birthweight of less than 2.0 kg who had mild respiratory illness, no significant difference was found in the WOB when the infants were supported by 6 cm H_2O CPAP or HHFNC delivered at 3, 4 and 5 L/min.[6] The infants, however, had a diverse range of postnatal ages 1–67 days and a variety of diagnoses including mild respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD) or apnoea of prematurity. In a subsequent study of 20 infants with moderate respiratory distress (fraction of inspired oxygen (FiO_2) between 21% and 32%), the WOB was higher during HHFNC (delivered at 3 or 5 L/min) than on CPAP (5–6 cm H_2O).[7] In addition, the degree of asynchrony as assessed by the phase angle measured by respiratory inductance plethysmography (RIP) and the laboured breathing index was greater

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during HHFNC.[7] In a third study of 20 infants with mild or moderate RDS less than 96 h old, no significant differences were found in the WOB and lung mechanics during periods of support on nasal CPAP (nCPAP) (2, 4 cm H_2O) and HHFNC (2, 4 L/min).[5]

Respiratory management of infants with evolving or established BPD is particularly challenging. Whether CPAP or HHFNC provides more effective respiratory support has not been assessed specifically in such a population. The aim of this study, then, was to determine whether CPAP compared with HHFNC reduced the WOB and thoracoabdominal asynchrony (TAA) and improved oxygen saturation (SaO_2) in infants with evolving or established BPD.

METHODS

Infants born at less than 32 weeks of gestation at King's College Hospital NHS Foundation Trust, London, UK, requiring CPAP and more than 40% of oxygen at or beyond 2 weeks of age were eligible for entry into this study between April 2014 and February 2015. Those infants with a postnatal age greater than 14 days but less than 28 days were diagnosed as having evolving BPD and those aged 28 days or older as established BPD. Infants whose parents gave informed written consent were entered into the study. The study was approved by the London—Westminster Research Ethics Committee and King's College Hospital Research Ethics Committee.

Infants were studied on 2 days for 2 h each on CPAP (SLE 2000, 5000 infant ventilator) and HHFNC (Fisher and Paykel using optiflow neonatal and infant nasal prongs). Infants were randomised on the first day to be first supported by either CPAP for 2 h and then by HHFNC for 2 h. On the second day, they received HHFNC and CPAP in the reverse order. The CPAP level was 6 cm H_2O and during HHFNC a flow rate of 8 L/min was used for infants with a weight more than 1 kg and 6 L/min for infants with a weight less than 1 kg. The flow levels were chosen after reviewing protocols from other units and discussion at our departmental guideline development meeting.

During the last 5 min of each 2 h period, physiological assessments were made. To assess the WOB, the transdiaphragmatic pressure time produce (PTPdi) was assessed. Oesophageal (Poes) and gastric (Pgas) pressures were measured using a dual pressure transducer tipped catheter (Gaeltec, Dunvegan, Scotland, UK). Correct positioning of the catheter was indicated by a positive deflection in Pgas and a negative deflection in Poes. Pressure signals were amplified (CD 280, Validyne) and recorded on a computer (Dell Optiplex 170L) running Labchart software (V.7.3.7 27, Powerlab 16SP, ADInstruments, Sydney, Australia) with analogue to digital sampling at 100 Hz (Powerlab 16SP, ADInstruments, Sydney, Australia). Transdiaphragmatic pressure (Pdi) was calculated by the acquisition software using digital subtraction of Poes from Pgas. PTPdi was obtained from the area subtended by the Pdi trace during inspiration (figure 1). As respiratory flow was not measured directly, the beginning of inspiration was determined by the rise in Pdi and end of inspiration was determined from rib cage (RC) movement using uncalibrated RIP (Respitrace Model 10.9230, Ambulatory Monitoring, New York, USA) in AC-coupled mode used to assess RC and abdomen (ABD) movement (figure 1). TAA was determined from 10 artefact-free breaths during the 5 min measurement period. For each breath, the RC and ABD movements were measured and a Lissajous figure was plotted (figure 2). Asynchrony between RC and ABD movements were quantified by determining the phase angle by comparing the difference between inspiratory and expiratory abdominal positions at mid-RC excursion (ABdiff) with the maximum abdominal excursion (ABmax). The phase angle φ was calculated as $\sin \varphi = \text{ABdiff}/\text{ABmax}$. PTPdi and TAA were assessed from the last 5 min of each 2 h period. During the study, respiratory rate, heart rate and oxygen saturation were continuously recorded (IntelliVue MP70 Philips patient monitor) and averaged for the 2 h period. The results from the two study days were meaned.

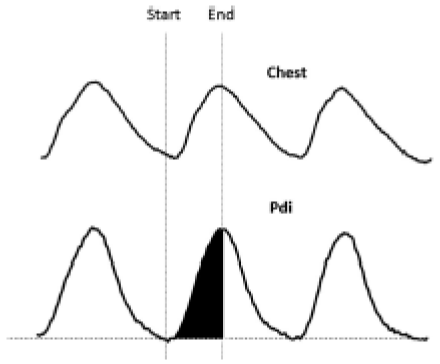

Figure 1 Calculation of transdiaphragmatic pressure time produce during inspiration is shown. The shaded area represents the area subtended by the transdiaphragmatic pressure (Pdi) trace during inspiration. The beginning of inspiration was determined by the rise in Pdi and end of inspiration was determined from rib cage movement using uncalibrated respiratory inductance plethysmography.

Sample size

A sample size of 20 infants allowed detection between the two respiratory support modes of a difference in the results of the physiological assessments of 1.0 SD with 80% power with 5% significance.

Analysis

The data were tested for normality and found to have a normal distribution, hence a paired t-test was used to assess whether differences were statistically significant. Regression models were used to examine the effect of the order of modes of respiratory support (CPAP/HHFNC or HHFNC/CPAP). Since there was no evidence for any effect of the order or of the day, the measurements for each of the two respiratory support modes were averaged over the 2 days. The residuals from the regression model were checked for their fit to a normal distribution. Due to the relatively small sample size and the difficulty in ensuring a normal distribution, the analysis examining mode was also run using a rank test (Wilcoxon matched pairs), which gave similar results. IBM SPPS statistical software (V.22; IBM Corporation, USA) was used. Analyses were conducted using Stat (V.12).

RESULTS

Parents of 30 eligible infants were approached and 20 agreed to recruitment. The infants who were recruited compared with those who were not did not differ significantly with regard to their gestational age (27 weeks (range 25–29 weeks) vs 28 weeks (range 25–32 weeks) ($p=0.47$)) or median birthweight (median 834 g (664–1020 g) vs 880 g (range 512–1500 g) ($p=0.94$)).

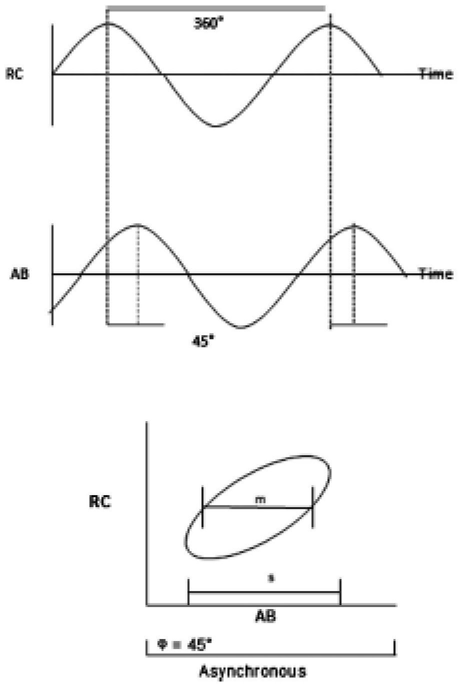

Figure 2 Example of idealised rib cage (RC) and abdomen (AB) motion and *X Y* plot (Lissajous figure) used in determining phase angle is shown. In the example shown, the RC and ABD are 45° out of phase.

The 20 infants who were included in the study had a median gestational age of 27.6 weeks (range 24.6–31.9 weeks) and birthweight of 880 g (range 512–1500 g) (table 1) When studied they required a median FiO_2 of 0.42 (range 0.4–0.58). There were no significant differences in the results of any of the physiological measurements between the two groups (table 2).

Table 1 Demographic data

Gestational age (weeks)	28 (24–32)
Birthweight (g)	888 (512–1500)
Antenatal steroids	
Surfactant	
Caffeine	
Post conceptional age (weeks) at assessment	31 (28–39)
Male (%)	11/20 (55%)
Ethnicity	
Caucasian	8 (40%)
Afro-Caribbean	5 (25%)
Asian	5 (25%)
Other	2 (10%)

The data are presented as median (range) or n (%).

Table 2 Physiological assessment results by respiratory support mode

	CPAP	HHFNC	p Value
PTP cm H_2O/s/min	244 (126–294)	220 (169.5–318)	0.85
TAA (degrees)	12.6 (4.5–23.3)	13.1 (4.2–23.8)	0.73
Oxygenation Saturation (%)	95 (93–100)	96 (94–99)	0.48

The results are expressed as the median (range).
CPAP, continuous positive airway pressure; HHFNC, humidified, high flow nasal cannula; TAA, thoraco-abdominal asynchrony.

DISCUSSION

We have demonstrated that in prematurely born infants with evolving or established BPD, there were no significant differences in the WOB, TAA or SaO_2 when the infants were supported by CPAP or HHFNC. We exclusively studied infants with evolving or established BPD, unlike previous studies.[5–7] Interestingly, in the one study which did include infants with BPD, and other pathologies, no significant difference was found in the WOB between CPAP and HHFNC.[6] We used higher flow rates during HHFNC (8 L/min for infants with weights more than 1 kg) than employed in the previous studies,[5–7] which may also explain our findings.

There have now been several randomised trials of HHFNC versus CPAP. In one study, 60 infants born at ≥28 weeks gestational age stable on nCPAP (5 cm H_2O) for at least 24 h with an FiO_2<0.30 were randomised to stay on nCPAP or be transferred to HHFNC at 2 L/min. The latter group required significantly more days of supplementary oxygen and total respiratory support.[8] The 5 cm H_2O CPAP compared with 2 L/min of HHFNC may have resulted in the differences in the results. In a larger study of 132 infants all less than 32 weeks of gestational age, infants were randomised to HHFNC at 8 L/min or nCPAP at 7–8 cm H_2O post extubation. Although a similar proportion failed extubation defined as intubation with 7 days, the nasal trauma score was significantly lower in the HHFNC group.[9] In a study of 432 infants of gestational age between 28 and 42 weeks with planned nCPAP support (recommended starting pressure 5–6 cm H_2O) either as a primary mode or post extubation, early failure and need for intubation was similar in the two groups.[10] Infants randomised to HHFNC received an initial flow dependent on gestational age (3 L/min for those weighing 1000–1999 g; 4 L/min for those weighing 2000–2999 g and 5 L/min for those weighing ≥3000 g). The duration of the study mode was significantly longer on HHFNC (median 4 vs 2 days, p<0.01), but there were no significant differences between the groups in the duration of supplementary oxygen, rate of BPD or length of stay. Hence, the authors concluded that HHFNC appeared to have similar efficacy and safety to nCPAP when applied immediately post extubation or as initial, non-invasive support for respiratory dysfunction.[10] Our results suggest that HHFNC using the flow rates we employed provides similar support as nCPAP in infants with evolving or established BPD.

Our study has a number of strengths and some limitations. We used a dual pressure tip transducer to assess the WOB as assessed by measurement of the PTPdi. Changes in Poes may not accurately reflect change in pleural pressures when chest wall distortion results in an uneven distribution of pleural pressure changes. In our study, there were no differences in the TAA between the two respiratory support modes and hence the comparison of the WOB results is valid. We used a crossover design, hence we cannot comment on long-term outcomes. Previous studies investigating the WOB were also of a crossover design[5–7] but were of single crossover design and did not analyse the effect of the order in which the infants were studied on a particular respiratory mode. We studied infants on 2 successive days with the order of respiratory support studied being reversed on the subsequent day and then we meaned the results of 2 days, hence we feel our results are robust. It is possible that had the infants been exposed to longer periods of HHFNC and CPAP different results may have been obtained. Assessment of 10 very low birthweight infants in a crossover design study of 2 h on HHFNC (mean flow rate of 4.8 or 5.4 L/min) or CPAP (5 cm H_2O) demonstrated greater diaphragmatic activity on HHFNC, thus suggesting that nCPAP was providing more effective respiratory support. Of note, however, there was no significant difference in the oxygen saturation levels between the two modes.[11] We used higher flow rates during HHFNC than in the previous study.[11] We recruited 20 of 30 eligible infants, but those recruited did not differ significantly with regard to gestational age or birthweight from those not recruited, hence we feel our results are generalisable.

In conclusion, we have demonstrated that CPAP did not provide superior respiratory support compared with HHFNC in infants with evolving or established BPD. Infants supported by HHFNC rather than nCPAP are reported to have less nasal trauma[9] and are more accessible to parents and staff.[2] BPD infants are often intolerant of nCPAP, and thus we suggest HHFNC to be an appropriate alternative.

Contributors AG and GFR designed the study. SS collected the data. JLP advised on the analysis. All authors were involved in production of the final manuscript.

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Competing interests AG has held grants from various ventilator manufacturers and has received honoraria for giving lectures and advising various ventilator manufacturers.

Ethics approval London-Westminster Research Ethics Committee and King's College Hospital Research Ethics Committee.

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Review article

Neonatal ventilation strategies and long-term respiratory outcomes

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ABSTRACT

Long-term respiratory morbidity is common, particularly in those born very prematurely and who have developed bronchopulmonary dysplasia (BPD), but it does occur in those without BPD and in infants born at term. A variety of neonatal strategies have been developed, all with short-term advantages, but meta-analyses of randomized controlled trials (RCTs) have demonstrated that only volume-targeted ventilation and prophylactic high-frequency oscillatory ventilation (HFOV) may reduce BPD. Few RCTs have incorporated long-term follow-up, but one has demonstrated that prophylactic HFOV improves respiratory and functional outcomes at school age, despite not reducing BPD. Results from other neonatal interventions have demonstrated that any impact on BPD may not translate into changes in long-term outcomes. All future neonatal ventilation RCTs should have long-term outcomes rather than BPD as their primary outcome if they are to impact on clinical practice.

Contents

1. Introduction

Chronic respiratory morbidity is a common outcome of very premature birth, particularly in those who had developed bronchopulmonary dysplasia (BPD), chronic oxygen dependency beyond 28 days after birth. BPD was initially described in infants who had severe lung disease, so-called old BPD. Affected infants usually required high inspired oxygen concentrations and intermittent positive pressure ventilation with high peak inflating pressures. It can, however, occur in very prematurely born infants who had minimal or even no initial respiratory distress, so-called new BPD. The latter has been suggested to be a maldevelopment sequence resulting from interruption/interference of the normal development signalling for terminal maturation [1]. Unfortunately, infants with BPD suffer chronic respiratory morbidity. They may require supplementary oxygen for many months,

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although few remain oxygen dependent beyond two years of age [2]. Hospital readmission is common, particularly for respiratory problems [3]. Troublesome respiratory symptoms requiring treatment can occur in childhood [4] and persist into adulthood [5]. Children and adults who had BPD have lung function abnormalities. In the first two years, they may have high airways resistance, gas trapping and ventilation inhomogeneity. Lung growth and remodelling results in a progressive improvement in lung function, but airflow limitation persists [6], such that airway obstruction and impaired gas transfer is seen in adults who had BPD [7].

BPD has a multifactorial aetiology, which includes volutrauma and oxygen toxicity. As a consequence, there has been much research in developing and optimizing new mechanical ventilation and noninvasive respiratory support techniques with the hope of reducing the occurrence of BPD and chronic respiratory morbidity. The aim of this review is, by examining the literature, to determine how successful the newer ventilator strategies have been in decreasing BPD and, more importantly, if their introduction has influenced long-term respiratory outcomes. It should also be noted that infants born at term and who required mechanical ventilation can also suffer chronic adverse effects [8]. Unfortunately, as this review will also highlight there have been few studies investigating respiratory support techniques in that population.

2. Noninvasive respiratory support

2.1. CPAP

An early meta-analysis of RCTs of prophylactic trials demonstrated no advantage in outcomes of prophylactic nCPAP [9]. Subsequently, there have been RCTs of differing design with differing results. The COIN trial [10] (early CPAP versus intubation and ventilation) demonstrated a significantly lower risk of death from need for supplementary oxygen at 28 days, but there was no significant difference in the need for supplementary oxygen at 36 weeks PMA and the CPAP group had a significantly higher incidence of pneumothorax. The SUPPORT trial (intubation and early surfactant versus early CPAP) [11] reported no differences in death or BPD and the CURPAP trial (prophylactic surfactant followed by CPAP versus early CPAP) reported no significant differences in the primary outcome of need for mechanical ventilation within five days. The Breathing Outcomes Study [12], a secondary study to SUPPORT, compared respiratory morbidities at six-month intervals from hospital discharge to 18–22 months corrected age (CA); infants randomized to CPAP had significantly fewer episodes of wheezing without a cold, respiratory illnesses diagnosed by a doctor, and physician or emergency room visits for breathing problems. Further studies are required to determine the optimal technique for delivering nCPAP. It has been suggested that weaning from CPAP by reduction in time rather than pressure might increase the likelihood of BPD [13]. The Cochrane review of three trials [14] highlighted that one trial in which nCPAP was just stopped had shown a significant decrease in the duration of oxygen therapy and a decreased length of stay. Trials are required to determine whether simply stopping nCPAP versus a reduction in pressure might influence long-term outcomes.

2.1.1. Nasal intermittent positive pressure ventilation

Non-randomized or short-term studies have demonstrated advantages of nasal intermittent positive-pressure ventilation (NIPPV) compared to nCPAP. A RCT [15] in which 1009 ELBW infants were enrolled, however, demonstrated no significant differences in death or survival with BPD between NIPPV and CPAP.

2.1.2. Heated, humidified, high-flow nasal cannula

Heated, humidified and high-flow nasal cannula (HHFNC) technique has become popular, as highlighted by 63% of units in Australia and New Zealand being reported to be using HHFNC in 2010 [16]. In addition, a survey of 57 level 2 or 3 neonatal units in the UK reported in 2013 that HHFNC was used in 77% of units [17]. In a multicentre trial of 303 infants less than 32 weeks of gestational age, however, infants randomized to HHFNC compared to those randomized to nCPAP did not differ significantly with regard to the primary outcome—treatment failure within seven days. There were no significant differences in the rates of death before discharge, need for oxygen supplementation at 36 weeks PMA, pneumothorax, PDA requiring treatment, NEC, retinopathy of prematurity (ROP) or IVH [18]. In another randomized trial of 432 infants of 28 to 42 weeks of gestational age, no significant difference was seen in early (<72 hours) extubation failure between infants on HHFNC (10.8%) compared to nCPAP (8.2%) [19]. Infants remained on HHFNC longer than on nCPAP (median, 4 versus 2 days, $p = 0.01$). There were no significant differences with regard to days on supplemental oxygen (median, 10 versus 8 days) or the incidence of BPD (20% versus 16%). There is insufficient evidence to support the routine use of HHFNC for premature infants and further research is required [20].

2.2. Pressure-limited ventilation

Pressure-limited ventilation (PLV) remains a popular mode of ventilation [21,22]. During intermittent positive pressure ventilation (IMV) or intermittent positive pressure ventilation (IPPV), ventilator inflations are delivered at a predefined rate regardless of the infant's spontaneous respiratory efforts. This can lead to asynchrony, active expiration and air leaks [23]. Asynchrony and air leaks can be reduced by the administration of neuromuscular blocking agents [24], but then higher peak pressures are required and infants can become oedematous. An alternative approach to abolish asynchrony is to use fast ventilator rates (60–120/min high-frequency positive pressure ventilation, HFPPV), which more closely reflects the infant's spontaneous respiratory rate; meta-analysis of the results of RCTs [25] show that HFPPV compared to slower rate PLV significantly reduces air leaks (RR, 0.69; 95% CI, 0.51–0.93), but only in prematurely born infants [9,11].

2.3. Permissive hypercapnia

Permissive hypercapnia, defined as partial pressure of blood carbon dioxide (pCO_2) of more than 7 kPa, may be routinely practiced in neonatal intensive care units in Europe [26]. In a cross-sectional survey of 173 units, hypercapnia was present in 31% of blood gases. Yet, systematic review of two randomized trials that enrolled 269 infants did not demonstrate any overall benefit of hypercarbia, with no significant reductions in death, BPD at 36 weeks PMA, IVH or PVL [27]. Indeed, one trial [28] was terminated prematurely as there were trends towards a higher mortality and incidence of neurodevelopmental impairment in the "minimal" ventilation arm in which the pCO_2 target was 55 to 65 mmHg compared to 35 and 45 mmHg and the combined outcome of mental impairment or death was significantly greater in the minimal ventilation arm.

2.4. Patient-triggered ventilation (PTV)

2.4.1. Assist control and synchronised intermittent ventilation

PTV was reintroduced into neonatal intensive care in the 1980s, initially as assist-control (AC, inflations are triggered by every spontaneous breath that exceeds the critical trigger threshold) and synchronised intermittent mandatory ventilation (SIMV, only the preset number of inflations are triggered regardless of the infant's spontaneous respiratory rate). It was hoped that these ventilation modes would be more likely to promote synchrony between the infant and ventilator inflations and hence reduce air leaks and bronchopulmonary dysplasia (BPD). Although improvements in oxygenation and reductions in asynchrony were demonstrated in physiological studies, meta-analysis of RCTs comparing AC/SIMV to PLV [25] demonstrated no significant differences in the rates of BPD, severe ICH, air leaks or mortality. The duration of

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ventilation, however, was shorter (weighted mean difference, 34.8 hours) with AC/SIMV. There have been no studies that have adequately tested whether AC/SIMV improves long-term outcomes. There have been two studies that have included term born infants comparing SIMV to IMV, no significant differences in the duration of ventilation, need for reintubation or the rates of pneumothorax or mortality [13,14].

2.4.2. *Pressure support*

During pressure support ventilation (PSV), the infant's inspiratory efforts determine both the initiation and termination of ventilator inflation. Ventilator inflation is terminated when the infant's inspiratory flow declines to a predefined level, which varies according to the type of ventilator. A recent Cochrane review [6] analyzed available trials comparing PSV and time-cycled ventilation. Only two randomized trials were eligible for analysis involving a total of 19 patients and addressing only short-term impact of PSV [1,7]. No trials addressed the impact of PSV on rate of BPD or other long-term outcomes. PSV with SIMV compared to SIMV alone has been shown to be more effective in ELBW infants ventilated beyond the first week after birth in that it was associated with a smaller proportion of infants being ventilator-dependent at 28 days, and in the sub-group with birth weights of 700–1000 g, a reduction in the duration of oxygen dependency [29]. The likely explanation for the success of PSV with SIMV versus SIMV alone is that, in the former ventilator strategy, all the infant's breaths are supported and this reduces their work of breathing [30], whether this affects long-term outcome has not been assessed. There are few studies in term born infants and again only with short-term outcomes [31].

2.4.2.1. *Proportional assist ventilation.* During proportional assist ventilation (PAV), the applied pressure is servo-controlled throughout each spontaneous breath, and the frequency, timing and rate of lung inflation are controlled by the patient. The applied pressure increases in proportion to the tidal volume and inspiratory flow generated by the patient, which can be enhanced to reduce the work of breathing. There are, however, only limited data on the efficacy of PAV infants and only short-term results have been reported. In a randomized crossover comparison of PAV and PTV (ACV or SIMV), which included 22 ventilator-dependent infants with evolving BPD, gas exchange was successfully maintained at significantly lower mean and peak pressures on PAV, but with longer desaturations [32]. In another short-term, randomized crossover study [33], 12 infants with a median gestational age of 25 (24–26) weeks were studied at a median of 43 (8–86) days. PAV compared with ACV was associated with a significantly reduced work of breathing and a lower oxygenation index (OI).

2.4.2.2. *Neurally adjusted ventilatory assist.* During neurally adjusted ventilatory assist (NAVA), the electrical activity of the diaphragm (Edi) is used to trigger, set the amount of pressure delivered and cycle off the ventilator [34]. In a retrospective analysis of the results of 52 neonates converted to NAVA from conventional ventilation, peak pressures and supplementary oxygen levels were lower during NAVA [20]. In older infants (mean age, 4.3 months), NAVA was also shown to improve patient–ventilator interaction [35]. In comparison to SIMV with PSV, amongst the 19 infants who completed a nine-hour protocol, the work of breathing was lower on NAVA and blood gases were maintained despite the use of lower peak pressures [36]; improvements in lung function have also been described [37]. NAVA has also been shown to be feasible in infants with a postero-lateral diaphragmatic defect [38]. These encouraging results should prompt RCTs with clinically relevant long-term outcomes.

2.4.2.2.1. *Volume-targeted ventilation (VTV).* Excessive volume, even for a short period after birth, can compromise lung function [39]. Studies in an animal model have indicated that it is large volumes rather than large pressures that cause ventilator-induced lung injury (VILI) [40]. During volume-targeted ventilation (VTV), a constant volume set by the practitioner is delivered to the infant regardless of changes in the infant's lung function and hence theoretically it should be possible to identify a volume-targeted level that is associated with the least chronic respiratory morbidity. The manufacturers use different mechanisms to achieve volume targeting and, as a consequence, there are differences in the airway pressure waveform, peak pressure and inflation time, and hence different mean airway pressure at apparently the same VT setting according to ventilator type [41], whether this influences long-term outcome has not been tested. Different names have been given to VTV and include volume limited, volume guaranteed, volume controlled or volume support ventilation. At least 18 randomized or quasi-randomized trials have been undertaken to compare VTV to pressure-limited ventilation in prematurely born infants and have been included in the most recent systematic reviews and meta-analyses [42]. This demonstrated that VTV modes were associated with a reduction in the incidence of BPD at 36 weeks PMA (RR, 0.65; 95% CI, 0.39 to 0.99; nine trials) and significant reductions in all IVH, grades 3–4 IVH, PVL, pneumothorax and hypocarbia. In addition, the durations of mechanical ventilation (mean difference, 2 days; 95% CI, 0.86–3.14) and supplementary oxygen (1.68 days, 95%CI, 0.88 to 2.47) were shorter with VTV modes. There was, however, no significant reduction in mortality and no long-term outcomes were reported. Difficulties in generalizing these results are that different ventilators were used in the two arms in some of the trials and different volume targeting ventilators were used in the various trials (see above). In addition, different levels of volume targeting were used and studies have shown that the VT level significantly affects the work of breathing both in infants with acute respiratory distress [43] and in the recovery stage [43]. Follow-up of 94 of 109 infants to two years of age has been performed from one of the RCTs [44] included in the meta-analysis. There were no significant differences in hospital readmission rates or frequency of respiratory illness between the two groups; however, fewer children in the VTV arm required treatment with inhaled steroids or bronchodilators ($p = 0.04$) [45]. In infants born at term, a VT level of 6 ml/kg was associated with a significantly lower work of breathing ventilation without volume targeting, whether this improved long-term outcomes was not investigated [46].

2.5. *High-frequency jet ventilator (HFJV)*

During high-frequency jet ventilation (HFJV), brief pulses of gas at high pressures are delivered through a small bore injector cannula in a triple lumen endotracheal tube or via an adaptor attached to the proximal end of an endotracheal tube. Rates of 200–600 bpm are used and the high-velocity pulses of gas entrain humidified gas down the endotracheal tube. In a RCT, which included term-born infants, there were significant improvements in oxygenation in those supported with rescue HFJV. There were no significant differences in longer term outcomes, that is, duration of ventilation, oxygenation or hospitalization, but the study was underpowered to test such outcomes [47].

2.6. *High-frequency oscillatory ventilation*

During high-frequency oscillatory ventilation (HFOV) small tidal volumes are delivered at rapid rates, usually in the range of 10–15 Hz. There have been many RCTs assessing prophylactic HFOV, which commenced in the first 24 hours after birth. The meta-analysis in the Cochrane database [48] concluded that the use of HFOV resulted in a significant, but modest reduction in the risk of BPD, but a meta-analysis of patient level data [49] did not show any advantage of HFOV over conventional ventilation with respect to short-term outcomes including BPD. There are problems in interpreting the data from the meta-analyses in that the trials were of very different design, different ventilators were used and some used a low volume strategy during HFO. In addition, different comparator ventilation techniques were used, so it is not clear whether positive results reflected the superiority of HFOV

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or the inferiority of the other technique; none of the trials used VTV for comparison. In the United Kingdom Oscillation Study (UKOS), 797 infants born prior to 29 weeks of gestation from 25 centres, were randomized uniquely within an hour of birth to HFOV or conventional ventilation [50]; no significant differences in short-term outcomes were demonstrated. There were also no significant differences in lung function results at one year of age [51], but the results were only from a subset who lived close to the London centre and small airway function was only assessed by measurement of gas trapping. In retrospect, this was an important limitation, as a follow-up study [52] demonstrated that small airway function, as assessed by maximal flow at functional residual capacity (V′max FRC) at 12 months corrected, was significantly better in BPD infants who had been supported by HFOV rather than CMV. Those results [52] were not from a randomized trial, but suggested that HFOV might preserve small airway function. That hypothesis was proven by an assessment of 319 children entered into the UKOS when aged 11 to 14 years, which demonstrated significant differences in small airway function in favor of HFOV (z score for FEF75, −0.97 with HFOV versus −1.19 with conventional therapy). There were significant differences in favor of several other measures of respiratory function including FEV1, forced vial capacity, peak expiratory flow, diffusing capacity and inpulse oscillometry. In addition, the HFOV group had significantly higher ratings from teachers in three of eight school subjects assessed.

2.6.1. Bronchopulmonary dysplasia and prediction of long-term outcome

BPD has been used as a surrogate for long-term outcome in neonatal ventilation RCTs, it has become increasingly apparent that this is inappropriate. In a RCT of placebo or vitamin A, a small but significant reduction in BPD was demonstrated [35], but no benefits were demonstrated in respiratory outcomes at one year [36]. Furthermore, in a RCT of human superoxide dismutase, there was no reduction in the combined outcome of death or BPD at 36 weeks PMA, but a follow-up study demonstrated significant reductions in episodes of respiratory illness severe enough to require the use of respiratory medications and reductions in hospital admissions and emergency room visits in the highest risk infants [37].

Key guidelines

- CPAP should be used following extubation of prematurely born infants, but how CPAP should be stopped needs further study.
- Volume-targeted ventilation may reduce BPD, VT levels of 6 ml/kg rather than lower levels reduce the work of breathing, but whether this influences long-term outcomes needs investigation.

Research directions

- It is essential to determine whether significant differences in the results of adolescents who had been entered into UKOS are maintained after puberty, those results would inform neonatal ventilation practice.
- All new ventilator strategies should be assessed in trials that are appropriately powered to assess long-term outcomes.

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REVIEW ARTICLE

Review finds insufficient evidence to support the routine use of heated, humidified high-flow nasal cannula use in neonates

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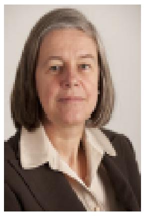

Keywords
Continuous positive airways pressure, Heated humidified high-flow nasal cannula, Neonates, Oxygen, Respiratory support

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ABSTRACT

A literature review was carried out following concerns about the use of heated, humidified, high-flow nasal cannulae (HHFNC) in premature infants. Randomised trials following extubation showed that HHFNC was associated with similar or greater reintubation rates than nasal continuous positive airway pressure, but significantly better nasal trauma scores. Infections with Ralstonia bacteria were an issue.

Conclusion: There is insufficient evidence to support the routine use of HHFNC for premature infants and further research is required.

INTRODUCTION

During heated, humidified, high-flow nasal cannula (HHFNC), heated and humidified gas is delivered at high-flow rates between 1–8 L/min via nasal cannulae. It has been suggested that HHFNC may be effective by eliminating the dead space (1), reducing the work of breathing (2), improving lung compliance at higher flow rates (2) and delivering some degree of continuous positive airway pressure (CPAP) (1,3). There are, however, concerns about the unpredictability of the positive airway pressures generated (4–6) and the possibility of increased risk of infection, particularly due to *Ralstonia* spp. (7) and gram-negative organisms (8). Nevertheless, the technique has become popular, with 63% of units in Australia and New Zealand reportedly using HHFNC in 2010 (9). A survey of 214 neonatal units in the UK, with a 100% response rate, highlighted that 55% of units used high-flow oxygen therapy 57 level two or three neonatal units in the UK reported that HHFNC was used in 77% of units (11). The survey highlighted that HHFNC was used mainly as an alternative to, or weaning from, CPAP and following extubation, but many other uses were reported (11). HHFNC was perceived to be easier to use and allow greater access to the baby. It

Key notes

- A literature review was carried out following concerns about the use of heated, humidified, high-flow nasal cannulae (HHFNC) in premature infants.
- Randomised trials following extubation showed that HHFNC was associated with similar or greater reintubation rates than nasal continuous positive airway pressure, but significantly better nasal trauma scores.
- There is insufficient evidence to support the routine use of HHFNC for premature infants and further research is required.

was demonstrated, however, that 39% of units used HHFNC without policies. The authors of the survey concluded that the current use of HHFNC appeared to be without clear criteria and mostly based on individual preference and that there was an urgent need for research to evaluate its use in newborns. Our aim, therefore, was to critically review the literature to determine whether there was sufficient evidence to support the routine use of HHFNC in certain circumstances for prematurely born infants.

DELIVERY OF DISTENDING PRESSURE

The distending pressure delivered by HHFNC is dependent on prong size. There have been several attempts to produce a formula to calculate the pressure generation during HHFNC at different flow rates on the basis of infant weight, but inconsistent results have been produced (1,12). Airway pressure increases with the nasal prong to nares ratio (13). In an in vitro system (5), and in 18 infants (14), the pressure increased with increased flow (5). In 15 patients with respiratory distress syndrome (RDS), the presence of a leak as small as 30% reduced the pressure to <3 cm H_2O (5). Among infants with a postmenstrual age of between 29 and 44 weeks, and a birth weight (BW) of 835–3735 g, no pressure was generated when the infants' mouths were open, regardless of whether flow rates of up to 5 L/min were used (4). When the infants' mouths were closed, the oral cavity pressure was related to both flow rate and weight. For the subgroup of infants with birth weights ≤1500 g, there was a linear relationship between flow rate and oral cavity pressure (4). In a model, small, medium and large nares were simulated by holes drilled in a plastic fixture, which was connected to a lung simulator that simulated spontaneous breathing (15). Nasal cannulae were inserted in the nares of the model, ensuring that the occlusion of the nares did not exceed 50%. Flow was adjusted from 2 to 6 L/min in 1 L/min increments. Not surprisingly, the greatest effects on tidal volume (VT) and pressure change as flow was increased, occurred with the smallest cannula. Collins et al. (16) compared pharyngeal pressures using two commonly used HHFNC devices, the Fisher & Paykel Healthcare HHFNC (Auckland, New Zealand) and the Vapotherm 2000 (Vapotherm Inc., Stevensville, MD, USA), in nine infants at flow rates of 2–8 L/min. There was no difference in pharyngeal pressures recorded between devices at flow rates of 2–6 L/min. At flow rates of 7 L/min, the Vapotherm delivered a mean pharyngeal pressure of 4.7, with a standard deviation (SD) of 2.2 cm H_2O, compared with a mean of 4.23 (SD 2.2) cm H_2O by the Fisher & Paykel device ($p = 0.04$). At a flow of 8 L/min, the mean pharyngeal pressure via the Vapotherm was 4.9 (SD 2.2) cm H_2O, compared with 4.1 (SD 2.3) cm H_2O with the Fisher & Paykel device ($p = 0.05$). Whether such differences are clinically important remains to be determined, and further studies are required to assess the relationship between flow and pressure in a variety of patient groups.

WORK OF BREATHING (WOB)

In a crossover study (2), 18 infants with a birth weight <2 kg and a mean gestational age (GA) of 28 weeks were randomised to 6 cm H_2O nCPAP or HHFNC delivered at 3, 4 and 5 L/min. No significant differences in the work of breathing (WOB) on the two respiratory support modes were reported (2). In another study, (17) the WOB was compared in a crossover study involving 20 infants (mean GA 28 weeks and BW 1.5 kg) at two levels of nCPAP settings 5 and 6 cm H_2O and two levels of HFNC settings 3 and 5 L/min (17). The WOB was assessed using respiratory inductive plethysmography (RIP). Infants on nCPAP had significant greater chest and abdomen synchrony on CPAP compared with HHFNC, but there was overlap of the confidence intervals; hence, the authors suggested the results were unlikely to be of clinical significance. The use of different devices to deliver CPAP complicates interpretation of the comparisons of the WOB of infants on HHFNC or nCPAP.

RESPIRATORY DISTRESS SYNDROME

No evidence of barotrauma, CPAP belly, nosocomial infection, nasal trauma, or nasal mucus plugging was found among 109 prematurely born neonates when the Vapotherm was used as the primary treatment for mild to moderate RDS or postextubation, rather than CPAP (18) (Table 1). Shoemaker et al. (8) performed a retrospective database review of 101 infants with RDS admitted to two regional referral centres over two eras. HHFNC usage increased in infants of all gestational ages and the use of NCPAP decreased ($p = 0.001$). The increased use of HHFNC was not associated with significant differences in death or bronchopulmonary dysplasia (BPD), but ventilator days per patient were decreased (19.4–9.9; $p = 0.03$). In addition, more infants born at <30 weeks of gestational age were intubated for failing early NCPAP, compared with early HHFNC (40–18%; $p = 0.001$), but there was no *a priori* sample size calculation. Nair et al. (19) reported the outcomes of 67 infants with RDS randomised in the first 6 h after birth to HHFNC or bubble CPAP. The trial was stopped prematurely because of the temporary recall of the Vapotherm 2000i oxygen delivery device (Vapotherm Inc.) related to reports of *Ralstonia* infections. Iranpour et al. (20) randomised 70 relatively mature, prematurely born infants (gestational age 30–35 weeks) with RDS to receive NCPAP of 6 cm H_2O from birth or NCPAP for the first 24 h, then HHFNC. Flow rates during HHFNC were determined from the formula of Sreenan et al. (12). There were no significant differences between the groups with regard to short-term morbidities, but the nasal trauma score was significantly lower in the HHFNC arm (20).

WEANING FROM NCPAP

Sixty infants who were 28 weeks of gestation or more, and were stable on nCPAP at 5 cm H_2O with an inspired oxygen of <0.3 for at least 24 h, were randomised to either continue on nCPAP until they required no supplementary oxygen for

Table 1 Studies assessing infants with RDS

Reference	Study design	Comparison	Sample size	Patient characteristics	Result
Sun and Tero (18)	Observational HHFNC crossover	Vapotherm used as primary treatment for mild to moderate RDS or postextubation rather than CPAP	109	Prematurely born neonates of BW between 500 and 1500 g	No statistically significant evidence of barotrauma, CPAP belly, nosocomial infection, nasal trauma or nasal mucus plugging
Shoemaker (8)	Retrospective database review	HHFNC (n = 65) nCPAP (n = 36)	101	Era one: mean GA 28.1 weeks, mean BW 1050 g Era two: mean GA 27.6 weeks, mean BW 1017 g	No statistically significant difference in adverse outcomes following the introduction of HHFNC and lower days ventilated (9.9 versus 19.4) with HHFNC ($p = 0.03$)
Nair (19)	RCT	HHFNC (5–6 L/min) versus 'bubble' nCPAP (5–6 cm H_2O)	67	HHFNC group; mean GA 32 weeks BW 1675 g nCPAP group: mean GA 31 weeks, BW 1493 g	Premature closure due to recall of HHFNC devices due to reports of *Ralstonia* infection Four infants in each group (approximately 12%) met predetermined failure criteria and were reintubated
Iranpour (20)	RCT	nCPAP (n = 6 cm H_2O) from birth or CPAP for the first 24 h then HHFNC	70	HHFNC (mean GA 32.3 weeks BW 1820 g) nCPAP: (mean GA 32.5 weeks, BW 2210 g)	There were no significant differences in the occurrence of necrotising enterocolitis (NEC), patent ductus arteriosus (PDA), intraventricular haemorrhage (IVH), chronic lung disease (CLD), pneumothorax, pulmonary haemorrhage, apnoea, sepsis and duration of hospitalisation

24 h or nasal cannula oxygen at 2 L/min, described as high-flow nasal cannula (21). During high-flow nasal cannula, the flow rate was maintained until no supplemental oxygen was required, then decreased by 0.5 L/min every 6 h to 0.5 L/min. The nCPAP group required less days in supplementary oxygen (median 14 versus 5 days; $p = 0.001$) and less total duration of respiratory support (18 versus 10.5 days; $p = 0.03$). Relatively low flow rates (2 L/min) were used and higher flow rates usually employed HHFNC might have resulted in a different outcome. In a recently reported, nonrandomised study, weaning from nCPAP by either low flow nasal cannula (<0.3 L/min) or HHFNC (initially 8 L/min) was compared. Use of HHFNC was associated with an approximately 50% reduction in the number of nCPAP days (median 13 versus 25 days), but no significant reduction in the total days of noninvasive respiratory support (37 versus 34 days, $p = 0.1$) (22).

EXTUBATION FAILURE

Comparison of prematurely born infants intubated for RDS extubated on to HHFNC to historical controls extubated on nCPAP revealed no significant differences in extubation failure rate, PDA, IVH, PVL and BPD (23) (Table 2).

In a multicentre trial, infants randomised to HHFNC compared with those randomised to nCPAP did not differ significantly with regard to the primary outcome, which was treatment failure within 7 days. If HHFNC failed, the infants could then be transferred to nCPAP and if nCPAP failed, infants were reintubated. Almost half of the infants not successfully supported by HHFNC were subsequently successfully treated with CPAP without reintubation. The incidence of nasal trauma was lower in the HHFNC group than in the CPAP group ($p = 0.01$). There were no significant differences in the rates of death before discharge, need for oxygen supplementation at 36 weeks of postmenstrual age (PMA), pneumothorax, patent ductus arteriosus (PDA), requiring treatment, necrotising enterocolitis (NEC), retinopathy of prematurity (ROP) or IVH (24).

In a randomised trial of 432 infants of 28-42 weeks of gestational age, no significant difference was seen in early (<72 h) extubation failure between infants on HHFNC (10.8%) compared with nCPAP (8.2%) (25). There was also no significant difference in the subsequent need for intubation or in adverse outcomes including air leak between the two groups. Infants remained on HHFNC longer than on nCPAP (median 4 versus 2 days, $p = 0.01$). There were no significant differences with regard to days on supplemental oxygen (median: 10 versus 8 days) or the incidence of BPD (20% versus 16%).

Collins et al. (26) randomly assigned 132 infants <32 weeks of gestational age to receive either HHFNC or nCPAP postextubation. The primary outcome of extubation failure in the subsequent 7 days was defined as at least one of

Table 2 Studies assessing infants post extubation

Reference	Study design	Comparison	Sample size	Eligibility and patient characteristics	Result
Holleman-Duray (23)	Historical comparison	HHFNC (4–6 L/min) (n = 65) versus nCPAP (8 cm H_2O) (n = 49)	114	GA 25–29 weeks HHFNC group: mean GA 27.6 weeks, BW 1060 g nCPAP group: mean GA 31.0 weeks BW 1000 g	No significant differences in extubation failure rate, PDA, IVH, PVL, BPD
Manley (24)	Multicentre RCT	HHFNC (5–8 L/min) (n = 152) versus nCPAP (5–8 cm H_2O) (n = 151)	303	GA < 32 weeks and receiving mechanical ventilation HHFNC: mean GA 27.6 weeks, BW 1041 g nCPAP: mean GA 31.0 weeks BW 1044 g	Primary outcome: treatment failure (apnoea, increase in FiO_2, respiratory acidosis, urgent need for reintubation) within 7 days did not differ significantly between the two groups (34.2% HHFNC; 25.8% nCPAP)
Yoder (25)	RCT	HHFNC (n = 212) versus nCPAP (n = 220)	432	HHFNC group: mean GA 33.5 weeks, BW 2201 g nCPAP group: mean GA 33.2 weeks BW 2108 g	No significant difference in early (<72 hrs) extubation failure (HHFNC 10.8% and nCPAP 8.2%) (p = 0.344)
Collins (26)	RCT	HHFNC (8 L/min) (n = 67) versus nCPAP (7–8 cm H_2O) (n = 65)	132	<32 weeks' GA requiring mechanical ventilation and deemed ready to extubate HHFNC: mean GA 27.9 weeks, BW 1123 g nCPAP: mean GA 27.6 weeks, BW 1105 g	Extubation failure in the first seven days occurred in 22% (HHFNC) and 34% (nCPAP) [p = 0.14]. There was no significant difference in the number of infants reintubated in the first week (17% HHFNC; 24% nCPAP) [p = 0.48]
Campbell (27)	RCT	HHFNC (unheated) mean flow rate 1.8 L/min (n = 20) versus nCPAP (5–6 cm H_2O) (n = 20)	40	HHFNC group: mean GA 27.4 weeks, BW 1008 g. nCPAP group: mean GA 27.6 weeks BW 925 g	More HFNC infants required reintubation (60% versus 15%) (p = 0.003). The HHFNC group required more supplementary oxygen and had more episodes of apnoea and bradycardia per day.

the following: apnoea (respiratory pause >20 sec), more than six episodes in 6 h or one requiring intermittent positive pressure ventilation, acidosis, pH<7.25 and arterial carbon dioxide levels >66 mmHg and more than a 15% sustained increase in the inspired oxygen concentration. No significant differences were found in the primary outcome or in the number of infants reintubated in the first week. The mean nasal trauma score, however, was lower in the HHFNC group (3.1 versus 7.4, p < 0.001). Among 40 infants with a mean gestational age of 27 weeks, who were randomised at extubation to receive either HHFNC or variable flow CPAP, 12 of the 20 infants randomised to HHFNC were reintubated, compared with only three of 20 on CPAP (p = 0.003) (27). In addition, those supported by HHFNC required more supplementary oxygen and had more episodes of apnoea and bradycardia per day (6 ± 8 versus 2 ± 3, p = 0.045). Digital photograph was used to score the nasal mucosa on days 1, 7 and 30 following extubation, and no nasal damage was noted in either group (27).

Four studies, including three postextubation studies, were considered in a Cochrane review, which concluded that, postextubation, HHFNC may be associated with a higher rate of intubation than nCPAP. In addition, the review highlighted that there was insufficient evidence to establish the safety or efficacy of HHFNC as a form of respiratory support for prematurely born infants (28).

COMPARISON OF METHODS OF DELIVERING HHFNC

A randomised comparison (29) was made of two methods that deliver high-flow gas therapy by nasal cannula following extubation. Group one (n = 15) was supported on Vapotherms for the first 24 h after extubation and then received standard high-flow nasal cannula (≥1 L/min) for the next 24 h. Group two (n = 15) received standard high-flow therapy for the first 24 h and then Vapotherm for the next 24 h. At 24 and 48 h after extubation, a neonatologist unaware of which modality the patient had been receiving examined the infant's nasal mucosa and a research nurse, unaware of the modality, noted the respiratory rates and respiratory effort scores from the randomised study's bedside record. After 24 h, infants on Vapotherms had better nasal mucosa (2.7 ± 1.2 versus 7.8 ± 1.7, p < 0.0005) and lower respiratory effort (1.2 ± 0.6 versus 2.0 ± 0.9,

$p < 0.05$) scores. No patients failed extubation – required reintubation or rescue by the other mode – while on a Vapotherm, but seven failed while on high-flow. Of these, two were reintubated and five were transferred to a Vapotherm, $p < 0.005$. In another study, HHFNC was compared using the Fisher and Paykel and Vapotherm to prevent reintubation either within 72 h (primary outcome) or 7 days (secondary outcome) after extubation of prematurely born infants. Forty infants with a gestational age of between 26 and 29 weeks of gestational age were randomised, and no significant differences were found in the primary or secondary outcome (30).

ADVERSE EVENTS

Nasal trauma has been reported to be less problematic with HHFNC than CPAP (20,26,29). In a recent study, a nasal trauma score for prematurely born infants receiving noninvasive respiratory support was devised and used to compare the incidence of nasal trauma in a subset of infants, born before 32 weeks of gestation, who had been entered into a randomised trial comparing nCPAP and HHFNC (26). Use of HHFNC was associated with significantly lower nasal trauma scores than nCPAP, and the difference was particularly marked in infants born <28 weeks of gestation (31). A randomised, crossover comparison of 24 h of treatment with nCPAP or HHFNC, followed by 24 h of the alternative therapy in infants with mild respiratory illness, demonstrated that parents preferred HHFNC, but highlighted no significant differences in a patient comfort score (32).

In 2005, six patients aged between 21 days and 8 years, who were supported by HHFNC in a healthcare facility in Pennsylvania, were reported to have *Ralstonia* species (gram-negative bacilli) (7). Surveillance then identified 10 hospitals where *Ralstonia* species were recovered from clinical specimens and/or Vapotherm devices. Four of the 10 hospitals cultured the organisms from the Vapotherm systems and reusable filter cartridges after they had been disinfected according to the manufacturer's previously recommended reprocessing protocol. A total of 18 paediatric patients with positive Ralstonia respiratory or blood cultures were reported from five hospitals in five states in the United States, including 17 who had been supported by a Vapotherm system. In response, Vapotherm developed new infection guidelines, including that the machines should be reprocessed after each patient and that the delivery circuit should be cleared using sterilisation rather than tap water.

The noise generated by two HHFNC devices (Fisher & Paykel NHF™; Vapotherm Precision Flow®) using flows of 4–8 L/min and a CPAP device (Dräger Babylog® 8000 plus, Drager Medical, Lubeck, Germany) at pressures of 4–8 cm H_2O and a flow 8 L/min have been compared (33). The noise was measured in the oral cavity of a newborn manikin in an incubator in a quiet environment. The Vapotherm HHFNC generated the highest noise level (81.2–91.4 dBAw). The Fisher & Paykel HHFNC noise levels were between 78.8 and 81.2 dBA and the CPAP device between 73.9 and 77.4 dBA. In a recently reported randomised crossover trial, the noise generated by HHFNC and nCPAP were similar (mean 70 versus 74 dBA, $p = 0.18$) (32). All noise levels were above the current recommendations of the American Academy of Pediatrics (34).

CONCLUSION

There is insufficient evidence to support the routine use of HHFNC for premature infants and further research is required.

CONTRIBUTOR STATEMENT

Both authors were involved in the conception and writing of the article.

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