Title: Optimisation of neonatal ventilation

Author: Deena Patel

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Optimisation of neonatal ventilation

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Professor Anne Greenough

Secondary Supervisor
Dr. Gerrard Rafferty
Abstract

Background: Infants born prematurely or at term may unfortunately suffer morbidity from ventilator related complications. New ventilation techniques have been developed aimed at reducing that morbidity, but have yet to be fully evaluated.

Aim: To optimise the delivery of new techniques using physiological outcome measures.

Methods: A series of studies were undertaken. The objectives were:

- In prematurely born infants with acute respiratory distress, to determine the optimal level of volume targeted ventilation.
- In term and prematurely born infants, to assess the effect on work of breathing of the addition of pressure support (PSV) to synchronised intermittent mandatory ventilation (SIMV) during weaning and then compare the efficacy of PSV to assist control (ACV) in a randomised trial.
- To perform in vitro and in vivo assessments of proportional assist ventilation (PAV).
- The physiological outcome measures were the transdiaphragmatic pressure time product (PTPdi), respiratory muscle strength, thoracoabdominal asynchrony, tension time index of the diaphragm and assessment of asynchronous events.

Results: A volume target of 4ml/kg in comparison to 6ml/kg or no volume targeting resulted in a higher PTPdi (p <0.001). In infants weaning from the ventilator, the PTPdi was 20% lower (p <0.001) during SIMV with PSV in comparison to SIMV alone. No significant difference in the duration of weaning was demonstrated between PSV and ACV. The in vitro PAV study highlighted abnormalities of airway pressure waveform and higher than excepted airway pressures during both elastic and resistive unloading.

Conclusions: Low levels of volume targeting even within the ‘physiological’ range significantly increased the work of breathing. A triggered mode supporting all the infant breaths was superior to when a limited number of breaths were supported. When similar inflation times were used, triggered modes supporting all breaths were equally efficacious. Unloading levels affect the efficacy of PAV; these may be determined by using the ventilator calculated respiratory mechanics.
Acknowledgments

I am extremely grateful to my supervisor, Professor Anne Greenough, who has with infinite patience provided invaluable guidance through the years. Her encouragement despite the inevitable delays, the failures and unfortunate broken leg is undoubtedly the reason this thesis has reached its fruition. I am also grateful to my second supervisor, Dr Gerrard Rafferty who helped me understand the science and got me through the equipment malfunctions. I would especially like to thank Professor Anthony Milner who has acted as a third supervisor and whose drawings and explanations were a revelation.

I thank Dr’s Andy Currie and Murthy for their help during my three months on the injury bench and all the dedicated medical and nursing staff on the unit at King’s without whom the studies would not have been able to be undertaken. I offer my sincere gratitude to the patients and their parents on the NNU, and to my family my love and the promise that it will be better now.

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<th>Description</th>
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</thead>
<tbody>
<tr>
<td>AD</td>
<td>Ano Domini</td>
</tr>
<tr>
<td>A/D units</td>
<td>analogue to digital units</td>
</tr>
<tr>
<td>ACV</td>
<td>assist control ventilation</td>
</tr>
<tr>
<td>ARDS</td>
<td>adult respiratory distress syndrome</td>
</tr>
<tr>
<td>ANOVA</td>
<td>analysis of variance</td>
</tr>
<tr>
<td>ASV</td>
<td>adaptive support ventilation</td>
</tr>
<tr>
<td>BAL</td>
<td>bronchoalveolar lavage</td>
</tr>
<tr>
<td>BPD</td>
<td>bronchopulmonary dysplasia</td>
</tr>
<tr>
<td>Bwgt</td>
<td>birthweight</td>
</tr>
<tr>
<td>CDH</td>
<td>congenital diaphragmatic hernia</td>
</tr>
<tr>
<td>cPdi&lt;sub&gt;max&lt;/sub&gt;</td>
<td>crying maximal transdiaphragmatic pressure</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CMV</td>
<td>controlled mechanical ventilation</td>
</tr>
<tr>
<td>cm</td>
<td>centimetres</td>
</tr>
<tr>
<td>CWD</td>
<td>chest wall distortion</td>
</tr>
<tr>
<td>CPAP</td>
<td>continuous positive airways pressure</td>
</tr>
<tr>
<td>dynP&lt;sub&gt;mus&lt;/sub&gt;</td>
<td>dynamic pressure applied by the respiratory muscles</td>
</tr>
<tr>
<td>EAdi</td>
<td>electrical activity of the diaphragm</td>
</tr>
<tr>
<td>EIT</td>
<td>electrical impedance tomography</td>
</tr>
<tr>
<td>EMG</td>
<td>electromyogram</td>
</tr>
<tr>
<td>E&lt;sub&gt;rs&lt;/sub&gt;</td>
<td>elastance of the respiratory system in the linear range</td>
</tr>
<tr>
<td>ETT</td>
<td>endotracheal tube</td>
</tr>
<tr>
<td>EU</td>
<td>elastic unloading</td>
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<tr>
<td>F</td>
<td>flow</td>
</tr>
<tr>
<td>/bw</td>
<td>frequency response</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>-----------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>FEF&lt;sub&gt;25%-75%&lt;/sub&gt;</td>
<td>forced expiratory fraction</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>forced expiratory volume</td>
</tr>
<tr>
<td>FiO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>fractional inspired oxygen</td>
</tr>
<tr>
<td>FVC</td>
<td>forced vital capacity</td>
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<tr>
<td>g</td>
<td>grams</td>
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<tr>
<td>GA</td>
<td>gestational age</td>
</tr>
<tr>
<td>H&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>water</td>
</tr>
<tr>
<td>HFOV</td>
<td>high frequency oscillatory ventilation</td>
</tr>
<tr>
<td>hr</td>
<td>hour</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>ICAM</td>
<td>intracellular adhesion molecule</td>
</tr>
<tr>
<td>IL</td>
<td>interleukin</td>
</tr>
<tr>
<td>IMV</td>
<td>intermittent mandatory ventilation</td>
</tr>
<tr>
<td>IPPV</td>
<td>Intermittent positive pressure ventilation</td>
</tr>
<tr>
<td>IQ</td>
<td>intelligence quotient</td>
</tr>
<tr>
<td>IT</td>
<td>inflation time</td>
</tr>
<tr>
<td>IVH</td>
<td>intraventricular haemorrhage</td>
</tr>
<tr>
<td>K&lt;sub&gt;1&lt;/sub&gt;</td>
<td>proportion of abnormal elastance to be unloaded i.e. elastic gain</td>
</tr>
<tr>
<td>K&lt;sub&gt;2&lt;/sub&gt;</td>
<td>proportion of abnormal resistance to be unloaded i.e. resistive gain</td>
</tr>
<tr>
<td>KDa</td>
<td>kiloDalton</td>
</tr>
<tr>
<td>kg</td>
<td>kilograms</td>
</tr>
<tr>
<td>kPa</td>
<td>kiloPascals</td>
</tr>
<tr>
<td>L</td>
<td>litres</td>
</tr>
<tr>
<td>MAF-box</td>
<td>muscle atrophy factor box</td>
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<tr>
<td>MAP</td>
<td>mean airway pressure</td>
</tr>
<tr>
<td>MAS</td>
<td>meconium aspiration syndrome</td>
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<tr>
<td>min</td>
<td>minutes</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<td>-------------</td>
</tr>
<tr>
<td>mcg</td>
<td>micrograms</td>
</tr>
<tr>
<td>ml</td>
<td>millilitres</td>
</tr>
<tr>
<td>mRNA</td>
<td>messenger ribonucleic acid</td>
</tr>
<tr>
<td>N</td>
<td>Newton</td>
</tr>
<tr>
<td>NAVA</td>
<td>neurally adjusted ventilatory assist</td>
</tr>
<tr>
<td>NICU</td>
<td>neonatal intensive care unit</td>
</tr>
<tr>
<td>NNT</td>
<td>number needed to treat</td>
</tr>
<tr>
<td>O₂</td>
<td>Oxygen</td>
</tr>
<tr>
<td>Pa</td>
<td>airway pressure</td>
</tr>
<tr>
<td>PaCO₂</td>
<td>arterial partial pressure of carbon dioxide</td>
</tr>
<tr>
<td>Pappl</td>
<td>pressure applied to the respiratory system</td>
</tr>
<tr>
<td>Paw</td>
<td>airway pressure applied by the ventilator</td>
</tr>
<tr>
<td>PAV</td>
<td>proportional assist ventilation</td>
</tr>
<tr>
<td>Pcw</td>
<td>chest wall recoil pressure</td>
</tr>
<tr>
<td>PDA</td>
<td>patent <em>ductus arteriosus</em></td>
</tr>
<tr>
<td>Pdi&lt;sub&gt;max&lt;/sub&gt;</td>
<td>maximum diaphragmatic pressure</td>
</tr>
<tr>
<td>PEEP</td>
<td>positive end expiratory pressure</td>
</tr>
<tr>
<td>Pe&lt;sub&gt;max&lt;/sub&gt;</td>
<td>maximum expiratory pressure generated</td>
</tr>
<tr>
<td>Pes</td>
<td>oesophageal pressure</td>
</tr>
<tr>
<td>pH</td>
<td>power of hydrogen</td>
</tr>
<tr>
<td>PIE</td>
<td>Pulmonary interstitial emphysema</td>
</tr>
<tr>
<td>P&lt;sub&gt;i&lt;/sub&gt;&lt;sub&gt;max&lt;/sub&gt;</td>
<td>maximum inspiratory pressure generated</td>
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<td>PIP</td>
<td>peak inspiratory pressure</td>
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<td>postmenstrual age</td>
</tr>
<tr>
<td>P&lt;sub&gt;max&lt;/sub&gt;</td>
<td>maximum pressure generated</td>
</tr>
<tr>
<td>Pmus</td>
<td>muscle pressure</td>
</tr>
<tr>
<td>PNA</td>
<td>postnatal age</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>--------------</td>
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<tr>
<td>Ppl</td>
<td>pleural pressure</td>
</tr>
<tr>
<td>PRVC</td>
<td>pressure regulated volume control</td>
</tr>
<tr>
<td>PSV</td>
<td>pressure support ventilation</td>
</tr>
<tr>
<td>PTV</td>
<td>patient triggered ventilation</td>
</tr>
<tr>
<td>PTP</td>
<td>pressure time product</td>
</tr>
<tr>
<td>PTPdi</td>
<td>pressure time product of the diaphragm</td>
</tr>
<tr>
<td>PVL</td>
<td>periventricular leukomalacia</td>
</tr>
<tr>
<td>QC</td>
<td>quality control</td>
</tr>
<tr>
<td>RCT</td>
<td>randomised control trial</td>
</tr>
<tr>
<td>RDS</td>
<td>Respiratory distress syndrome</td>
</tr>
<tr>
<td>ref.</td>
<td>reference</td>
</tr>
<tr>
<td>RIP</td>
<td>respiratory inductive phlethysmography</td>
</tr>
<tr>
<td>RR</td>
<td>relative risk</td>
</tr>
<tr>
<td>Rrs</td>
<td>respiratory system resistance</td>
</tr>
<tr>
<td>RU</td>
<td>resistance unloading</td>
</tr>
<tr>
<td>s</td>
<td>second</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>SIMV</td>
<td>synchronised intermittent mandatory ventilation</td>
</tr>
<tr>
<td>TAA</td>
<td>thoracoabdominal asynchrony</td>
</tr>
<tr>
<td>ϕ</td>
<td>(theta) degrees of motion</td>
</tr>
<tr>
<td>Ti</td>
<td>inspiratory time</td>
</tr>
<tr>
<td>T&lt;sub&gt;lim&lt;/sub&gt;</td>
<td>time from contraction start to point of fatigue</td>
</tr>
<tr>
<td>T&lt;sub&gt;i/Ttot&lt;/sub&gt;</td>
<td>ratio of inspiratory time to total breathing cycle duration</td>
</tr>
<tr>
<td>TNF&lt;sub&gt;α&lt;/sub&gt;</td>
<td>tumour necrosis factor alpha</td>
</tr>
<tr>
<td>Tr</td>
<td>time for change from 10 to 90% of final resting pressure</td>
</tr>
<tr>
<td>TS</td>
<td>termination sensitivity</td>
</tr>
<tr>
<td>TTdi</td>
<td>tension time index of the diaphragm</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Term</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------------------------------------</td>
</tr>
<tr>
<td>TTi</td>
<td>tension time index</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
</tr>
<tr>
<td>V</td>
<td>volume above FRC</td>
</tr>
<tr>
<td>VAPS</td>
<td>Volume assured pressure support</td>
</tr>
<tr>
<td>$V'_E$</td>
<td>minute ventilation</td>
</tr>
<tr>
<td>VG</td>
<td>‘volume guarantee’</td>
</tr>
<tr>
<td>VILI</td>
<td>ventilator induced lung injury</td>
</tr>
<tr>
<td>VLBW</td>
<td>very low birthweight</td>
</tr>
<tr>
<td>$V'_{max}$ FRC</td>
<td>maximal expiratory flow at functional residual capacity</td>
</tr>
<tr>
<td>VT</td>
<td>volume target</td>
</tr>
<tr>
<td>Vte</td>
<td>expired tidal volume</td>
</tr>
<tr>
<td>Vti</td>
<td>inspired tidal volume</td>
</tr>
<tr>
<td>VTV</td>
<td>volume targeted ventilation</td>
</tr>
<tr>
<td>WOB</td>
<td>work of breathing</td>
</tr>
</tbody>
</table>
Publications arising from this thesis


Chapter 1: Introduction
1.1 Background

In the UK the 2005-2006 data show that approximately 7% of all newborn infants are born prematurely,¹ with up to 70% of infants born at less than 1500g requiring mechanical ventilation.² Mechanical ventilation in those situations can be life saving, but is not without its complications. In particular up to 50% of infants with a birthweight of less than 750g develop bronchopulmonary dysplasia,³ a condition with significant long term morbidity. New ventilation techniques have been developed, but despite this and the advances in neonatal care the burden of ventilator related complications, including bronchopulmonary dysplasia (BPD), have not decreased and in some cohort comparisons have been increased.⁴⁻⁵ In the neonatal setting, the new ventilation techniques have yet to be fully optimised and evaluated but thus far the limited data from randomised trials do not suggest that they reduce the incidence of lung injury or BPD.⁶⁻⁷ It is essential that new ventilation modes are assessed prior to their widespread clinical use to determine how they should be optimally delivered and then further investigated as to their effects on modulating the mechanisms associated with ventilator related injury. Ventilation related complications can be due to high pressures and volumes, the adverse interaction of the infant’s respiratory efforts with mechanical inflation, inadequate support increasing the work of breathing and poor respiratory muscle strength necessitating prolonged ventilation, which can all be critically assessed by physiological measurements.
1.2 Incidence of respiratory failure in newborns

Approximately 7% of all newborn infants in UK are born prematurely\(^1\) and many may require mechanical ventilation for respiratory distress syndrome.\(^2\)\(^-\)\(^9\) Infants born at or near term may also require artificial mechanical ventilation. The most common diagnoses for term infants requiring mechanical ventilation are pulmonary related including respiratory distress syndrome, meconium aspiration, persistent pulmonary hypertension, pneumonia or congenital lung abnormalities.\(^10\) The remaining one third of term born infants receive respiratory support for non pulmonary causes e.g. peri-operative support or hypoxic ischaemic encephalopathy.\(^10\) Data from the United States shows that the percentage of infants requiring mechanical ventilation after birth decreases with increasing maturity; 100% of surviving infants born at less than 26 weeks needing assisted ventilation compared to 3% of post mature (greater than 40 weeks) infants.\(^9\) Similarly 1991 to 1999 data from the Vermont Oxford network demonstrated that although the proportion of infants born less than 1500 gm requiring a form of assisted invasive mechanical ventilation decreased over that decade by 6%, the percentage in 1999 was 74.4\%.\(^2\) Infants often require prolonged ventilation; a Norwegian epidemiological study showed that a median of four days of mechanical ventilation was required by infants born less than 28 weeks of gestation and a median 37 days (inter-quartile range 29-69 days) for infants born at 23 completed weeks of gestation.\(^8\) Thus, mechanical ventilation remains necessary for the support of newborn infants with respiratory failure.

1.3 History of mechanical ventilation

1.3.1 Introduction

The first record of artificial ventilation was that by Galen in the second century AD; he described distension of a dead animal’s lungs by blowing air through the ‘rough artery’ [trachea].\(^11\)
The evolution of modern day, sophisticated mechanical ventilation and organised intensive care, however, is relatively recent and followed the Copenhagen Polio epidemic in the 1950s. The development of microprocessor technology and proximal flow sensors has revolutionised neonatal mechanical ventilation since the late 1990s due the ability to provide accurate pressure and volume delivery even for very low birth weight infants.

1.3.2 Early history

Experimental artificial respiration of dead animals during vivisection continued for many centuries. The first recorded attempts to resuscitate humans are from the mid 1700s. Throughout that century descriptions were recorded of mouth to mouth resuscitation, and the use of the bellows in aiding resuscitation.

During the 1820s, concerns were raised about the effectiveness of bellows and a series of experiments by Leroy demonstrated fatal pneumothorax in an animal with use of bellows. Consequently the use of positive pressure ventilation was effectively banned for use in medical practice. Thus, as an alternative negative pressure ventilation was developed. Various devices were invented including a negative pressure jacket invented by Alexander Graham Bell to ventilate the neonate in 1869.

It was not, however, until the development of the Drinker-Shaw iron lung in 1928 that the negative pressure ventilator was used on a widespread basis in clinical practice.

Positive pressure ventilation re-emerged firstly in the operating theatre and with neonatal delivery room respirators such as the Dräger Pulmotor (1907). During the Second World War positive pressure valves were introduced allowing the administration of an intermittent positive pressure with a passive exhalation phase.
1.3.3 Development of positive pressure ventilation and intensive care

The widespread use of positive pressure ventilation in clinical non-operative practice began during the 1952 Copenhagen polio epidemic. After a number of deaths from respiratory failure despite the use of negative pressure iron lung ventilation a trial of positive pressure ventilation was instituted. This proved successful, however the lack of available equipment meant that although patients were ventilated via a tracheotomy and a cuffed tube; a hand ventilator had to be utilised. The experiences from this epidemic provided not just the momentum for the development of commercially available mechanical ventilators, but also for the formation for intensive care units and specialised centres.

Lassen et al, detailed a series of 23 adult cases of ‘acute respiratory crises’ from 1955-1960 where tracheotomy and artificial ventilation were utilised. They emphasised reliance on monitoring of arterial oxygen and carbon dioxide clearance as well as pH to evaluate the effectiveness of artificial ventilation. Increasing experience of mechanical ventilation highlighted the importance of being able to appropriately assess the adequacy of mechanical ventilation. Astrup and colleagues emphasised the relevance of measuring pH, arterial carbon dioxide and oxygen partial pressures.

By the late 1950s a number of mechanical ‘automated’ ventilators had been introduced and by the late 1960s patients requiring mechanical ventilation were being cared for in intensive care units. During this period of rapid development Frumin et al, found that insertion of expiratory resistance increased arterial oxygenation, this is now termed positive end expiratory pressure.
1.3.4. New developments

The most simplistic form of ventilation is intermittent positive pressure ventilation (IPPV). Following the development of artificial ventilation and organising care of critical patients within a specifically designed facility, the predicament that evolved was one of how to effectively wean or gradually take away respiratory support. Over the last 40 years many different modes of ventilation have been proposed and developed in order to facilitate both adequate support and weaning. A number of modes of mechanical ventilation are currently available. They may be classified by the system devised by Chatburn.\textsuperscript{29} The classification characterises the following:

1. Control: the variable controlled by the ventilator describing gas delivery i.e. pressure, flow or volume
2. Limit: whether pressure, flow or volume is limited to a preset value
3. Trigger: when the inflation is triggered
4. Cycle: when the inflation ends.

With the advent of microprocessor technology many of these can now be applied to the extremely low birth weight infant. (See Appendix A1 for characteristics of various neonatal modes). An aim of the thesis is to assess some of the newer ventilatory modes.

1.4 Complications of mechanical ventilation

Mechanical ventilation whilst potentially lifesaving is also associated with a number of potential complications conferring significant morbidity. These complications may arise due to the endotracheal tube, the interaction of the machine and patient, the effects of the injury related to mechanical ventilation or ventilator associated pneumonia.
1.4.1 Pneumothorax and pulmonary interstitial emphysema

Since the 1820s, pneumothoraces have been a known complication of positive pressure ventilation. Pneumothorax and other airleak syndromes such as pneumomediastinum or pulmonary interstitial emphysema (PIE) remained a frequent occurrence in the ventilated neonate during the 1970 to 80s and were associated with poor blood gases and adverse outcomes. PIE is gas outside of the alveoli situated within the connective tissue of the peribronchovascular sheaths, interlobular septa, and visceral pleura following alveolar and terminal bronchiolar rupture. PIE is not uncommon in premature infants who require high pressure mechanical ventilation for severe lung disease with poor compliance, and can be associated with significant morbidity. The incidence of pneumothorax in prematurely born infants has decreased from 15% in the early 1980s, to 6% by the late 1990s. Various interventions were shown to reduce the risk of pneumothorax in ventilated infants such as high frequency positive pressure ventilation, volume targeted ventilation and the use of early surfactant in respiratory distress syndrome (RDS). The source of the extra-alveolar air is most likely from alveolar rupture. The mechanism for this is likely due to the positive pressure ventilation and alveolar distension or the effects of the infant fighting the ventilator.

Thus employing modes of ventilation in order to limit the effects of pressures, volume and adverse interactions of the patient and ventilator may favourably impact on air leak syndromes. It is an aim of this thesis to examine volume targeted, pressure support and proportional assist ventilation to assess the patient ventilator interaction and in volume targeted and proportional assist cases optimise the delivery of these modes.
1.4.2 Intraventricular haemorrhage
In 1983 Perlman et al.,\textsuperscript{38} observed in premature infants requiring mechanical ventilation for RDS, a pattern of fluctuating cerebral blood-flow velocity and the subsequent development of intraventricular haemorrhage (IVH).\textsuperscript{38} The use of neuromuscular blockade medication resulted in decreased incidence and severity of IVH,\textsuperscript{39} suggesting that elimination of spontaneous effort of the infant and therefore any potential adverse interaction of the infant and ventilator reduced the incidence of IVH. Therefore, the development of modes that improved the interaction between the patient and ventilator or resulted in superior synchrony might be beneficial in reducing the rates of IVH and thus the long term morbidity of premature infants.

1.4.3 Bronchopulmonary Dysplasia
Northway and colleagues first described bronchopulmonary dysplasia (BPD) in 1967 in prematurely born infants who developed chronic respiratory symptoms and changes on chest radiography after more than ten days of positive pressure ventilation and high levels of oxygen supplementation.\textsuperscript{40} Bronchopulmonary dysplasia may affect newborn infants of any gestation, although the incidence is inversely related to gestation at birth and birthweight.\textsuperscript{3, 41}

The terms BPD and chronic lung disease have often been used interchangeably with a lack of uniformity regarding the diagnostic criteria for BPD. A consensus definition was therefore suggested (Table 1.1).\textsuperscript{42} Despite advances in neonatal care such as the administration of antenatal steroids, new ventilatory strategies, exogenous surfactant and improved nutrition, the incidence of BPD remained similar at 22% in a 1997-2002 cohort compared to 19% in a cohort of babies in 1990-91, and was approximately 50% in babies with birth weights 500-750g in the 1997-2002 cohort.\textsuperscript{3} Even in a cohort of 1011 near term (34 weeks and above) and term infants with primary pathologies
including term respiratory distress syndrome, meconium aspiration and congenital anomalies for example diaphragmatic hernia, 10% of infants were diagnosed with BPD, defined as the need for supplemental oxygen at 30 days postnatal age.\textsuperscript{10}

### Table 1.1: US National Institute of Health conference\textsuperscript{42} suggested diagnostic criteria for BPD based on both gestational ages at birth and disease severity. All infants must have required supplemental oxygen (>21%) for at least 28 days after birth.

<table>
<thead>
<tr>
<th>Mild BPD</th>
<th>Birth gestation &lt; 32 weeks</th>
<th>Birth gestation &gt; 32 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>21% oxygen and no respiratory support at 36w PMA or discharge home</td>
<td>21% oxygen and no respiratory support at 56 days postnatal age or discharge home</td>
</tr>
<tr>
<td>Moderate BPD</td>
<td>Need for &lt;30% oxygen at 36 weeks PMA or discharge home</td>
<td>Need for &lt;30% oxygen at 56 days postnatal age or discharge home</td>
</tr>
<tr>
<td>Severe BPD</td>
<td>Need for ≥ 30% oxygen and/ or positive pressure ventilation or CPAP at 36 weeks PMA or discharge home</td>
<td>Need for ≥ 30% oxygen and/ or positive pressure ventilation or CPAP at 56 days postnatal age or discharge home</td>
</tr>
</tbody>
</table>

Abbreviations: CPAP (continuous positive airways pressure), PMA (postmenstrual age).

1.4.3.1 Pathology

BPD as described by Northway et al., in prematurely born infants was characterised by inflammation, progressive fibrosis, smooth muscle hypertrophy, airway epithelial lesions and radiographic changes consistent with hyperinflation, interstitial fibrosis and emphysematous areas. In the post surfactant era, the characteristics of the disease have changed and infants with minimal or even no signs of initial lung disease can develop BPD, this is termed “new BPD”. The radiographic appearances of infants with new BPD are of small volume, hazy lung fields. The pathological changes include a reduction in the number of alveoli with a slowing or arrest in lung development seen in BPD infants at post-mortem as manifested by a reduction in radial alveolar counts and larger alveoli on microscopy. Pulmonary microvascular development has also been shown to be abnormal in preterm animal models. The underlying pathogenesis of new BPD therefore been postulated to be due to a maldevelopment sequence resulting from interference/abnormality in the signalling of lung alveolarisation and maturation.

1.4.3.2 Multifactorial aetiology of BPD

Injury due to mechanical ventilation has long since been considered a significant aetiological factor in the development of BPD and remains so in the post surfactant era. Many other factors may also contribute to the development of BPD, however inflammation is a possible common mediator. Inflammatory cytokines have been implicated in both antenatal lung maturation and abnormal alveolarisation in animal models.
1.4.3.3 Pathophysiology

Although the aetiology of BPD is multifactorial, all the injuries that result, initiate a host response.\textsuperscript{54} In infants who develop BPD the early inflammatory response persists beyond the first week resulting in chronic inflammation.\textsuperscript{54} Interleukin (IL)-1 and IL-6, pro-inflammatory cytokines, may be found in bronchiolar lavage (BAL) fluid on day 1 and peak by the end of the second week.\textsuperscript{55-56} During the first week, the concentration of IL-1\(\beta\), which has been shown to play a central role in inflammation including release of inflammatory mediators and cells, increases.\textsuperscript{57} Tumour necrosis factor alpha (TNF\(\alpha\)) levels are shown to increase later in the process and peak at day 14-28.\textsuperscript{55} TNF\(\alpha\) and IL-1 both induce fibroblast activity and collagen production resulting in fibrosis.\textsuperscript{58} IL-8 has also been shown to be increased, most markedly on day ten, in infants that develop BPD\textsuperscript{59-60} and is known to induce neutrophil chemotaxis.\textsuperscript{61} A mediator of neutrophil migration across the endothelial barrier, intracellular adhesion molecule (ICAM)-1 is also markedly increased on day ten in the BAL of infants that developed BPD compared to those that did not.\textsuperscript{62} IL-10, an anti-inflammatory cytokine regulates IL-1\(\beta\), IL-8 and TNF\(\alpha\). Levels of IL-10 mRNA have been shown to be undetectable in BAL samples.\textsuperscript{63} In addition, decreased IL-10 production in response to endotoxin stimulation was seen in prematurely born compared to term born infants, suggesting a dampened anti-inflammatory response.\textsuperscript{64} That dampened anti-inflammatory response might result in a persistence of the pro-inflammatory response. The inflammatory response also results histologically in a loss of endothelial basement membrane in infants that died within a week of birth from severe RDS.\textsuperscript{65} Leukotriene levels are elevated in the first two weeks in infants at risk of BPD compared to others with RDS who are no longer ventilated\textsuperscript{60} and remain raised at seven months in infants with BPD.\textsuperscript{66} Leukotrienes are known to cause bronchoconstriction, oedema and mucus production.
Impact of BPD

Chronic respiratory morbidity is a common outcome in infants who develop BPD. Some infants may require home oxygen therapy for many months. Re-admission rates of infants with BPD are about 45% in the first year and most commonly due to respiratory tract problems such as Respiratory Syncytial Virus lower respiratory tract infections. In a cohort of premature infants born less than 32 weeks gestation, those requiring home oxygen had increased healthcare utilisation in the preschool years (2 to 4 years) than birthweight and gestational age matched infants not needing home oxygen. At two years only one infant still required home oxygen, possibly indicating that the cost of care was not solely related to the provision of home oxygen itself. Problems of airway function persist over time despite gradual improvement in functional residual capacity (FRC) and compliance seen from 1 year to 5 years of age. A prospective study conducted from birth assessed the lung function of 24 infants with BPD and demonstrated that although there were improvements in compliance and resistance, maximal expiratory flow at functional residual capacity ($V'_{\text{max}}$ FRC), a marker of small airway function, was reduced by more than 40% of predicted in 70% of infants at two years of age. Lung function abnormalities persist in the school age child when compared to both term and prematurely born controls. Lung function at seven years as measured by forced expiratory volume (FEV$_1$), forced vital capacity (FVC) and forced expiratory fraction (FEF$_{25\%-75\%}$) was significantly reduced in prematurely born infants with BPD compared to without BPD and also term controls matched for sex and socioeconomic factors ($p<0.001$). Furthermore, studies in individuals with ‘classical’ BPD have shown lung function abnormalities and exercise intolerance in adolescents and young adults. Pulmonary hypertension and cor pulmonale are complications of BPD and confer significant mortality as well as morbidity especially in those in whom pulmonary artery pressure does not decrease over time. Impaired growth is another adverse outcome of BPD, perhaps due to
the increased resting metabolic demand.77-78 In a later study which compared BPD infants to two sets of controls, non BPD, very low birthweight (VLBW) infants and term controls,79 the healthy term infants were taller at seven years than either the BPD or VLBW, non BPD group, however there was no significant difference between the later two groups.79 Body Mass Index was higher in the term than the BPD group, but with no significant difference between term and non BPD VLBW group.79 Prolonged ventilation for BPD has been associated poor neurodevelopmental prognosis.80 Short et al, compared a cohort of 98 BPD infants and their matched controls, the BPD infants had lower IQ scores than their matched preterm counterparts.81 The infants with BPD within the cohort that were treated with steroids were found to be even more adversely affected,81 potentially explaining the poor outcome of the whole BPD group as this factor was not adjusted for and early postnatal steroid treatment is a known risk factor for poor developmental outcome.82

BPD is therefore a well recognised complication of mechanical ventilation and preterm birth which has been shown to have significant long term consequences for affected infants. Any mode of ventilation that may decrease the incidence or severity of BPD would be beneficial in reducing the burden of disease.

1.4.4 Diaphragmatic atrophy, prolonged ventilation and nosocomial sepsis

The aim of mechanical ventilation is to unload the work of breathing of the patient; the assumption is that a fatigued diaphragm will be allowed to rest and recover. Indeed, results from an animal model showed that even a short duration of mechanical ventilation of 18 hours may enhance diaphragmatic fatigue resistance in comparison to anaesthetised but not ventilated animals.83 Intermittent positive ventilation (IPPV) when used with high levels of support suppressing spontaneous breathing effort or when used with muscle relaxants to avoid spontaneous breathing motion however may
result in diaphragm dysfunction and atrophy.\textsuperscript{84-87} This in turn may result in prolonged mechanical ventilation which may potentially increase the risk of additional complications.\textsuperscript{88-89}

Diaphragm atrophy associated with prolonged ventilation may hinder the ability of the ventilated infant to wean from the ventilator. Consequences of prolonged ventilation include increased risk of nosocomial infection\textsuperscript{89} and the potential for further opportunity for ventilation related trauma. A retrospective analysis of more than 5000 extremely low birth weight infants in the USA highlighted an association between prolonged duration of ventilation and mortality and adverse neurological outcome.\textsuperscript{88} The percentage of infants diagnosed with cerebral palsy increased with an increased duration of ventilation, with an odds ratio for neurological impairment of 1.18 per week of ventilation, such that all five infants ventilated for $\geq 120$ days had a diagnosis at 18 month follow up of cerebral palsy.\textsuperscript{88}

\textbf{1.5 Intermittent positive pressure ventilation}

IPPV is a pressure limited time triggered and time cycled modality. In this modality, the positive end expiratory pressure (PEEP) and peak inspiratory pressure (PIP) are set by the clinician and not exceeded. PEEP is the pressure applied at the end of expiration to maintain alveolar recruitment and is applied for the entire respiratory cycle. PEEP is the baseline pressure above which the inflation pressure is applied to reach the peak inspiratory pressure. All ventilator delivered breaths are mandatory and time triggered based on the clinician set frequency and inflation time. Thus this modality provides prescribed support independent of the patient’s spontaneous effort.
1.6. Mechanisms of ventilator associated complications

In order to reduce the complications, understanding of the mechanisms by which mechanical ventilation results in the injury, resultant BPD and other complications such as prolonged ventilation is needed.

1.6.1 Ventilator induced lung injury

Injury associated with mechanical ventilation; or ‘ventilator induced lung injury’ (VILI) is both the leak of gas from alveolar disruption i.e. the air leak syndromes of pneumothorax and PIE as well as the damage contributing to the development of BPD. The relationship between artificial ventilation and lung injury has been of concern since the 1820s. Early experimental evidence showed the association of high pressures leading to injury (barotrauma). A lower incidence of BPD has been described in non randomised studies with ventilation protocols that resulted in lower distending pressures and prevention of alveolar collapse. Further evidence has also shown injury and alveolar oedema relating to high volumes and lung over-distension.

1.6.1.1 Barotrauma

In 1939, Charles Macklin published a series of observations on air leak syndromes. He described experiments in cats and other animals where over-inflation of alveoli resulted in small ruptures and a dissection of gas along the perivascular sheaths; clinical parallels in human patients were made to ‘pulmonic interstitial emphysema’ but most often with pneumomediastinum. The observation of a central area of atelectasis with surrounding areas of over-distension where rupture occurred led to the theory that a descending pressure gradient from the inflated areas to the vascular sheaths resulted in air leak. The incidence of pulmonary barotrauma was shown to be associated with increased PIP in adult patients. Webb and Tierney observed increased alveolar
oedema with increased peak pressures and alveolar distension. The increased risk of barotrauma in ventilated patients was shown not to be solely related to applied pressures but also importantly to the existence of specific underlying disease, most commonly adult respiratory distress syndrome (ARDS).

1.6.1.2 Volutrauma

The work of Dreyfuss and colleagues illustrated that excessively large tidal volumes can result in lung injury. Comparison was made between the ultrastructure of lungs at necropsy of rats ventilated with low pressure high volume (LoP-HiV), high pressure (45cmH2O) high volume (HiP-HiV) and high pressure low volume (HiP-LoV). In the animals ventilated with high tidal volumes (40 to 44ml +/- 3ml/kg) widespread alveolar oedema and diffuse alveolar damage was seen in contrast to the low tidal volume (19ml +/-3ml/kg) ventilated and control animals. The addition of end expiratory pressure conferred a protective effect, with only interstitial oedema around large vessels and no evidence of alveolar oedema or epithelial cell alteration on electron microscopy. Interestingly, rats ventilated with the lower tidal volume, high pressure strategy had normal lung ultrastructure, as did the control group. This may indicate the need for alveolar stretch or distension to propagate injury. Results from studies of surfactant deficient prematurely born lambs suggested that high volumes applied even in the first few minutes after birth might be injurious. Ventilation with 36ml/kg for six breaths prevented the response to surfactant treatment. In a study of prematurely born lambs randomised to receive 30 minutes of ventilation after birth at 5ml/kg, 10ml/kg or 20ml/kg, those receiving 20ml/kg had a diminished response to subsequent surfactant therapy as compared to the lambs ventilated at 5 or 10ml/kg, suggesting ‘dose’ dependant lung damage with increasing tidal volumes. More recently, lambs resuscitated for 15 minutes with 15ml/kg tidal volume before receiving surfactant and ventilatory support were found to have elevated levels of cytokines in their lung tissue.
compared to control lambs (no active resuscitation). In a study in a mouse model, ventilation with high tidal volumes for two hours resulted in an increased level of TNFα early in the injury process, as well as increased levels of macrophages in lung lavage fluid compared to low tidal volumes. In adults with ARDS, serial bronchoalveolar lavage (BAL) fluid samples from 18 patients ventilated with a lung protective strategy employing high PEEP and low tidal volume of 5-8ml/kg were compared to those from 19 control patients ventilated with a mean tidal volume of 11ml/kg, to achieve a pre-specified arterial carbon dioxide tension. After 40 hours the lung protective strategy group (low tidal volumes) had significantly lower levels compared to baseline of polymorphonuclear cells, TNFα, IL-1β, IL-8, IL-6 and TNFα receptor 55 (TNFαsR55) (p < 0.001), in contrast, in the control group (lower PEEP and higher tidal volume) concentrations of IL-1β, TNFα and IL-6 in BAL fluid were increased. The findings of the ARDS network trial were consistent with those results and showed a lower plasma level of IL-6 in the patients ventilated with a tidal volume of 6ml/kg compared to those ventilated with tidal volumes of 12ml/kg.

1.6.1.3 Low end expiratory volume injury

A hypothesis established in the 1970s suggested that lung injury in the animal may be triggered by the presence of alveolar collapse in a surfactant deficient lung that would require opening from a collapsed state during each inspiration. Morphological features of lung injury were greater in lungs of rats ventilated with a PEEP below that of the inflection point of the pressure volume curve compared to those with a PEEP above this point. This added weight to the hypothesis that the repeated collapse and recruitment of terminal airspaces contributed to lung injury. Ventilating lambs without PEEP resulted in decreased compliance and oxygenation, as well as decreased surfactant function, which in turn exacerbated the tendency towards atelectasis with
two of the six animals developing pneumothoraces.\textsuperscript{105} Furthermore, Mead \textit{et al.},\textsuperscript{106} proposed that if a collapsed region of lung is surrounded by fully expanded regions, the distending pressure applied will be amplified by the surrounding structures, the magnitude of which will be greater than transpulmonary pressure by $(V/V_0)^{2/3}$, (where $V$ is the volume of the region if fully expanded and $V_0$ is the volume in its gasless state). This magnitude of amplification may, therefore, be substantial resulting in a marked increase in regional stress.\textsuperscript{106} The localised stress may translate to an increased tendency towards airleak phenomena due to the considerably raised pressure required to distend the atelectatic segment. Additionally, lung injury as a result of high tidal volumes during conventional ventilation may be modulated by the addition of PEEP as it has been shown to result in a lower concentration of pro-inflammatory cytokines in rats ventilated with large tidal volumes.\textsuperscript{107}

1.6.1.4 Modulation of injury with recruitment and low tidal volume

Meredith \textit{et al.},\textsuperscript{108} hypothesised that the pathogenesis of hyaline membrane disease was not solely the result of surfactant deficiency but a “culmination of a multifactorial process” which includes atelectasis due to surfactant deficiency\textsuperscript{109} but also ventilation related trauma.\textsuperscript{108} The hypothesis was tested using 12 premature baboons ventilated with either IPPV (a low mean airway pressure of 12-13cmH\textsubscript{2}O and high tidal volume strategy) or high frequency oscillatory ventilation (HFOV) i.e. a higher mean airway pressure of 16-19cmH\textsubscript{2}O but smaller tidal volume.\textsuperscript{108} Histological examination demonstrated that the baboons ventilated with HFOV as opposed to IPPV had better saccular inflation and only focal micro-atelectasis in addition to a relative absence of hyaline membranes.\textsuperscript{108} A comparison of the results from rabbits ventilated at high and low mean airway pressure on HFOV showed that those oscillated at a low mean airway pressure had significantly higher lung injury as evidenced by severe airway epithelial damage as compared to those ventilated at high mean airway pressure (p <0.05).\textsuperscript{110}
Froese et al.\textsuperscript{111} performed a study comparing the ventilation of rabbits with a combination of high or low tidal volumes and high or low end expiratory volumes. Rabbits with a high end expiratory volume with low tidal volumes (i.e. high volume recruitment HFOV) were shown to have higher concentrations of phospholipids in BAL fluid, as a marker for surfactant and better pressure-volume deflation curves than those receiving ventilation with a low end expiratory volume; demonstrating less depletion of surfactant with the former pattern of ventilation.\textsuperscript{111}

The above evidence would suggest that whilst high tidal volumes are injurious adequate alveolar recruitment or lung gas volume is also important in ensuring surfactant function and preventing lung damage.

1.6.1.5 Inflammation

Increasing evidence suggests that the mechanical injury described above leads to cell damage and activation of an inflammatory process as part of a final common pathway. Neutrophil infiltration of lung tissue is seen with acute lung injury including that of surfactant deficiency.\textsuperscript{112} Rabbits that had undergone saline lavage of the lungs to induce lung injury were histologically characterised by a large number of neutrophils and clinically by hypoxia.\textsuperscript{112} Further if given nitrogen mustard at the start of the experiment to deplete the neutrophils the oxygenation was better than the neutrophil replete animals.\textsuperscript{113} Injurious ventilation was shown to increase lung neutrophil accumulation\textsuperscript{114} and in addition was likely to be associated with macrophage activation and be associated with increased levels of TNF$\alpha$.\textsuperscript{107, 115-116}

Direct trauma to the cell membrane resulting in disruption leads to the release of intracellular inflammatory mediators and cytokines into the interstitium.\textsuperscript{117}
mechanism for the stimulation of cytokine release and/or production is the phenomenon of mechanotransduction. Mechanotransduction occurs when mechanical stimuli such as stretch are detected by airway receptors (mechanoreceptors), this signal is transuded through the cell to stimulate gene transcription of cytokines. Transcriptional RNA for TNFα and c-fos has been shown to be increased in the BAL fluid of rats receiving mechanical ventilation. C-fos is a representative immediate-early response proto-oncogene with a stretch responsive promoter.

Tremblay et al, showed that, in rats mechanical ventilation resulted in an increase in levels of both pro and anti-inflammatory cytokines in lung lavage fluid. Patterns of ventilation such as avoiding too high tidal volumes have been shown to alter the level of inflammatory cytokines. Furthermore the likelihood of ventilator induced pneumonia increases with prolonged ventilation resulting in inflammation and subsequent injury. The degree of the anti-inflammatory response is dampened by increasing prematurity. Thus, by virtue of their immaturity and decreased anti-inflammatory response prematurely born infants are more susceptible to the pro-inflammatory effects of injurious mechanical ventilation and therefore it is imperative that the new mechanical ventilation techniques aim to minimise or avoid injury.

1.6.2 Diaphragmatic dysfunction
IPPV has been shown to result in impairment of diaphragmatic function in animal models, most specifically a decrease in pressure generation capacity. Following 48 hours of IPPV, a 42% decrease in force generating capacity was demonstrated in rat diaphragms tested at a frequency of 100Hz, compared to rats that had been spontaneously ventilating. This was similar to the effects seen in similar studies in baboon and rabbit models. The effects of IPPV on force generating capacity were shown to increase with length of time of ventilation and to be partially due to
myofibril injury.\textsuperscript{87} Evidence from both animal studies and human post-mortem findings has shown that prolonged controlled mechanical ventilation associated with complete inactivity of the diaphragm may induce diaphragm muscle atrophy and dysfunction.\textsuperscript{124-126}

1.6.2.1 Mechanisms of ventilation related diaphragm dysfunction

Diaphragm muscle atrophy has been shown in animals to occur as early as 18 hours after commencing mechanical ventilation.\textsuperscript{125} At post-mortem, neonates that had been ventilated for twelve rather than seven days were shown to have lower diaphragmatic muscle mass and histological findings of atrophy.\textsuperscript{124} Atrophy of any muscle can be due to decreased muscle protein synthesis, increase in protein degradation or a mixture of both processes. In animal models, mechanical ventilation has been associated with increased proteolysis\textsuperscript{125} and decreased protein synthesis\textsuperscript{127}. Diaphragm biopsies performed in ventilated brain dead organ donors showed marked atrophy of myofibres as well as markers of increased proteolysis.\textsuperscript{126}

1.6.2.2 Diaphragm fibre adaptation

The diaphragm is a skeletal muscle and has two main fibre types. The muscle fibres are classified according to their myosin heavy chain content: slow twitch or type 1 fibres which have a lower force generation capacity and type 2 fibres or fast twitch fibres. The adult human diaphragm has a high proportion of slow fibres which confer a greater degree of endurance. Mechanical ventilation of adult rats of 18 hours duration was shown to decrease the cross sectional area of both fibre types but with a larger decrease seen in type 2 fibres.\textsuperscript{125} Prolonged mechanical ventilation resulted in remodelling of the diaphragm such that there was a transformational change in composition of pure type 1 to faster hybrid fibres, suggesting a potential for decreased endurance of the diaphragm.\textsuperscript{126} Infants less than 37 weeks gestation were shown to
have significantly fewer type 1 fibres at post mortem than both full term infants and older children (>2 years).\textsuperscript{129} The fatigue resistant type 1 fibres increase in proportion with postnatal development.\textsuperscript{130}

1.6.2.3 Diaphragm fatigue

The diaphragm is relatively more resistant to fatigue than other muscles,\textsuperscript{86} since only a small amount of its capacity is used in spontaneous breathing in a healthy individual\textsuperscript{131} and thus it has a large reserve, but also because the adult human diaphragm has a high proportion of slow twitch fibres. Consequently, the diaphragm can tolerate high respiratory loads for a significant period of time.\textsuperscript{132} A prolonged duration of mechanical ventilation resulted in a change in the diaphragm fibre type composition of adult rats from slow (type I) to faster fibres which might reduce the endurance of the diaphragm.\textsuperscript{128} An imposed inspiratory resistance load in rabbits induced progressive ventilatory failure, however, diaphragm twitch pressures were maintained until the terminal event of respiratory arrest.\textsuperscript{133} Physiological studies performed on 19 adult patients being weaned from the ventilator showed an increased work of breathing (WOB) in all patients.\textsuperscript{134} Twitch pressures in those who failed extubation and those who were successfully extubated were not significantly different, although a higher tension time index was found in the patients that failed, an indicator of poor endurance.\textsuperscript{134} Mechanical ventilation was re-instituted in the failure group before task failure (respiratory arrest) could occur.\textsuperscript{134} The authors additionally postulated that the increased work of breathing and therefore increased effort demonstrated was an adaptive response that attempted to 'defend alveolar ventilation' in the circumstance of decreasing ventilatory support.\textsuperscript{134}

Quantification of inspiratory effort can be used to assess not only the adequacy of ventilatory support but also to compare the effectiveness of levels of support.
Assessment of WOB has been used in both the paediatric and neonatal population in the intensive care setting to examine the effectiveness of support provided by both invasive and non-invasive forms of ventilation.\textsuperscript{135-137} Within this thesis in order to optimise the delivery of new modes of ventilation, assessment of WOB will be made to examine the effectiveness of the level of support provided, determine the most appropriate method of delivering the mode or determine the most advantageous modality. Additionally an assessment of diaphragmatic endurance will be attempted in infants prior to extubation to help assess the superiority of two weaning modes.

1.6.2.4 Neonatal diaphragm fatigue

Fatigue of the neonatal diaphragm has yet to be convincingly demonstrated in studies;\textsuperscript{138-140} however, infants do have a lower proportion of fatigue resistant type 1 fibres which gradually increase during postnatal development.\textsuperscript{130} The paucity of fatigue resistant fibres in addition to the burden of disease characteristic of the prematurely born infant results in a load capacity imbalance. Furthermore increased susceptibility to muscle fatigue occurs with hypoxia\textsuperscript{141} and acidosis,\textsuperscript{142} both of which occur frequently in the unwell neonate.

1.6.2.5 Attenuating diaphragmatic dysfunction

Intermittent spontaneous breathing during mechanical ventilation has been shown to reduce the adverse effects of IPPV on diaphragm fibres and force in rats.\textsuperscript{143} Spontaneous activity of the diaphragm during mechanical ventilation would therefore seem desirable in order to attenuate the effect of IPPV. Unfortunately, spontaneous effort in addition to IPPV may result in asynchronous breathing, active exhalation and thus lung damage.\textsuperscript{31} Triggered ventilation however aims to synchronise mechanical
ventilation with patient effort; allowing spontaneous diaphragm activity whilst potentially reducing asynchrony.

Sassoon et al.\textsuperscript{144} compared contractile properties and muscle atrophy factor-box (MAF-box) expression in rabbits ventilated for three days with IPPV or assist control ventilation (ACV) and a control group that remained spontaneously breathing without support.\textsuperscript{144} The MAF-box gene was chosen as this has been shown to be upregulated in conditions associated with muscle atrophy.\textsuperscript{145} In the IPPV group, suppression of spontaneous diaphragmatic activity was maintained by manipulation of ventilator settings.\textsuperscript{144} The maximum tetanic force was reduced by 43\% in the IPPV group compared to controls (13.4 versus 25.7 N/cm\textsuperscript{2}, \(p<0.05\)), but with ACV this was attenuated to a reduction of only 14\% as compared to controls (22.2 versus 25.7 N/cm\textsuperscript{2}, \(p >0.05\)).\textsuperscript{144} In addition MAF-box gene expression was upregulated in the IPPV group compared to controls (174\%, \(p < 0.03\)), but the mRNA levels in the ACV group were similar to those of the control group.\textsuperscript{144} Those results suggest that the induction of MAF-box protein leading to atrophy and diaphragm force reduction is not seen with ventilation via an assist mode that preserved diaphragmatic contractions during artificial ventilation.

In summary, triggered ventilation attenuates the effects of ventilation induced diaphragm atrophy which may decrease the likelihood of prolonged mechanical ventilation. Muscle strength and the duration of mechanical ventilation may therefore be discriminatory factors when assessing the effectiveness of newer modalities of triggered ventilation and hence will be used as outcome measures in this thesis.
1.6.3 Asynchrony and adverse patient ventilator interaction

Infants often breathe spontaneously whilst being ventilated, rather than being fully sedated. This may result in the ventilator providing mechanical inspiratory support out of phase with the infants own respiratory cycle, this is termed asynchrony. Asynchrony between patient and ventilator has been shown to be associated with multiple complications. In one study of 34 infants receiving artificial ventilation, all eight of the infants who developed a pneumothorax were found to have respiratory traces showing a pattern of breathing described as ‘active exhalation against a ventilator inflation’. A subsequent randomised trial of pancuronium administered to induce muscle paralysis showed a significant, \( p < 0.0004 \), reduction in the rate of pneumothorax in the pancuronium treatment group. In 1983 Perlman et al, observed an association, in premature infants requiring mechanical ventilation for respiratory distress syndrome, between a pattern of fluctuating cerebral blood-flow velocity and the subsequent development of intraventricular haemorrhage. The same group later also showed that muscle paralysis eliminated the fluctuations in blood flow with a resultant decrease in incidence and severity of IVH. Those studies suggest that elimination of spontaneous effort of the infant and subsequent episodes of asynchrony or ‘fighting’ reduces the incidence of both pneumothoraces and IVH. Further support that active exhalation results in complications, comes from an analysis of data obtained from ten infants with a mean gestational age of 25 weeks who were experiencing repeated episodes of hypoxaemia. The study showed that episodes of active exhalation were followed by a decrease in tidal volume and flow and subsequent hypoxaemia.

1.6.4 Summary

Modes of ventilation may be designed to attenuate specific mechanisms that contribute to ventilator related complications. A mode of ventilation that would facilitate rapid weaning of ventilation and avoid the need for protracted periods of ventilation would be
desirable. Modes of ventilation that allow diaphragmatic activity but avoid adverse patient ventilator interactions and modes that avoid volutrauma may have an advantage in maintaining diaphragm muscle strength and avoiding harmful complications if correctly applied. Assessing these factors may provide objective measures to determine the more advantageous method of supporting and weaning infants from the ventilator and hence is an aim of this thesis.

1.7 Ventilatory manoeuvres to facilitate synchrony

A 2005 meta-analysis on the use of neuromuscular paralysis for premature newborns being mechanically ventilated for RDS found that the results of three trials including infants with evidence of asynchrony at enrolment, reported a significantly lower risk of IVH (risk ratio of 0.55 [95%CI 0.34,0.89] and pneumothorax (risk ratio 0.29 [95% CI 0.11, 0.77]). The use of pancuronium however, is not without complications and prolonged paralysis been associated with fluid retention, contractures, hypoxaemia and diaphragmatic dysfunction. Rather than eliminating the infant’s spontaneous respiratory efforts, attempts have been made to synchronise the ventilator to the patients’ spontaneous breaths. These include matching ventilator rates and time cycles to the intrinsic rate of the infant and the use of patient triggered or synchronised modes of ventilation.

1.8 Patient triggered ventilation

During patient triggered ventilation (PTV), there is synchronisation of the start of mechanical inflation with the beginning of patient effort achieved by using a device that senses effort signalling the ventilator to commence inflation.
1.8.1 Triggering devices

Pneumatic capsules such as the Graseby capsule have been used as a method for detecting abdominal movement during a respiratory effort\(^{151}\) and are still occasionally used as a triggering and sensor device for infants receiving non-invasive respiratory support. Most current ventilators are triggered by signals from a device placed within the ventilator circuit. When a pressure triggering device is used, the mechanical inflation is triggered by a reduction in baseline pressure which accompanies the infant’s inspiratory effort. The current generation of neonatal ventilators have a proximal flow sensor close to the patient airway, the potential for asynchrony increases with increasing distance from the patient.\(^{152}\) On the introduction of flow triggering systems in the 1990s, studies \(^{153-154}\) suggested that the inspiratory work of breathing was lower with a flow compared to pressure trigger. This being due to the additional imposed work of 'sucking' against closed vales during pressure triggering as opposed to the continuous flow in the flow triggering systems.\(^{154}\) In one study of nine adult mechanically ventilated patients, the inspiratory pressure time product (a measure of work of breathing) was decreased by approximately 40% during SIMV when a flow trigger as compared to a pressure trigger was used (p<0.0001).\(^{154}\) Flow triggering has been suggested to be more sensitive than pressure triggering in very immature infants when used at maximum sensitivity.\(^{155}\) In a study of ten prematurely born infants with a median gestation of 26 weeks, an airflow triggering system was shown to successfully trigger a greater proportion of inspiratory efforts than an airway pressure triggering system (p = 0.005).\(^{155}\) The studies within this thesis will all therefore be carried out with an airflow triggering device.
1.8.2 Triggered modalities

The two commonly utilised modes in the neonatal intensive care at the start of this thesis were synchronised intermittent mandatory ventilation (SIMV) and assist control ventilation (ACV). Both modes may be pressure or flow triggered.

1.8.2.1 SIMV and ACV

SIMV is a patient triggered, time cycled and pressure limited mode that delivers a mandatory number of ventilator inflations as set by the clinician, regardless of the infant’s respiratory rate. In order to avoid stacking of breaths (inflations in series without sufficient window to allow full exhalation) and to aid synchronisation the mode functions in specific time windows. If at any time during “a window” a spontaneous effort exceeds the trigger threshold, a mechanical inflation is delivered. If at the end of that window no effort has been detected a mandatory breath is delivered. SIMV can be used ‘alone’ as a pressure targeted mode or with volume targeting.

ACV provides positive pressure inflations in response to every inspiratory effort above the triggered threshold. This mode is also time cycled and therefore as with SIMV if the inspiratory time of the patient is shorter than the preset inflation time active exhalation may occur. The name of this mode varies according to the ventilator manufacturer. Specifically the time cycled, pressure limited and patient triggered modality supporting every triggered breath is named ACV on the Stephanie ventilator, SIPPV on the Dräger and ‘PTV’ on the SLE 5000. The term PTV however should be avoided as this should correctly encompass all triggered modalities.
1.8.2.2 Patient triggered ventilation versus intermittent positive pressure ventilation

Meta-analysis in 2004 of the results of five randomised trials of ACV or SIMV compared to IPPV demonstrated no significant difference in the incidences of severe IVH, oxygen dependency at 28 days, oxygen dependency at 36 weeks postmenstrual age (PMA) or death. The use of ACV or SIMV, however, was associated with a significantly shorter duration of ventilation (weighted mean difference 34.8 hours, 95% CI - 62.1 to -7.4 hours). The largest trial within the meta-analysis was the multicentre trial led by Baumer. That trial reported a higher rate of pneumothorax in the subgroup of infants less than 28 weeks gestational age when ventilated with PTV as compared to IPPV (18.8% compared to 11.8%). PTV, however, was provided using an airway pressure triggering device which has been demonstrated to function less effectively in the most immature infants, resulting in increased asynchrony which may explain the higher pneumothorax rate in that subgroup.

1.8.2.3 Assist control versus synchronous mandatory ventilation

SIMV in comparison to ACV may increase the oxygen cost of breathing. Comparison of ACV to SIMV in infants less than 35 weeks gestation demonstrated that ACV was associated with faster weaning, the median duration of weaning was 24 hours versus 50 hours (p<0.05) when the SIMV rate was reduced below 20 inflations per minute. The prolonged weaning during SIMV, may have been due to the increased the work of breathing necessary to overcome the resistance of the endotracheal tube during the decreased number of supported spontaneous breaths. In a randomised trial of 213 infants with acute respiratory distress, similar numbers of infants were extubated by 14 days whether randomised to pressure regulated volume control (PRVC: a type of ACV where the pressure plateau is adjusted breath by breath to attain an inspiratory target volume) or to SIMV. Within that study, at 12 hours of age the mean ventilator rate was 30 inflations per minute in the SIMV group compared
to 40 inflations per minute on PRVC with similar total minute ventilation in both groups perhaps therefore, providing similar levels of support.\textsuperscript{159} No differences were found in the 2004 meta-analysis of trials comparing ACV and SIMV in the duration of weaning though a non-significant trend was demonstrated in favour of ACV.\textsuperscript{36}

1.9 Newer modalities

1.9.1 Pressure support ventilation

Neonatal pressure support ventilation (PSV), is a patient flow triggered, pressure limited and flow cycled modality during which both the initiation and termination of mechanical inflation is determined by the infant's inspiratory effort. The inflation pressure plateau and the maximum inflation time are set by the clinician. Initiation of the mechanical inflation is triggered by flow of gas into the lungs above a set critical threshold. Termination of inflation occurs when inspiratory flow has reduced to a preset percentage of the peak inspiratory flow or when the maximum inflation time has elapsed. Inflation is terminated with the Dräger Babylog\textsuperscript{®} (Dräger, Lübeck, Germany) ventilator at a pre-set 15% of peak inspiratory flow or as with the BIRD-VIP (Bird Products Corp, California, USA) and SLE 5000 (SLE, Croydon, UK) ventilators termination percentage can be manually adjusted, this is termed the termination sensitivity (TS). Pressure support may be used alone, or with volume targeting or SIMV. The level of inspiratory support added to the spontaneous breaths may be altered.\textsuperscript{160-161} The form of PSV available on the current generation of neonatal ventilators differs from that available on adult ventilators where demand flow is utilised.

1.9.1.1 Short term clinical studies

Increasing the termination sensitivity between 5% and 25% has been shown to decrease the asynchrony rate at the expense of the inflation time.\textsuperscript{162} In comparison to
SIMV, PSV has been shown to increase the duration of rhythmic breathing suggesting a higher degree of synchrony of patient and ventilator.\textsuperscript{163} It is important, however, to note that a reduction in the duration of inflation is associated with a decrease in mean airway pressure (MAP); yet no significant difference in blood gases were noted when comparing ACV and PSV in 20 minute crossover epochs.\textsuperscript{164} The maintenance of blood gases may be explained by an increase in patient contribution to ventilation as has been shown in adult patients.\textsuperscript{165} This is an important factor to consider when using PSV in newborn infants, particularly premature neonates; who have little reserve and in whom an increase in work of breathing may result in increased calorie consumption and potentially prolonged ventilation.\textsuperscript{166-167}

PSV plus volume target may confer additional benefit by providing not only a synchronised initiation and termination of inflation but delivery of a target tidal volume. In a short term crossover study of SIMV compared to PSV with volume targeting in fourteen premature infants with RDS, higher minute ventilation, respiratory rate and mean airway pressure were found in the PSV with volume targeting group.\textsuperscript{168} The authors speculated that those differences may have been secondary to the shorter inspiratory times during PSV plus volume target and resultant higher peak pressures to maintain a target volume.\textsuperscript{168} In contrast, in another crossover study comparing those same modes in 25 premature infants the mean airway and peak inspiratory pressures were decreased in the PSV with volume group.\textsuperscript{164} Osorio \textit{et al.}\textsuperscript{160} studied the effects of two levels of PS as an adjunct to SIMV on the breathing effort of fifteen premature infants in a crossover design during the weaning stage of ventilation. During PSV with SIMV, additional spontaneous breaths above the mandatory SIMV breaths were supported with PSV. The two levels of PS were 3cmH\textsubscript{2}O and 6cmH\textsubscript{2}O above the baseline PEEP.\textsuperscript{160} The higher level of PSV resulted in a reduction of per breath respiratory effort as measured by oesophageal pressure swings compared to SIMV.
alone and the lower level of PSV.\textsuperscript{160} Those studies demonstrate that a PSV adjunct may be beneficial in reducing the work of breathing of non-mandatory breaths. Additionally PSV provides a greater degree of synchrony of ventilator inflation to the patient respiratory effort.

1.9.1.2 Randomised trials

PSV with SIMV has been compared to SIMV alone in a randomised trial of 107 extremely low birth weight (<1000g) infants needing mechanical ventilation for greater than 12 hours after birth and excluding those with congenital anomalies, lung hypoplasia and airleak syndromes.\textsuperscript{6} During PSV with SIMV, the mandatory rate was decreased by ten breaths per minute and the non-SIMV breaths were supported with PSV breaths at 30 - 50% of SIMV inflation pressure.\textsuperscript{6} The decrease in ventilator rate was advocated in order to avoid a large increase in mean airway pressure with the addition of PS support.\textsuperscript{6} Fewer infants were still ventilated at 28 days (47\% versus 69\%, p=0.04) with PSV with SIMV rather than SIMV alone.\textsuperscript{6} Analysis of respiratory outcomes of infants with birthweight between 700g to 1000g demonstrated that those supported by PSV with SIMV required fewer days of supplementary oxygen than those supported by SIMV alone (median 58 versus 41 days, p=0.034).\textsuperscript{6} That effect may have been as a consequence of a reduced work of breathing in the PSV group. An aim of the thesis is to determine if the addition of PSV to SIMV compared to SIMV reduces the work of breathing for infants and the magnitude of such an effect. A further aim is to determine whether ACV or PSV, both modes that fully support all of the infant’s breaths, is a superior mode for weaning and to determine the physiological mechanism of any advantages in a randomised trial. Differences in inflation times and asynchrony between the two modes may confer an advantage in weaning success.
1.9.2 Proportional assist ventilation

During proportional assist ventilation (PAV), the timing and frequency of ventilator inflations are controlled by the patient. The applied pressure is servo-controlled throughout each spontaneous breath, increasing in proportion to the flow and/or volume generated by the infant; this can be enhanced to relieve the work of breathing due to both compliance (elastic unloading) and resistance (resistive unloading) abnormalities.\(^{169}\)

1.9.2.1 Ventilator theory

The goal of this modality is to maintain mechanical ventilation at a level that compensates for the patients’ abnormal or additional work load due to disease and that due to the additional resistance of the ventilator circuit. The theory is based on the principles of the equation of motion.\(^ {169}\) During spontaneous breathing, the pressure generated by the respiratory muscles must primarily overcome the resistive flow force and that generated by elastic recoil (equation 1.1). Abnormal load may be due to decreased compliance of the respiratory system (i.e. increased elastance) or increased resistance of the respiratory system including that of the endotracheal tube. In the ventilated infant, the ventilator applied pressure in addition to that generated by the respiratory muscles needs to be sufficient to overcome the natural opposing forces and the abnormal load (equation 1.2a +b). During mechanical ventilation a third factor to overcome is inertia; at low rate ventilation and during spontaneous breathing this factor is very small and can therefore be ignored. The applied inflation pressure can potentially reduce the pressure generated by the infant’s respiratory muscles in order to obtain the total required applied pressure to overcome all loads against breathing. If the applied airway pressure (Paw) is then altered according to the instantaneous functions of volume and flow (equation 1.3) then the ventilator can proportionally supplement infant effort; this is also termed unloading.
Equation 1.1.\textsuperscript{169}

\[ P_{appl} = \text{dyn} P_{mus} = V E_{rs} + F R_{rs} \]

Equation 1.2a + b.\textsuperscript{169}

(a) \[ P_{mus} + P_{aw} = V E_{rs} + F R_{rs} \]

(b) \[ P_{mus} = (V E_{rs} + F R_{rs}) - P_{aw} \]

Equation 1.3.\textsuperscript{169}

\[ P_{aw} = K_1 (V) + K_2 (F) \]

Where:

\begin{itemize}
  \item \text{Pappl} = \text{pressure applied to the respiratory system}
  \item \text{dynPmus} = \text{dynamic pressure applied by the respiratory muscles}
  \item \text{Paw} = \text{airway pressure applied by the ventilator}
  \item \text{E}_{rs} = \text{elastance of the respiratory system in the linear range}
  \item \text{R}_{rs} = \text{respiratory system resistance}
  \item \text{V} = \text{volume above FRC}
  \item \text{F} = \text{flow}
  \item \text{K}_1 = \text{proportion of abnormal elastance to be unloaded i.e. elastic gain}
  \item \text{K}_2 = \text{proportion of abnormal resistance to be unloaded i.e. resistive gain}
\end{itemize}

During PAV the amount of unloading is set as a proportion i.e. \text{K cmH}_2\text{O per unit increase in volume for elastic unloading or per unit flow for resistive unloading.}

Therefore, as an increased spontaneous volume is detected the ventilator delivers additional pressure, the magnitude of which is determined by the proportion \text{K}_1, termed the elastic gain. The higher the gain set, the greater airway inflation pressure delivered per unit of signal input (volume or flow), reducing the work performed by the infant.
(figures 1.1 and 2). Inspiration terminates as the infant effort decreases; at this point due to the elastic recoil of the lung there is insufficient opposing force to maintain inflation and exhalation begins.

During inspiration volume rises gradually but flow peaks early in inspiration and declines later. As such resistive load leads compliance by 90 degrees (figure 1.3). The effort related to flow generation and therefore to work against respiratory system resistance is higher earlier in inspiration but is zero at the onset and end of inspiration. Therefore, hypothetically the application of resistance unloading in infants with high resistive loads such as BPD may be particularly useful.

Figure 1.1: The effect of elastic unloading on airway pressure. The effects of two levels of unloading are shown, as the gain is increased the pressure delivered in relation to volume detected increases.\textsuperscript{169}
Figure 1.2: The diagram shows the effect on airway pressure of resistive unloading during inspiration at two different levels of gain. In both cases the inflation pressure is proportional to inspiratory flow and increases with increased gain.

Figure 1.3: Diagram of tidal volume and flow showing that flow leads volume by approximately 90°, and that the wave forms of elastic and resistive unloading follow the volume and flow traces. (Diagram first published in self authored article, see ref.:170).
1.9.2.2 Clinical use

Very few clinical studies assessing PAV in prematurely born neonates have been undertaken and those that have been performed have had short term outcomes. This and the technical problems that have emerged may explain the fact that PAV has not yet been widely adopted as a form of neonatal ventilation. The safety and efficacy of PAV was examined in a crossover study of 45 minute epochs each of ACV,IPPV and PAV in 36 infants with birthweight between 600 to 1200g and postnatal age of less than ten days.\[171]\ No significant differences were demonstrated in episodes of apnoea or hypoxaemia, but the oxygenation index was significantly lower during PAV (p<0.05) as was the variability in arterial blood pressure (p<0.05).\[171]\ Twenty two chronically ventilated prematurely born infants with a mean postnatal age of 23.9 days were entered into a crossover study conducted in two centres with longer epochs of four hours of each of PTV (SIMV or ACV) and PAV on two occasions for each mode.\[172]\ The mean airway pressure was lower in the infants when ventilated on PAV than on PTV (mean 5.6 versus 6.6 cmH\textsubscript{2}O, p <0.001).\[172]\ Of the total 22 infants, 18 received SIMV and only four ACV; one of the two centres only used SIMV. In the SIMV only centre the magnitude of difference between pressures was found to be larger between the two arms of the study.\[172]\ In PAV all breaths are supported as opposed to the smaller number of supported breaths in SIMV, which may explain the maintenance of blood gas results at lower pressures on PAV in the SIMV centre. The infants on PAV, however, experienced significantly longer desaturations despite the apnoea back up support that provided mandatory breaths after a ten second apnoea, emphasising the need for more effective backup ventilation during this mode.\[172]\ A new backup support has been developed which has resulted in a reduction in the incidence and duration of desaturations.\[173]
Hypothetically infants chronically ventilated with evolving chronic lung disease would be the ideal candidates for PAV as they have an abnormal load due to their lung disease, are less likely to be sedated and have fewer apnoea episodes due to their relative maturity. An objective of the thesis will be to examine the effects of PAV on the adequacy of ventilation, synchronicity and work of breathing on infants with evolving chronic lung disease in a pilot study using data from dynamic lung model studies to inform unloading settings.

1.9.2.3 Technical difficulties

Oscillations in the airway pressure waveform have been demonstrated with overcompensation for the resistive load and high pressures noted with excessive amounts of elastic unloading. High pressures may be avoided by applying a maximum pressure limit, but abnormal airway pressure waveforms with very short inflation times may occur. It is important then to determine the most appropriate unloading setting, which may be different according to disease state. Various methods have been proposed including compensation for endotracheal tube resistance, using the results of oesophageal manometry and observation of chest wall distortion. Those methods all have disadvantages, for example, only compensating for endotracheal tube resistance may not be sufficient, especially in an infant with bronchopulmonary dysplasia whose resistance is high. Oesophageal manometry is not a method suited to routine clinical practice and observation of chest wall distortion is subjective. A simpler more reliable method is therefore needed. The current neonatal ventilator that delivers PAV (Stephanie® neonatal ventilator) displays the patient’s compliance and resistance load (the resistive load is the respiratory resistance of the patient and the resistance of the endotracheal tube). Those data could be utilised to calculate the level of unloading required to reduce the infants resistance and elastance to normal levels. Experiments using a static lung model have shown that the
ventilator display gives an accurate reading of compliance, but that the resistance may be over-estimated by 25%.\textsuperscript{175} In order for this mode to be able to be confidently used for neonatal respiratory support, PAV needs to be tested using dynamic lung models to assess the reliability of using the displayed compliance and resistance to calculate unloading, the impact of unloading on pressure waveforms and the effect of unloading on inspiratory effort. An aim of this thesis is to develop such dynamic lung models and hence further assess PAV.
1.9.3 Volume Targeted Ventilation

Volume targeted ventilation (VTV) aims to deliver a constant tidal volume, regardless of whether there is a change in the infant’s lung mechanics. The advent of small lightweight proximal flow sensors and microprocessors has made neonatal volume targeted ventilation feasible since the late 1990s. In traditional ‘volume controlled ventilation’, the ventilator delivers a set volume into the circuit with pressure rising passively, inversely proportional to the lung compliance. There were concerns relating to the accuracy of ‘volume controlled’ ventilation in the neonate due to the leak of gas around the endotracheal tube; modern neonatal ventilators include a leak compensation function. Additionally in the paediatric and adult patient the ratio of compressible circuit volume to lung volume is small, but in the preterm infant the ratio is large. The development of the neonatal ventilator with flow sensors at the patient end of the ventilator circuit allows more accurate measurement of delivered pressure and volumes. Resolution of the small volumes delivered is now possible with sophisticated microprocessors.

Volume targeted ventilation is delivered by adjustments in peak inspiratory pressure and/or inflation time from breath to breath and has the potential to ‘auto wean’ corresponding to improvement in the infant’s lung disease and resultant increased lung compliance. A number of different neonatal ventilators deliver VTV, a variety of VTV forms are available and are mostly modifications of pressure limited ventilation. The SLE 5000 ventilator (SLE, Croydon, UK) with version 4 software (or later) adjusts peak inspiratory pressure in response to the tidal volume generated with the previous inflation but also terminates inflation short of the preset inflation time if the volume has already been delivered during that inspiration. The Dräger Babylog® 8000plus (Dräger, Lübeck, Germany) ventilator delivers Volume Guarantee ventilation. This modality adjusts peak inspiratory pressure +/- 3 cmH₂O to achieve a target tidal volume.
based on the expired tidal volume of the previous inflation. Both these modes may be used with any of the patient triggered modes on the ventilators. The Stephanie® neonatal ventilator (F. Stephan GmbH Medizintechnik, Germany) delivers volume targeted ventilation in a variety of different methods. The V.I.P Bird Gold (Viasys Healthcare, USA) delivers volume assured pressure support (VAPS). VAPS is a hybrid mode that begins as a triggered PSV breath. If the desired volume has been delivered then the breath is flow cycled. However, if the volume has not been achieved then the inspiratory phase is prolonged until the volume is achieved. All of these ventilators when assessed were shown to deliver different airway pressure waveforms during VTV. In particular, the SLE 5000 and V.I.P Bird delivered shorter inflation times, with the Stephanie® and Dräger Babylog® ventilators delivering lower peak airway pressures. The shorter inflation times delivered with the SLE 5000 and V.I.P. Bird result in a different inspiratory waveform with a sharper upstroke and a potentially high inspiratory pressure if too high a PIP limit is set. A sharp upstroke may provoke an active expiratory reflex. High pressures in the presence of a leak around a non-cuffed endotracheal tube will result in a larger discrepancy between ventilator generated volume and volume delivered to the lung. These differences may influence alveolar recruitment.

1.9.3.1 Rationale for use of VTV

Administration of exogenous surfactant to infants with respiratory distress syndrome may rapidly improve lung compliance. In ventilator modes during which tidal volumes are not controlled, the rapid improvement in compliance may result in hypocarbia as tidal volumes increase. For example, in a study of 142 infants less than 32 weeks gestational age ventilated on either IPPV or PTV, 37.3% of all infants experienced inadvertent hypocarbia defined as a PaCO₂ of 3.3kPa or lower during the first 72 hours after birth, despite protocolised regular blood gas measurement. Hence the ability to
control the delivered tidal volume and consequently minimise both hypocarbia and the effects of volume related trauma discussed earlier would be desirable.

1.9.3.2 Clinical studies

The feasibility of VTV in newborn premature infants was examined by Cheema et al. Infants with RDS were studied in a double crossover study of triggered ventilation with and without ‘volume guarantee’ (VG); the target tidal volume during the one hour epochs of VG was set to equal the mean tidal volume of the previous 30 minutes of ACV or SIMV. There were similar expired tidal volumes and minute ventilation with and without the addition of VG, but the delivered peak inspiratory pressures were lower with the addition of VG than with triggered modalities alone (p<0.001 with SIMV and with ACV). No differences were noted between the groups in transcutaneous oxygen or carbon dioxide partial pressure in this study.

Hypocarbia in the prematurely born infant has been shown to increase the likelihood of periventricular leukomalacia and resultant cerebral palsy. A number of studies therefore, have focused on the effect of volume targeting on arterial carbon dioxide tension. A review of initial blood gases of prematurely born infants ventilated on a VG mode was undertaken in an Australian neonatal intensive care unit. The study found that severe hypocapnia (PaCO$_2$ less than 25mmHg) did not occur on VG 92% of the time on the basis of the first blood gas. In a randomised trial of eighteen preterm infants with RDS, PaCO$_2$ values were lower than the target range of 35-45 mmHg less often when ventilated with ACV plus VG (20.1%) than with ACV alone (36.3%), p<0.05. Additionally a study of 40 infants randomised to ACV or ACV plus VG showed that the incidence of hypocarbia (PaCO$_2$< 5kPa or 37mmHg) was reduced from 57% in the ACV group to 32% in the VG group however, this result did not reach statistical significance.
In support of a hypothesis that employing volume targeted ventilation may reduce ‘ventilator induced lung injury’ related inflammatory response, Lista et al, compared volume targeted (in the form of VG) and triggered ventilation alone and assayed inflammatory cytokines from tracheal aspirates.\textsuperscript{188} The addition of VG to PSV was associated with a reduced level of IL-6 and 8 in tracheal aspirates on day three in infants compared to PSV alone.\textsuperscript{188} IL-6 and 8 have been previously shown to be raised in infants who went on to develop BPD.\textsuperscript{55,59}

Meta-analysis of four randomised VTV trials demonstrated a significant reduction in the duration of ventilation and the pneumothorax rate, but no difference in BPD or death.\textsuperscript{7} Only a small number of infants, however, were included in each trial, with the results of a total of 178 infants included in the meta-analysis. The trials\textsuperscript{177,186,188-189} used different ventilators, which deliver VTV in a variety of different ways.\textsuperscript{179-180} In addition the ventilators in the control arms differed within one study.\textsuperscript{189} During VTV then, for the same level of tidal volume generated, different airway pressure waveforms, inspiratory times and mean airway pressures may have been delivered\textsuperscript{180} potentially effecting the results. Moreover the studies included in the meta-analysis have used targeted volumes varying from four to eight mls per kg. Subsequent to that meta-analysis,\textsuperscript{7} other trials have been published. Singh et al\textsuperscript{190} randomised a total of 109 infants born between 24 and 31 weeks gestation, 57 to VTV and the remainder to pressure limited ventilation. Overall, there was no difference in their predefined success criteria including time to reach MAP less than 8cmH\textsubscript{2}O; however on subgroup analysis of groups stratified \textit{a priori}, infants born less than 1000g reached the primary endpoint faster if assigned to VTV rather than pressure limited ventilation (p=0.03).
1.9.3.3 Levels of VTV

Tidal volumes during volume targeted ventilation between 3 and 8 ml/kg have been used. Dawson et al,\textsuperscript{187} have shown that infants ventilated with a volume target of 4ml/kg had a PaCO\textsubscript{2} within an acceptable target range of 25mmHg to 65mmHg, the authors definition of severe hypocarbia and hypercarbia respectively. Other evidence encourages caution in the use of low target volumes, which may result in increased inflammation or increased infant effort.\textsuperscript{120, 191} In a crossover study of SIMV with and without VG at two levels (3ml/kg and 4.5ml/kg) both levels of volume target resulted in an increased contribution to spontaneous minute volume (V\textsubscript{E}) by the infant, with the V\textsubscript{E} being higher at VG 3ml/kg than at 4.5ml/kg,\textsuperscript{192} implying that at the lower level of volume target the infant’s work of breathing was increased. Infants ventilated at a target volume of 3ml/kg trended towards a higher transcutaneous CO\textsubscript{2} level, which may suggest that despite an increased minute ventilation, carbon dioxide clearance was impaired at the lower tidal volume.\textsuperscript{192} Ventilation of thirty preterm infants during the acute phase of RDS showed that those randomised to a volume target of 3ml/kg had a higher level of pro-inflammatory cytokines in tracheal aspirates as compared to those ventilating at a level of 5ml/kg (p<0.05),\textsuperscript{120} suggesting that the lower tidal volumes resulted in a higher degree of lung inflammation. Infants randomised to the 3ml/kg arm of the study remained on mechanical ventilation for a mean of 16.8 days, longer than those ventilated at 5ml/kg (mean 9.2), p =0.05.\textsuperscript{120} The authors hypothesised that the longer need for respiratory support may have been due to ineffective ventilation and alveolar collapse.\textsuperscript{120} Another hypothesis may be that the lower tidal volume and resultant increased spontaneous minute ventilation may have led to an increased work of breathing and relative fatigue of the infant delaying weaning. Polimeni et al,\textsuperscript{191} aimed to assess the efficacy of SIMV plus VG at two different levels on reducing the episodes of hypoxaemia as experienced with SIMV alone. There was no reduction in the
frequency of episodes however the duration of episodes was reduced when ventilated at 6ml/kg but not when ventilated at 4.5ml/kg.\textsuperscript{191}

Therefore, although too high tidal volumes should be avoided there is a paucity of data on the most appropriate volume targeted level for the neonate. An aim of this thesis, therefore, was to determine the most suitable target volume for infants to better inform any future randomised trials of volume targeting.
1.10 Outcome measures

It is clear from the previous sections that many factors determine the success of mechanical ventilation both in the acute stage and in the weaning process. Whilst it is important to ensure that modalities of ventilation limit any potential trauma and subsequent BPD, they must adequately support the infant during acute respiratory failure and in addition facilitate successful weaning from the ventilator thus ensuring the shortest possible time on the ventilator and a decrease in the likelihood of complications associated with prolonged ventilation. Therefore this thesis will utilise physiological measurements and duration of ventilation as outcome measures to optimise the three new modalities discussed to ensure they adequately support the infant and also to compare these modalities to more traditional modalities used for neonatal ventilation. The physiological outcome measures will be work of breathing, respiratory muscle strength, parameters of asynchrony, diaphragmatic endurance and in addition an assessment of blood gases where appropriate.

1.11 Assessment of work of breathing

The work of the respiratory muscles may be assessed in two ways; either by calculating the mechanical work or by evaluating the oxygen cost of breathing. All muscle contraction expends energy, however not all muscle contraction results in a change of muscle length. Muscle contraction may be isometric, i.e. no change in length or non-isometric where the muscle either shortens (miometric) or lengthens (pliometric). During miometric contraction when the muscle is working against opposing forces, positive mechanical work is being performed and may be measured.
To assess spontaneous work performed, Campbell described a method to estimate muscle force (Pmus) by measuring pleural (Ppl) and chest wall recoil (Pcw) pressures (where Pmus = Ppl + Pcw) using an oesophageal balloon.\textsuperscript{194} Oesophageal pressure (Pes) is used as an approximation of Ppl and Pcw is obtained by progressive stepwise exhalation and plotting Pes against volume.\textsuperscript{193} Unfortunately, this volitional method of obtaining Pcw is not possible in the sedated individual or young child. In the passively ventilated patient Pcw can be obtained, since in this situation Pmus is zero and thus the relaxation curve obtained from Pes measurements is that of the chest wall compliance.\textsuperscript{193} This curve can then be later superimposed over that obtained during spontaneous breathing effort on the ventilator. This method assumes that lung mechanics are the same during passive ventilation and supported spontaneous breathing such as during ACV.\textsuperscript{195-196} The difficulties in measuring Pcw are less relevant in the ventilated neonate since there is some argument to suggest that due to the highly compliant chest wall the elastic recoil pressure may be disregarded.\textsuperscript{197} The Campbell method has been used to assess the WOB in neonates ventilated with patient triggered ventilation.\textsuperscript{198} However, this method for assessing energy expenditure does not take into account work performed by the inspiratory muscle before flow is generated and the work due to the tonic contraction of the diaphragm throughout the respiratory cycle. Therefore this method was not selected for assessment of infants in whom the work of breathing may be high before flow is generated.

The pressure time product (PTP) is an alternative method quantifying the effort expended by the respiratory muscles. PTP is thought to provide a better reflection of oxygen cost of breathing than the rate of mechanical work.\textsuperscript{199-200} PTP assesses the energy expenditure during both isometric and non isometric contraction. Field \textit{et al.}\textsuperscript{200} demonstrated a significant correlation between the oxygen cost of the respiratory muscles and the tension time index (TTi); where TTi is the ratio of the PTP to the
product of maximum pressure generated \( (P_{max}) \) and the duty cycle. This method was therefore chosen to assess inspiratory effort within the studies.

1.11.1 Assessment of the diaphragmatic pressure time product

PTP is defined as the pressure developed by the respiratory muscles integrated to the time taken for the contraction. The pressure time product of the diaphragm (PTPdi) can be calculated from the time integral of the transdiaphragmatic pressure (Pdi), where Pdi is the difference between pressures in the thoracic (pleural) and abdominal compartments, which are represented by the oesophageal (Pes) and gastric (Pgas) pressures respectively (Equation 1.4).

\[
PTP_{di} = \int_0^T P_{di} \, dt
\]

where

\[
P_{di} = P_{gas} - P_{es}
\]

PTP has been used to quantify the effort expended by infants; however there is little normative data. Conceivably the ‘normal’ effort expended by an infant may differ according to gestational age; therefore a secondary aim was to collect PTP data and analyse for correlation to gestational age. Within the studies outlined by this thesis PTP was used to assess infants acting as their own controls or within the randomised study (controlling for gestation if unequal distribution only).

Gastric pressure (Pgas) can be ascertained using a catheter mounted transducer to obtain a value of pressure within the abdominal compartment. However, pleural
pressure cannot easily be directly measured and as such is measured indirectly from oesophageal pressure (Pes) which has been shown to reflect pleural pressure (Ppl) in adults and infants. During contraction of the diaphragm, the oesophageal pressure becomes more negative and the gastric pressure rises thus producing a change in the Pdi. An assumption is made that if the patient does not produce any inspiratory effort then any change in pressure in one compartment, due for example to mechanical inflation, is reflected in the other compartment. Consequently no change in Pdi is seen; thus changes in Pdi are associated with effort.

Oesophageal balloons and water filled catheters have both been used to measure oesophageal pressures in infants. The use of balloon or water catheters for both measurement of Pes and Pgas requires the placement of two catheters via the nares. Catheter mounted transducers have been introduced and used with equal success as balloon catheters; they are passed orally or nasally, however the transducers for both the gastric and oesophageal measurements are on one catheter. Though they are expensive, catheter mounted transducers have the advantage of being more robust, more comfortable and have a higher frequency response, and hence, will be used for the studies in this thesis.

1.12 Thoracoabdominal asynchrony

Asynchrony between chest wall (rib cage) and abdominal wall motion occurs frequently in the prematurely born infant due to the compliant chest wall. The degree of synchrony may be influenced by the underlying lung mechanics and in infants with BPD the degree of asynchrony has been shown to be proportional to the abnormality of resistance and compliance. Quantification of thoracoabdominal asynchrony (TAA) in the ventilated patient may yield information regarding respiratory muscle function. Muller et al, showed a correlation between chest wall distortion and the development of
muscle fatigue. The degree of paradox between the ribcage and abdominal motion is related to the inspiratory load which in turn may lead to relative fatigue.

Thoracoabdominal motion may be assessed using respiratory inductive phlethysmography (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. The phase angle can then be used as an index of asynchrony. RIP is a non invasive measurement, but unless detected motions approach a sinusoidal breathing pattern, the interpretation may be difficult.

TAA may also be assessed using the signals obtained from an oesophageal probe to obtain the phase of motion of the thoracic cavity and gastric probe for the phase of the abdominal cavity (Macklem diagram). This method requires the patient to tolerate an occlusion test but has a distinct advantage if an oesophageal/gastric probe is already sited, as less equipment is required. In this thesis however, RIP will be used to measure TAA due to the relative ease of interpretation and non-invasive nature which will allow also its use for assessment in a less stable infant.

1.13 Diaphragmatic endurance

Roussos and Macklem quantified diaphragmatic fatigue by measuring time elapsed (T_{lim}) from the beginning of a sustained contraction to the point where the target transdiaphragmatic pressure can no longer be generated. By increasing the target Pdi they found that the critical Pdi at which the T_{lim} was less than one hour was 40% of the Pdi_{max}. The limit of endurance of the inspiratory muscles was investigated by Bellemare and Grassino. In their work they assessed the influence of the developed Pdi and the timing of the breathing cycle on the T_{lim}, with the working hypothesis that a
spectrum of critical Pdi may exist depending on the ratio of inspiratory time to total breathing cycle duration (TI/Ttot). Four adult patients during 45 minutes of inspiratory resistive loading were asked to maintain a steady breathing pattern to achieve a target Pdi and the Tlim of each target Pdi as a fraction of the Pdimax recorded. They were able to demonstrate that as the force generated by the diaphragm in steady breathing as fraction of its maximum force generation capacity (Pdi / Pdimax) increases, the Tlim will decrease but in a curvilinear fashion. A linear inverse relationship was demonstrated with Tlim and the product of Pdi / Pdimax and TI/Ttot on a logarithmic scale. This product is known as the tension time index of the diaphragm or TTdi. In those healthy subjects a TTdi above a value of 0.15 was associated with fatigue. TTdi can also be described as the ratio of the PTPdi to the product of the maximum pressure that can be developed by the diaphragm and the total breath cycle (duty cycle) duration, (Equation 1.5).

Equation 1.5:

\[
TTdi = \frac{PTPdi}{(Pdi_{max} \times T_{tot})}
\]

TTdi and its non-invasive counterpart have been shown to be a 100% sensitive and specific predictor of extubation failure in ventilated paediatric patients. Additionally Field et al, found a strong linear correlation between the respiratory muscle oxygen consumption and the TTdi in healthy subjects during inspiratory resistance breathing. TTdi therefore may provide a useful measurement of a patient’s endurance and ‘readiness’ to extubate from the ventilator. Unless infants are supported by individual modalities long term it is unlikely that TTdi would be a useful outcome measure in the studies. However, TTdi data can be usefully obtained from recordings made for PTPdi.
collected from the longer term randomised study planned. Pre-extubation data will therefore be collected where possible.

1.14 Respiratory muscle strength

Prolonged mechanical ventilation has been shown to result in diaphragmatic dysfunction, specifically a decrease in pressure generation capacity,\(^{86-87, 123}\) an effect that increases with length of time of ventilation.\(^{123}\) This effect is less pronounced during ventilation with modes allowing spontaneous breathing including triggered ventilation than with IPPV.\(^{143-144}\) Therefore assessment of the respiratory muscle strength would be valuable when comparing two modes of triggered ventilation.

Maximum inspiratory pressure (Pi\(_{\text{max}}\)) has been used as a global assessment of respiratory muscle strength. The manoeuvre requires the patient to attempt a maximum effort against a closed or occluded airway.\(^{214}\) Pi\(_{\text{max}}\) and its expiratory counterpart Pe\(_{\text{max}}\) are volitional tests that require patient co-operation. In infants, airway occlusion is performed during crying to obtain a maximal pressure.\(^{217}\) In the ventilated patient, a unidirectional valve is used to ensure that maximal inspiratory and expiratory efforts are performed at functional residual volume and total lung capacity respectively.\(^{218}\) It has been suggested that Pi\(_{\text{max}}\) may be a predictor of successful extubation in neonates,\(^{219-220}\) although not when the value was corrected for birth weight.\(^{221}\) Measurement of Pi\(_{\text{max}}\) and Pe\(_{\text{max}}\) using a unidirectional valve will be used in this thesis to facilitate the determination of the impact of the new modes of ventilation on diaphragmatic dysfunction.
1.15 Blood gases

Blood gases provide valuable information as to the efficiency of gas exchange and the adequacy of the level of support provided. For example, hypocarbia indicates that the level of ventilator support needs to be weaned; and hypercarbia may indicate insufficient support. Arterial blood gases however, require an indwelling arterial line and blood sampling, as a consequence in this thesis, results of blood gases will be used to gather additional information when available; they will not be used as a primary outcome measure.

1.16 Duration of ventilation

A mode of ventilation that would result in a shorter duration of ventilation would be of value in reducing complications of mechanical ventilation. This may include reducing diaphragm atrophy, nosocomial infection and BPD, but also may result in a reduction of NICU costs. As a result the duration of ventilation has been determined to be an appropriate outcome measure for which data will be collected when directly comparing different modes of ventilation.

1.17 Hypotheses

The hypotheses to be tested were as follow:

1. In infants with acute respiratory distress, lower compared to higher levels of volume targeted ventilation would significantly increase the work of breathing.

2. The addition of PS to SIMV compared to SIMV alone during the weaning phase of mechanical ventilation of infants would result in a decreased work of breathing.

3. Assist control ventilation will be superior as a weaning mode than pressure support ventilation.
4. During PAV, elastic and resistive unloading will each reduce inspiratory load in dynamic lung models representing various disease states.

5. Infants with evolving BPD will have a greater degree of synchrony and lower work of breathing when ventilated with PAV compared to ACV.

1.18 Aims

1) To determine the level of volume targeting associated with the lowest work of breathing for premature infants ventilated with acute respiratory distress.

2) To determine whether the addition of PS to SIMV compared to SIMV alone would reduce the work of breathing of infants weaning from ventilation and the magnitude of any such effect.

3) To establish the relationship between $PTP_{d}$ and birthweight and gestational age.

4) In a randomized trial of ACV and PSV during weaning to undertake physiological measurements to determine if any differences in duration of weaning were explained by a difference in the work of breathing, the rate of asynchrony or the level of respiratory muscle strength.

5) To develop dynamic lung models that mimic the mechanical conditions of a variety of neonatal respiratory disorders and to determine whether using the unloading values calculated from the ventilator derived compliance and resistance data would result in appropriate unloading levels.

6) In a pilot study to compare PAV to ACV in infants with evolving or established BPD by determining levels of work and thoracoabdominal synchrony.
Chapter 2: Methods
2.1 Overarching protocol

Infants born and cared for at King’s College Hospital were eligible for entry into the studies if mechanically ventilated. Infants with neuromuscular disease, hypoxic ischaemic encephalopathy, congenital heart disease, chromosomal disorders and those receiving neuromuscular blockade were excluded.

2.2 Ethics approval

The *in vivo* studies were approved by the King’s College Hospital Research Ethics committee (REC reference number: 07/H0808/147). Informed, written consent was obtained from parents.

2.3 Summary of studies

2.3.1 Volume ventilation

In infants with acute respiratory distress a crossover study of 20 infants was performed to determine the volume level during VTV associated with the lowest inspiratory work of breathing (PTPdi).

2.3.2 Pressure support ventilation

In infants in the recovery stage of respiratory distress (infants whose respiratory failure has improved sufficiently to enable a reduction in the inspired oxygen concentration to 40%) two studies were performed. Firstly a crossover study to determine whether the addition of PSV to SIMV compared to SIMV alone reduces PTPdi. Twenty infants were studied on PSV with SIMV and SIMV alone each for one hour in random order. Secondly, a randomised controlled trial of 36 infants to determine whether ACV or PSV is superior in terms of duration of weaning and whether any differences could be
explained by differences in PTPdi, Pi\textsubscript{max} or asynchrony assessed at regular intervals including pre-extubation.

2.3.3 Proportional assist ventilation
Dynamic lung models were developed to represent various mechanical conditions. The models were then used to assess the application of PAV in those conditions and determine whether the use of ventilator derived compliance and resistance values would result in appropriate unloading. Appropriate unloading was assessed by examining delivered airway pressures and decreases in simulated pleural pressures. Following the lung model study a pilot crossover study was carried out to compare the PTPdi, Pi\textsubscript{max} and asynchrony during PAV to ACV in infants with evolving BPD, defined as ventilator dependence for greater than two weeks of age.

2.4 Summary of equipment set up for in vivo studies
Equipment was set up similarly for each in vivo study. Oesophageal and gastric pressures were measured using a dual pressure tipped transducer (Gaeltec Ltd, Dunvegan, Scotland, UK). The signals from the sensors were amplified using a dedicated amplifier (Model S7b Gaeltec Ltd, Dunvegan, Scotland, UK). Airflow was measured using a pneumotachograph (Mercury F10L, GM Instruments, Kilwinning, Scotland) connected to a differential pressure transducer (MP45, range ± 2 cm H\textsubscript{2}O, Validyne, Northridge, CA, USA). The pneumotachograph was inserted between the endotracheal tube and ventilator manifold. Airway pressure was measured from a side port on the pneumotachograph using a differential pressure transducer (MP45, range ± 100 cm H\textsubscript{2}O Validyne Corp, Northridge CA, USA). The signals from the airway pressure and flow transducers were amplified (CD 280, Validyne, Northridge, CA, USA) and the pressure and flow signals recorded and displayed in real time either on a laptop (Latitude CP\textsubscript{i} Dell Inc, Round Rock, Texas, USA) or desktop computer (Optiplex
170L, Dell Inc, Round Rock, Texas, USA) running a custom written software application (Labview Version 5.0, National Instruments, Austin TX, USA) with 100 Hz analogue to digital sampling (16 bit DAQ card, DAQ 6036E, National Instruments, Austin TX USA for the laptop or PCI-MIO-16XE-50, National Instruments, Austin TX, USA for the desktop). Respiratory muscle strength was assessed by measuring the maximum inspiratory pressure generated during an airway occlusion during crying ($P_{\text{imax}}$). The ventilator manifold was briefly disconnected and a two-way non re-breathing valve attached to the distal end of the pneumotachograph to measure $P_{\text{imax}}$.

Thoraco-abdominal synchrony was assessed using un-calibrated respiratory inductive plethysmography (RIP, Respitrace model 10.9230, Ambulatory Monitoring Inc. NY USA) in AC coupled mode. Inductance coils embedded in two elastic bandages were placed around the ribcage and mid-abdomen and connected to the Respitrace equipment. Voltage signals from RIP in addition to signals from the airway pressure and flow transducers were recorded and displayed in real time on a desktop computer (Optiplex 170L, Dell Inc, Round Rock, Texas, USA) running a custom written software application (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 TX, USA).

2.5 Equipment maintenance

Equipment was cleaned prior to use and disinfection/sterilization of all non-disposable equipment carried out using manufacturer and hospital infection control approved techniques after each patient contact. Items were cleaned and sterilised by first rinsing in sterile water and then placed in a chemical bath. Tristel® (chlorine dioxide) solution was used for sterilization of pressure transducers and pneumotachograph. Perasafe® (0.2% peracetic acid) was used for non-disposable Stephanie® ventilator parts as
approved directly with the company. External housings of the ventilators used were cleaned according to the unit policy.

2.6 Measurement of respiratory muscle strength

Respiratory muscle strength was assessed by measurement of maximal inspiratory pressure ($P_{i_{\text{max}}}$) and maximal expiratory pressure ($P_{e_{\text{max}}}$) from airway pressure measurements at the airway opening.

2.6.1 Equipment to measure airway pressure

Airway pressure (Paw) was measured from a side port of a pneumotachograph (Mercury F10L, GM Instruments, Kilwinning, Scotland) that was connected to a differential pressure transducer (MP45, range $\pm$ 2 cm H$_2$O, Validyne, Northridge, CA, USA) and inserted between the endotracheal tube and ventilator manifold (figure 2.1). The signal from the pressure transducer was amplified using a carrier amplifier (CD 280, Validyne, Northridge, CA, USA). One centimetre of rubber tubing was placed into the top of the endotracheal tube 'hub' into which the pneumotachograph was snugly inserted, to minimise dead space and allow a stable connection between the measuring system described above and the patient. The measured deadspace of the pneumotachograph and attached tubing was one millilitre. A two way non re-breathing valve (Intersurgical Ltd, Berkshire, UK) was attached to the distal end of the pneumotachograph when required in order to perform occlusions to measure muscle strength.
Figure 2.1: Ventilator manifold attached to measurement pneumotachograph. The white tip then inserts into the endotracheal tube.

2.6.1.1 Calibration of the airway pressure transducer

Calibration of the airway pressure transducer was carried out prior to each measurement. A two point calibration of pressure transducers was performed using a portable pressure meter (Comark, Welyn Garden city, UK). The linearity of the Comark pressure meter was tested against a water manometer (figure 2.2).
Figure 2.2: Linearity of Comark Pressure meter against a water manometer (mmH₂O).

2.6.1.2 Linearity of the airway pressure transducer

The linearity of the airway pressure transducer was assessed by plotting the digital output (A/D units), from the analogue to digital converter against applied pressure measured with a digital pressure meter (Comark, Welwyn Garden City, London UK) (Figure 2.3). The linearity of the airway pressure transducer was tested in 10 cmH₂O increments across the range ± 150 cmH₂O and was linear (figure 2.3).
2.6.1.3 Frequency response

The ability of a system to accurately measure the speed of change is termed the ‘frequency response’. The frequency response of each transducer/amplifier system was tested. This was carried out by creating a sudden change in magnitude of the measure, e.g. by bursting a balloon whilst recording the parameter over time as described below. The time taken for change from 10 to 90% was determined. Application of the Fourier transformation equation gave a value for the frequency response of the system (equation 2.1).

Figure 2.3: Linearity of the airway transducer.
Equation 2.1:
\[
/f_{bw} = 1/(3 \times T_r)
\]

Where
- \(f_{bw}\) = frequency response
- \(T_r\) = time taken for the pressure change from 10 to 90% of the final resting pressure

In the ideal situation this value should be at least ten times that of the ‘fundamental (natural) frequency’ of the physiological variable being measured. The breathing frequency of an infant may be 100 to 120 breaths per minute i.e. a frequency of 2Hz; thus the frequency of the tenth harmonic is 20Hz and the frequency response of the transducer system should be greater than that value. The response to an instantaneous change in pressure was recorded on a laptop 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).

2.6.1.4 Frequency response of the airway pressure transducer system

The system consisted of the transducer, connecting tubing and amplifier. The tubing connecting the transducer to the side port of the pneumotachograph was placed inside an inflated balloon. An almost instantaneous change in pressure was achieved by bursting the balloon (figure 2.4). The time taken for the pressure change from 10 to 90% of the final resting pressure (Tr) was 13ms. The frequency response of the system was 25Hz.
Figure 2.4: The response to a sudden decrease in pressure associated with the bursting of a balloon on the measurement of pressure.

2.6.2 Occlusion technique for measuring $P_i_{\text{max}}$ and $P_e_{\text{max}}$

To measure $P_i_{\text{max}}$, the inspiratory limb of the valve was occluded at end expiration, while to measure $P_e_{\text{max}}$ the expiratory limb of the valve was occluded at end inspiration. The timing of the occlusion was judged by observing the infant’s spontaneous respiratory efforts such that the occlusion for $P_i_{\text{max}}$ was performed at end expiration and for $P_e_{\text{max}}$ at end inspiration. Occlusions were maintained until the infant had made at least five spontaaneous efforts or a maximum time of ten seconds. Tactile stimulation of the infants feet during the measurement was used to encourage maximal pressure generation. Three occlusions were performed each separated by two minutes for the patient to settle to quiet tidal breathing. Infants were monitored throughout airway occlusion to avoid pronounced bradycardia of less than 100 beats per minute or desaturation of less than 80%.
2.6.3 Acquisition and storage of data
Amplified signals from the airway pressure transducer were recorded and displayed in real time either on a laptop or desktop computer running custom written software application(s) (Labview Ver 5.0, National Instruments, Austin TX, USA and Spectra® software version 3.0.0.9, Grove Medical Ltd, U.K.) with 100 Hz analogue to digital sampling (16 bit DAQ card, DAQ 6036E, National Instruments, Austin TX USA for the laptop or PCI-MIO-16XE-50, National Instruments, Austin TX, USA for the desktop).

2.6.4 Analysis of data
The data were analysed manually by magnifying the airway pressure waveform and adjusting the digital callipers in Labview software to measure the height of the deflection during inspiration against an occluded airway for $P_{i\text{max}}$. Against an inspiratory occlusion the $P_{i\text{max}}$ is seen as a negative deflection from the zero line. For $P_{e\text{max}}$ a positive deflection from baseline is seen during occlusion of the expiratory valve. The maximum muscle strength was defined as the single highest value generated against an occlusion.

2.7 Measurement of the transdiaphragmatic pressure time product
The transdiaphragmatic pressure time product ($PT_{Pdi}$) provides a measure of the work of breathing for the diaphragm. $PT_{Pdi}$ was calculated breath by breath by integrating the area subtended by the transdiaphragmatic pressure ($P_{di}$) against time during inspiration. The phase transition of respiratory flow from zero to negative flow and from negative to positive flow was used to denote the start and end of inspiration respectively. $PT_{Pdi}$ was expressed per minute (cmH$_2$O.s/min), using respiratory timing. Measurement and acquisition of $P_{di}$ and flow is described below.
2.7.1 Measurement of transdiaphragmatic pressure

Transdiaphragmatic pressure was calculated from the digital subtraction of oesophageal pressure from gastric pressure (figure 2.5). A dual pressure sensor tipped catheter (Gaeltec Ltd, Dunvegan, Scotland, UK) (figure 2.6) was used to measure oesophageal pressure (Pes) and gastric pressure (Pgas). The two pressure transducers were mounted on the catheter five centimetres apart with the lower transducer 0.3 cm from the catheter tip. The signals from the sensors were amplified using a dedicated amplifier (Model S7b Gaeltec Ltd, Dunvegan, Scotland, UK).

![Diagram showing pressure changes](image)

**Figure 2.5:** Schematic representation of the gastric and oesophageal pressure change.
Figure 2.6: Gaeltec dual sensor pressure transducer used to measure gastric and oesophageal pressure.

2.7.1.1 Calibration

Calibration of both the Pgas and Pes transducer was carried out prior to each measurement. A two point calibration of the pressure transducers was performed using a portable pressure meter (Comark, Welyn Garden city, UK). The catheter was placed inside a syringe and a seal formed. The syringe was then attached to the pressure meter and a pressure applied via a volume of gas.

2.7.1.2 Linearity of the gastric and oesophageal pressure transducers

The linearity of the gastric and oesophageal pressure transducers and amplifiers was assessed by plotting the digital output (A/D units) from the analogue to digital converter against applied pressure measured with a digital pressure meter (Comark, Welwyn Garden City, London UK). The linearity of oesophageal and gastric transducers were assessed across the range of -50 to +50 cmH2O in 5 cmH2O increments and were linear (figure 2.7 and 2.8).
**Figure 2.7:** Linearity of the oesophageal transducer.

**Figure 2.8:** Linearity of the gastric transducer.
2.7.1.3 Frequency response of the dual pressure transducer

In order to test the frequency response of the dual pressure sensor tipped catheter and amplifier, the catheter was inserted into an inflated balloon which was then burst. The 90 -10% response time was 2.56ms for the gastric transducer and 2.5ms for the oesophageal transducer, therefore their frequency responses were 130Hz and 134Hz respectively.

2.7.1.4 Positioning the catheter

The catheter was sited oro or naso-gastrically and positioned so that the lower transducer was in the stomach and the upper transducer in the lower third of the oesophagus. In order to correctly site the catheter, the distance between the ear to mouth to below the xiphisternum was measured and the catheter inserted to that length. A positive deflection on the Pgas trace on inspiration confirmed positioning within the stomach; a negative deflection on the Pes trace during inspiration indicated the upper transducer was in the oesophagus. Accurate positioning of the oesophageal probe within the lower third of the oesophagus was confirmed by close agreement between Paw and Pes during an occluded inspiration. To perform the occlusion test the pneumotachograph was attached to the ET tube and the top end occluded at end expiration. Recordings of Paw and Pes were made. Agreement within 94% and 103%\(^2\)\(^0\) of the change in Paw and change in Pes indicated that the balloon was correctly located in the lower third of the oesophagus.\(^2\)\(^2\) Paw was measured as described above in section 2.6.1. Once the position was confirmed the catheter was marked at the tip of the nares or mouth with a black marker and secured to the patient using tape.
2.7.1.5 Validity of Pes as a measure of Ppl

Pes can be reliably used as an estimation of intrathoracic pressure;\textsuperscript{205, 224} this technique for measuring Ppl has also been validated in the well supine infant\textsuperscript{205, 225} and ventilated infant.\textsuperscript{226} The effects of chest wall distortion (CWD), which occurs frequently in premature infants, on Ppl and therefore Pes have been investigated. LeSouëf \textit{et al}, hypothesised that the pressures measured by an oesophageal probe in cases of CWD are more likely to reflect local pleural pressure changes than mean intrathoracic pressure; larger changes were thought to be measured adjacent to the diaphragm.\textsuperscript{227} However, later studies using a liquid filled catheter rather than a balloon in infants both ventilated and spontaneously breathing without support have shown that Pes measurements even in the presence of CWD are reliable provided the probe is accurately positioned within the small space between the carina and cardia.\textsuperscript{206, 228} The intention, therefore, was to use the occlusion test described to ensure correct positioning of the catheter mounted dual transducers to be used in the study in order to obtain accurate measurement even in the presence of chest wall distortion.

2.7.2 Measurement of flow

Airflow was measured using a pneumotachograph (Mercury F10L, GM Instruments, Kilwinning, Scotland) connected to a differential pressure transducer (MP45, range \(\pm 2\) cm H\(_2\)O, Validyne, Northridge, CA, USA) and inserted between the endotracheal tube and ventilator manifold as described for measurement of airway pressure. The signal from the pressure transducer was amplified using a carrier amplifier (CD 280, Validyne, Northridge, CA, USA).
2.7.2.1 Calibration

Calibration of the pneumotachograph was carried out prior to each measurement. A two point calibration was performed using a low flow rotameter (0-12 L/min Platon, Roxspur Measurement & Control Ltd, Bramley, Hants, UK).

2.7.2.2 Linearity of flow transducer

The linearity of the pneumotachograph and associated differential pressure transducer and amplifier was assessed by plotting the digital output (A/D units) from the analogue to digital converter against flow from the rotameter across the range 0 -10 L/min in 1 L/min increments at various oxygen concentrations. The system was found to be linear at all oxygen concentrations (figure 2.9).

![Figure 2.9](image_url): Graph showing the linearity of the airflow transducer system including the pneumotachograph in oxygen concentrations between 21% and 100%.
2.7.2.3 Frequency response of airway flow system

A balloon was placed over one end of the pneumotachograph and inflated. Partial occlusion of the open end of the pneumotachograph provided a constant background flow during which the balloon was burst. The system included the pneumotachograph, related tubing, flow transducer, amplifier and computer. The 90-10% response time was 1.02ms; therefore the frequency response was 326Hz.

2.7.3 Acquisition and storage of pressure and flow data for PTPdi assessment

Amplified signals from the dual pressure catheter, flow and airway pressure transducers were recorded and displayed in real time either on a laptop or desktop computer running a custom written software application (Labview Version 5.0, National Instruments, Austin TX, USA) with 100 Hz analogue to digital sampling (16 bit DAQ card, DAQ 6036E, National Instruments, Austin TX USA for the laptop or PCI-MIO-16XE-50, National Instruments, Austin TX, USA for the desktop).

2.7.4 Analysis of PTPdi

Recordings for PTPdi were made over a period of five minutes. Infant efforts were analysed by digital integration of inspiratory transdiaphragmatic pressure and time. Zero flow denoted the beginning and end of inspiration thus describing the limits for the area beneath the curve (figure 2.10). The result for a single breath was then automatically multiplied by the respiratory rate by the software to give the PTPdi per minute. In order to minimise the effect of breath by breath variability twenty consecutive breaths or efforts whether or not these were supported by the ventilator were analysed individually and the mean was then calculated to give a PTPdi overall result with units of cmH₂O.s/min.
Figure 2.10: Schematic diagram demonstrating assessment of PTPdi. Inspiratory boundaries are delineated by points of zero flow. The shaded area represents the inspiratory portion of the area under the Pdi curve or the inspiratory PTPdi.

2.8 Assessment of tidal volume

Tidal volume was obtained by digital integration of the flow signal. Amplified signals from the flow transducer were recorded and displayed in real time either on a laptop and/or desktop computer running a custom written software application (Labview Version 5.0, National Instruments, Austin TX, USA and/or with Spectra® software version 3.0.0.9, Grove Medical Ltd, U.K.) with 100 Hz analogue to digital sampling (16
bit DAQ card, DAQ 6036E, National Instruments, Austin TX USA for the laptop or PCI-MIO-16XE-50, National Instruments, Austin TX, USA for the desktop).

2.9 Measurement of tension time index of the diaphragm

Tension time index (TTdi) was calculated in infants in whom PTPdi and Pi\textsubscript{max} were assessed. Airway occlusions performed to measure Pi\textsubscript{max} simultaneously provided a measurement for inspiratory Pdi\textsubscript{max} when a dual pressure transducer was \textit{in situ} to measure Pes and Pg\textsubscript{as} and thus Pdi (figure 2.11). Recordings taken for PTPdi analysis were then used to assess the TTdi.

![Figure 2.11](image)

**Figure 2.11:** Measurement of Pi\textsubscript{max} and Pdi\textsubscript{max} during an occlusion. Heavy line represents Pdi\textsubscript{max} and the lighter line Pi\textsubscript{max}. (Diagram first published in self authored article, see reference: 229).
2.9.1 Analysis of TTdi

TTdi was calculated by the Labview software using the equation $P_{di_{mean}}/P_{di_{max}} \times T_i/T_{tot}$.

$P_{di_{mean}}$ was calculated as the average $P_{di}$ across a whole breath. The inspiratory time ($T_i$) and the total respiratory cycle time ($T_{tot}$) were determined by the software program from the air flow trace (figure 2.12). TTdi was calculated as the average of twenty breaths.

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**Figure 2.12.** Measurement of mean inspiratory transdiaphragmatic ($P_{di_{mean}}$), inspiratory time ($T_i$) and the total time for the breath ($T_{tot}$) determined by respiratory flow. The "solid" waveform represents $P_{di}$ and the dashed waveform the respiratory flow. The dashed vertical lines indicate points of zero respiratory flow, indicating the change between inspiration and expiration. (Diagram first published in self authored article, see reference 229)
2.10 Assessment of active expiration

The occurrence of active expiration was assessed during the PTPdi measurement. Active expiration was defined as an expiratory effort occurring during a mechanical inflation which resulted in a halting or reversal of flow. The number of inflations associated with active expiratory efforts was expressed as a percentage of the mechanical inflations during the last five minutes of the recording. Analysis was performed using the stored Labview data acquired during simultaneous measurement of Pes in conjunction with airway pressure and flow.

2.11 Measurement of thoraco-abdominal motion

To provide data on thoracoabdominal asynchrony, chest and abdominal wall motion patterns were assessed using the non invasive method of uncalibrated respiratory inductive plethysmography (RIP) (Respirtrace Corporation, Ardsley NY, USA) in AC uncoupled mode. Inductance coils embedded in two elastic bandages were placed around the rib cage under the axillae and around the abdomen halfway between the bottom of ribcage and iliac crest. Voltage changes proportional to the change in band inductance were in turn proportional to changes in the underlying cross sectional area or excursion and direction of excursion. Relative changes in compartmental volume were not assessed using RIP within these studies and therefore the bands were not calibrated for relative volume assessment of each compartment. Instead the signals were adjusted to be easily visible on the recording software by using the internal calibration routine within the Respirtrace equipment and recording software and set at zero (0 volts) and at a large gain deflection for one volt. The voltages from both bands were acquired and recorded as a sinusoidal waveform for both the abdominal and ribcage bands.
2.11.1 Frequency response of the inductance bands

Inductance bands were wrapped around a balloon which was inflated to distend the bands and subsequently burst using a needle. The sudden loss of stretch produced a voltage change that was recorded. The change in voltage against time was plotted in Excel (Microsoft Corporation 2003); ‘tr’ was calculated as 6.07ms and therefore the frequency response of the Respitrace system was 54.9Hz.

2.11.2 Acquisition and storage of motion data

Abdominal and ribcage motion as well as airway pressure and flow were recorded and displayed real time on a 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).

2.11.3 Analysis of TAA waveforms

Inductance voltage data of ribcage and abdominal motion were analysed by highlighting individual breaths as recorded in the Spectra® software and exporting wave data to an Excel spreadsheet (Microsoft Corporation 2007). Individual breaths were delineated by points of zero voltage (Figure 2.13a and b). A scattergram was plotted with abdominal data points along the x-axis and ribcage data points along the y-axis to form an elliptical motion plot or Lissajous figure.
**Figure 2.13a:** Example of idealised respiratory motion of ribcage (RC) and abdomen (AB). A single breath is selected as a full 360 degree motion. In this example the ribcage and abdomen are fully synchronous.

**Figure 2.13b:** Idealised respiratory motion showing asynchrony. In this example the ribcage and abdominal motion are out of phase by 90 degrees.

An index of asynchrony was then determined by dividing the width of the loop at mid ribcage excursion (‘m’) by the width at the extremes of abdominal excursion (‘s’).

Degrees of motion (φ) was calculated from the radian, where \( \sin \varphi \) (in radians) = m/s, where \( \varphi \) is < 90° and where 90° < \( \varphi \) > 180°, \( \varphi = 180 - \sin \text{[m/s]} \).\(^{212}\) Completely
synchronous motion has a phase angle of zero degrees (figure 2.14a) and paradoxical motion an angle of 180 degrees (figure 2.14b†). Perfect ellipses as shown in the diagrams assume sinusoidal breathing;²¹² some infants may not breathe in a sinusoidal pattern for example infants with BPD²¹⁰. Loops derived from non-sinusoidal waveform are non-elliptical, however even in non-elliptical traces the phase angle can still be calculated in the same way.²³⁰-²³¹ The margin of error engendered by calculating phase angles from a non-elliptical loop has been estimated to be within 10%.²¹² For each measurement five individual breaths were selected, the phase angle calculated and the result reported as the average of the five breaths.

Figure 2.14: Idealised Lissajous

Where $\varphi = 180 - \sin [\text{m/s}]$.

(Diagram adapted with permission from reference 211, see footnote page 102 for copyright information).
2.12 Blood gas analysis

Analyses of blood pH, PCO₂ and PO₂ were performed using the analysers on the NICU (ABL 700 series, Radiometer, Copenhagen). A one ml syringe was used to draw 0.2ml of blood from an indwelling arterial line that had been inserted prior to the study for clinical reasons. In chronically ventilated infants without indwelling lines, capillary samples were taken via a heel prick. The blood gas machine is calibrated automatically against gases four times in each 24 hour period and undergoes a quality control (QC) check with the bioengineer at least once per 24 hours.

2.13 Variability of physiological measurements

Variability / repeatability coefficients of TAA, PTPdi, P_{i max} and P_{e max} measurements within the studies were assessed.

2.13.1 P_{i max} and P_{e max}

The P_{i max} and P_{e max} results of ten consecutive patients measured within the PSV RCT were analysed. The maximal pressure from the five breaths of each of the three occlusions was recorded for each patient. The mean and standard deviation of the maximum values from each of the three separate occlusions was used to calculate the coefficient of repeatability [(SD/mean) x 100] for each patient. The within-subject coefficient of variability and 95% confidence intervals (CI) were then calculated using the root mean square method. For P_{i max} the coefficient of variability was 17% (95% CI 5.4-24%) and for P_{e max} 18% (95% CI 12-22%).
2.13.2 PTPdi

The repeatability of PTPdi results was assessed in three patients. This was performed by removing and repositioning the dual transducer catheter between two of the 100 second epochs within a single measurement event. Twenty consecutive breaths from each of these epochs were analysed to produce an average PTPdi for each epoch. The results were assessed for repeatability for each of the three patients and the within-subject variability obtained for PTPdi using the root mean square method was 7.4% (95% CI 2.8-8.2%).

2.13.3 TAA

Phase angle measurements from five consecutive (to avoid choice bias) breaths were analysed from a random ten patients within the PSV RCT. The mean and standard deviation for five breaths were calculated and the coefficient of repeatability calculated for each patient. The within-subject coefficient of variability was calculated as 10.6% (95% CI 6.6-13.9%) using the root mean squared method.

2.14 Assessment of outcomes for in-vitro study

PAV was assessed as per the protocol detailed (chapter 6) in a variety of simulated clinical conditions; dynamic lung models with different mechanical properties were developed to simulate these conditions. PAV was delivered by a Stephanie® neonatal ventilator (F. Stephan GmbH, Medizintechnik, Kirchstrasse, Germany).

2.14.1 Models

The dynamic lung models were constructed to have mechanical properties that could be easily altered to simulate various clinical conditions in the neonate. In order to measure the effect of PAV, the models needed to have a mechanism with which to firstly produce effort to trigger the ventilator and secondly to be able to measure
changes in ‘pleural pressure’. The developed models had adjustable or various
compliance and resistance characteristics and an externalisation of the ‘airway’ in order
to measure airway flow and pressure via an attached pneumotachograph. Details of
the lung models and their construction are presented in the methods of chapter 6.

2.14.2 Equipment

2.14.2.1 Measurement of flow, tidal volume and airway pressure
During in vitro assessment of PAV the inspiratory flow was assessed to determine both
the accuracy of the PAV algorithm to unload resistance and also to determine the tidal
volume. Tidal volume measurements were used to calculate the expected airway
pressure delivery during elastic unloading and compare to the observed airway
pressure delivered. In order to measure flow, a pneumotachograph was positioned
between the airway opening of the model and ventilator manifold. Airway pressure was
measured from a side port of the pneumotachograph as described at section 2.6.1.
Transduced signals were amplified and recorded. The linearity, frequency response
and calibration of the airway and flow transducers are described at sections 2.6.1.1 to
2.6.1.4 and 2.7.2.2 to 2.7.2.3 respectively.

2.14.2.2 Measurement of pressure within casing (‘pleural pressure’)
The pressure within the casing of the model was assessed a measure of the simulated
pleural pressure. The data were used to assess the degree of unloading delivered by
PAV and to assess any time delay between effort and ventilator inflation.

‘Pleural’ pressure, the pressure within the casing of the model was measured via a side
port from the casing connected by tubing to a third differential pressure transducer
(MP45, range ± 100 cm H₂O Validyne Corp, Northridge CA, USA). The transducer was
linear for pressures between -100 and + 100 cmH₂O (figure 2.15). The signals from
the pressure transducers were amplified using a carrier amplifier (CD 280, Validyne, Northridge, CA, USA). A two point calibration of the pleural pressure was performed using a digital pressure meter (C950315/IS, Comark Limited, Welwyn Garden City, UK). The frequency response of the transducer was 142Hz.

2.14.2.3 Acquisition and storage of data

The analogue pressure and flow signals were digitized and then 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 TX, USA). Tidal volume was obtained by digital integration of the flow signal. The data were then stored on the hard drive of the computer.

![Diagram](image.png)

**Figure 2.15:** Linearity of the transducer measuring the bottle or 'pleural' pressure.
2.15 Statistical analysis

Data were analysed for normality using the Kolmogorov-Smirnov test. Student’s t test was used to compare two normally distributed groups and ANOVA with post hoc correction used for more than two groups. Non parametric data were analysed using the Mann Whitney U test and the Freidman’s test for analysis of variance with Dunn’s test for multiple comparison. 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 16 SPSS Inc, Chicago IL, USA) and GraphPad Prism (version 3 for Windows, GraphPad Software, SanDiego California USA) were used.
Chapter 3: Optimisation of volume target levels in acute respiratory distress†

† Work from this chapter has been published: Patel DS, Rafferty GF, Lee S, Hannam S, Greenough A. Work of breathing and volume targeted ventilation in respiratory distress. Arch Dis Child Fetal Neonatal Ed 2010 Nov; 95(6): F443-F446.
3.1 Introduction

During volume targeted ventilation (VTV), the delivered tidal volume remains near constant for each breath. A range of targeted volumes, however, have been used,\(^7\) which might influence the success of this mode. A study of 3ml/kg compared to 4.5ml/kg volume target showed that at the lower volume the spontaneous minute ventilation was significantly increased suggesting a shift of mechanical work to the infant.\(^{192}\) The aim, therefore, of this study was to test the hypothesis that lower compared to higher levels within the physiological range of volume targeted ventilation will significantly increase the work of breathing in infants with acute respiratory distress. The results of this study have been presented and published.\(^{232}\)

3.2 Methods

3.2.1 Eligibility

Infants born at less than 34 weeks of gestational age and less than 48 hours of age were eligible for entry into the study. Infants with congenital cardiac abnormalities or neurological impairment or who were receiving neuromuscular blocking agents were not included. All infants were inpatients on the NICU at King’s College Hospital. Informed, written consent was obtained from parents before their infant was entered into the study.

3.2.2 Protocol

Infants were first ventilated without volume targeting (baseline) and then received volume targeted levels of four, five and six ml/kg (figure 3.1). The order in which the infants received the different volume targeting levels was randomised between infants. After each period of volume targeting, the infant was returned to baseline. Each step was maintained for 20 minutes.
All infants were supported by SLE 5000 (SLE Ltd, South Croydon, UK) ventilators via shouldered endotracheal tubes, which have minimal or no leak. Infants were initially supported by pressure limited, time cycled ventilation using SLE 5000 ventilators, (software version 4.1 SLE Ltd, South Croydon, UK). For many infants this was a controlled non-triggered mode however, if they were asynchronous with the ventilator they were changed to patient triggered ventilation either SIMV or ACV as per the unit’s protocol. SIMV was only used if the infant developed hypocarbia which was unresponsive to reduction in the peak pressure and extubation was inappropriate. Infants were ventilated with the single use flow sensor in situ throughout the study regardless of ventilatory mode.

During VTV, the maximum (set) peak inspiratory pressure (PIP) was only delivered to the infant if the volume targeted level was not achieved during the previous inflation. Inflation was terminated once the delivered inspiratory volume exceeded the volume target, which meant that the delivered inflation time could be shorter than the preset inflation time. As a consequence, if the delivered inflation time was less than 0.2 seconds the inflation time was lengthened by altering the wave form to give a shallower upstroke to the inflating pressure. Infants were studied a minimum of four hours after administration of surfactant therapy, if given.

A blood sample was taken from the indwelling arterial line before the study was commenced i.e. at baseline and then repeated on completion of the study. The study was carried out only if the pH (7.25 to 7.35) and PaCO₂ (4.0 to 6.5 kPa) were within the predefined limits.
3.2.3 Outcome measures

The work of breathing was assessed by measuring the inspiratory pressure time product of the diaphragm (PTPdi) which was recorded over the last five minutes of each step. The baseline PTPdi was calculated by averaging the PTPdi results at the four periods at baseline. The mean PTPdi was calculated from 20 consecutive artefact free (e.g. without electrical interference) breaths including those that were and were not supported by ventilator inflations. The peak inflating pressure, expired tidal volume, the infant’s respiratory rate and the total minute volume were calculated from ten breaths at each level.

**Figure 3.1**: Protocol of volume targeting levels
3.2.4 Analysis
In a previous study\textsuperscript{234} a 50% difference in the mean PTPdi at volume targeted levels of 4 and 6 ml/kg was demonstrated. A conservative estimate was used in this study; that is a 40% difference in the PTPdi might be detected between infants supported by a volume targeted level of 4 ml/kg compared to 6 ml/kg. Recruitment of eighteen patients was required to detect such a difference with 80% power at the 5% level. Data were assessed using the Kolmogorov-Smirnov test and found to be not normally distributed. Differences, therefore, were assessed for statistical significance using the Friedman test with Dunn’s multiple comparison test. SPSS 16 (SPSS, Chicago, IL) and GraphPad Prism version 3 (GraphPad Software, SanDiego California USA) were used.

3.3 Results

3.3.1 Demographics
Eighteen infants (ten male) with a median gestational age of 29 (range 25 to 34) weeks and birthweight of 1.14 (range 0.67 to 1.85) kg were studied at a median postnatal age of 19 (range 3-43) hours. Ten patients were assessed when receiving IPPV, six SIMV and two ACV. Eighty three percent of the mothers had received antenatal steroids and 89% of the infants had received surfactant therapy prior to the study. Thirteen infants were receiving a morphine infusion (at 5 to 10mcg/kg/hr) during the study.

The baseline ventilator settings were a median peak inspiratory pressure of 16 (14-21) cmH\textsubscript{2}O, PEEP of 4 (4-5) cmH\textsubscript{2}O, mean airway pressure of 7 (5-8) cmH\textsubscript{2}O, inspiratory time of 0.36 (0.34-0.4) seconds, ventilator rate or back-up rate of 40 (20-60) breaths per minute and inspired oxygen fraction of 0.22 (0.21-0.40). Five of the infants were receiving caffeine at the time of the study.
3.3.2 Outcomes

The mean PTPdi was higher at a volume targeting level of 4 ml/kg compared to the baseline (p < 0.001) and 6 ml/kg (p < 0.001) (table 3.1 and figure 3.2). There were no significant differences between the mean PTPdi at baseline compared to the PTPdi levels at a volume targeted level of 5 ml/kg and 6 ml/kg or between the mean PTPdi at volume targeted levels of 5 ml/kg compared to 4 ml/kg and 6 ml/kg. The blood gases before and after the study did not differ significantly.

![Graph showing PTPdi values across different volume targeted levels.](image)

**Figure 3.2:** Transdiaphragmatic pressure time product values at each level of volume targeted ventilation. Individual's data points are linked.
Table 3.1: PTPdi (cmH₂O.s/min) of infants at each level of volume targeting level. 
Data are shown as median (range)

<table>
<thead>
<tr>
<th>Level</th>
<th>PTPdi</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASELINE</td>
<td>112 * (37-178)</td>
</tr>
<tr>
<td>4</td>
<td>154 (52-308)</td>
</tr>
<tr>
<td>5</td>
<td>106 (43-260)</td>
</tr>
<tr>
<td>6</td>
<td>89 # (33-254)</td>
</tr>
</tbody>
</table>

In comparison to 4 ml/kg, * p < 0.01, # p < 0.001,

Higher compared to lower levels of volume targeting were associated with significantly higher peak inspiratory pressures (p < 0.0001), expired tidal volumes, Vte (p < 0.0001) and inflation times, Ti (p < 0.0001), with lower respiratory rates (p < 0.0001), but there were no significant differences in the minute volume (p = 0.74) (table 3.2). The mean PIP at baseline was significantly higher than that at volume targeting levels of 4 ml/kg (p < 0.001) and 5 ml/kg (p < 0.05), but not significantly different from that at 6 ml/kg. The PIP at 4 ml/kg was lower than at 5 ml/kg (p < 0.01) and 6 ml/kg (p < 0.001) and at 5 ml/kg compared to 6 ml/kg (p < 0.05). The Vte at 4 ml/kg was significantly lower than at 5 ml/kg (p < 0.01) and 6 ml/kg (p < 0.001), but the Vte at 6 ml/kg and 5 ml/kg were not significantly different. The infant respiratory rate at 4 ml/kg was higher than at 5 ml/kg (p < 0.01) and 6 ml/kg (p < 0.001) and at 5 ml/kg compared to 6 ml/kg (p < 0.05). The Ti was lower at 4 ml/kg than at 5 ml/kg (p < 0.01) and at 6 ml/kg (p < 0.001), but there were no statistically significant differences between the Ti at 6 ml/kg and 5 ml/kg.
Table 3.2: Peak inspiratory pressure (PIP), tidal volume, minute volume and respiratory rate and inspiratory time (Ti) at each volume targeted level. Data are shown as median (range).

<table>
<thead>
<tr>
<th>Volume targeted level</th>
<th>Baseline</th>
<th>4 ml/kg</th>
<th>5 ml/kg</th>
<th>6 ml/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIP (cmH₂O)</td>
<td>16 (14-21)</td>
<td>8.2 (5.9-17.6)</td>
<td>12.2 (7-20.6)</td>
<td>13.6 (9-22)</td>
</tr>
<tr>
<td>Expired tidal volume (ml/kg)</td>
<td>6.4 (4-10.1)</td>
<td>4.8 (3.7-7.1)</td>
<td>5.5 (4.1-7.4)</td>
<td>6.4 (4.0-7.5)</td>
</tr>
<tr>
<td>Infant respiratory rate (bpm)</td>
<td>60 (40-80)</td>
<td>69 (42-124)</td>
<td>60 (39-101)</td>
<td>51 (35-80)</td>
</tr>
<tr>
<td>Minute volume (l/min)</td>
<td>0.39 (0.16-.79)</td>
<td>0.40 (0.19-.71)</td>
<td>0.40 (0.15-.71)</td>
<td>0.39 (0.22-0.69)</td>
</tr>
<tr>
<td>Ti (s)</td>
<td>0.36 (0.34-0.4)</td>
<td>0.23 (0.13-.33)</td>
<td>0.25 (.15-.38)</td>
<td>0.31 (0.18-.4)</td>
</tr>
</tbody>
</table>

3.4 Discussion

The results of this study have demonstrated that the WOB was significantly higher in infants with acute respiratory distress when they were ventilated with a VT level of 4 ml/kg compared to pressure limited ventilation without VT or a VT level of 6 ml/kg. There has been increasing concern about volutrauma, as it has been demonstrated that volutrauma in the first minutes after birth can be injurious to the lung. In that study, however, the outcome of prematurely born lambs exposed to six manual inflations of 35-40 ml/kg were compared to those who did not receive manual inflations. In another study, Bjorklund et al showed that five sustained inflations of 8 ml/kg, 16 ml/kg and 32 ml/kg resulted in dose-dependent lung damage in preterm lambs. Those
volumes\textsuperscript{97,235} are far in excess of the 4-6 ml/kg used in this study and it seems unlikely that use of 6 ml/kg rather than 4 ml/kg will significantly increase volutrauma. In addition, the mean Vte at each VT level exceeded the set value which suggests that all the VT settings used were too low with respect to at least some of the infants’ physiological measurements.

As the level of VT was increased, there was a progressive increase in the peak inflating pressure (PIP), but even at a level of 6 ml/kg the PIP was lower than at baseline, though not significantly. There were significant differences in the Vte at 4 ml/kg and baseline and between the different VT levels. The minute volume, however, was similar and there were no significant differences in the blood gases before and after the study. This was achieved by the infants altering their respiratory rate to compensate for the changed Vte. It has been previously demonstrated that infants on SIMV compared to ACV have greater spontaneous respiratory activity such that a similar total minute ventilation (i.e. spontaneous plus mechanical) was achieved on the two modes.\textsuperscript{236}

The results in infants with acute respiratory distress were similar to those found during weaning in a previous study\textsuperscript{234} that is, a VT level of 6 ml/kg rather than 4 ml/kg was demonstrated to be associated with a significantly lower WOB. PTPdi is influenced by gestational age but the two groups i.e. the acute and weaning groups did not differ with regard to their maturity at birth. A more likely explanation for the similar findings in the two studies is that the infants in this study were examined after any surfactant treatment had been completed and as a consequence, they were not receiving high levels of ventilatory support.
To avoid the bias of instrumental deadspace and its potential effects on VTV,\textsuperscript{237} the same equipment remained \textit{in situ} throughout the study. The dead space of the pneumotachograph used was 1 ml. The measured instrumental dead space of the endotracheal tube, in line suction and flow sensor of the Dräger Babylog\textsuperscript{®} 8000plus (Dräger Medical, Lubeck, Germany) was reported to be 2.7 ml.\textsuperscript{237} Five infants were receiving caffeine at the time of the study, but were assessed at all levels of VT, so the infants acted as their own controls. Among infants being weaned from the ventilator a previous study demonstrated a much higher WOB than in presently studied infants with acute respiratory distress, indeed the WOB was on average 50% higher.\textsuperscript{234}

These findings support other evidence (discussed in section 1.9.3.3) that very low tidal volumes may have a detrimental effects such as raised inflammatory cytokines with prolonged duration of ventilation\textsuperscript{120} and increased duration of hypoxaemic episodes.\textsuperscript{191}

In summary the results demonstrate that the WOB of infants with acute respiratory distress is decreased by approximately 40% when a VT level of 6 ml/kg rather than 4 ml/kg is used. Additionally, during acute respiratory distress, a VT level of at least 5 ml/kg rather 4 ml/kg might avoid an increased WOB.
Chapter 4: Work of breathing during SIMV with and without PSV§

4.1 Introduction

PSV with SIMV has been compared to SIMV alone in a randomised trial of 107 extremely low birth weight (<1000g) infants. During PS with SIMV, the non SIMV breaths were supported with PSV breaths at 30-50% of SIMV inflation pressure. Fewer infants were still ventilated at 28 days (47% versus 69%, p=0.04) with PS with SIMV rather than SIMV alone. Analysis of the 700g to 1000g birthweight strata demonstrated that those supported by PS with SIMV required fewer days of supplementary oxygen than those supported by SIMV alone (median 58 versus 41 days, p=0.034). That effect may have been as a consequence of a reduced work of breathing since every additional spontaneous breath above the SIMV rate was supported with PSV rather than a direct benefit of flow cycling and increased synchronicity. It was postulated, therefore, that the addition of PS to SIMV would result in a reduced work of breathing as compared to SIMV alone. The aim of this study was to test that hypothesis and determine the magnitude of the effect when PS was added at 50% of the difference between the peak inflating and positive end expiratory pressures. The results of this study have been published.

4.2 Methods

4.2.1 Eligibility

Neonates on the NICU at King’s College Hospital being weaned from mechanical ventilation using SIMV were eligible for entry into this study. Infants with congenital cardiac abnormalities and hypoxic ischaemic encephalopathy were excluded. Informed, written consent was obtained from parents before their infant was entered into the study.
4.2.2 Study protocol

The infants were supported by SLE 5000 ventilators and studied while receiving PS with SIMV and SIMV alone. A flow sensor proximally inserted into the ventilator circuit (i.e. close to patient) was used in both modes to trigger inflation initiation and in PS breaths to trigger the termination of inflation. Each mode was delivered for one hour and the order in which the modes were studied was randomised between infants. The backup ventilator mandatory breath rate was set at no more than 45 breaths per minute and was maintained at the same rate for both time epochs. PS supported inflations were delivered at 50% of the difference between the peak inflating and positive end expiratory pressure as per the study by Reyes et al. The flow cycling criterion (termination sensitivity) was decreased if inflation time was less than 0.25 seconds, in an attempt to minimise premature termination.

4.2.3 Outcome measurements

Work of breathing was assessed by measurement of the PTPdi during the last five minutes of each one hour epoch. The mean PTPdi was calculated from 20 consecutive artefact free (e.g. without electrical interference) breaths including those that were and were not supported by ventilator inflations. Assessment of ventilator pressures, tidal volume and respiratory rate was made during the last five minutes of each epoch.

Arterial blood gas analysis was performed at the end of each one hour epoch; blood samples were obtained from indwelling arterial catheters. The pH was calculated by the blood gas analyser from the hydrogen ion activity.
4.2.4 Analysis
Recruitment of 20 infants into the study allowed detection of a difference of equivalent to one standard deviation (SD) in the mean PTPdi between the two groups with at least 80% power at the 5% level. In a previous group of infants, the mean PTPdi was 197 (SD +/- 56) cm H₂O.sec/min. The data were demonstrated to have a normal distribution using the Kolmogorov Smirnov test, hence differences were assessed for statistical significance using the paired Student’s t-test.

4.3 Results

4.3.1 Demographics
Twenty infants with a mean gestational age of 31 (range 24 to 38) weeks, birthweight of 1.63 (range 0.61 to 3.8) kg and postnatal age of 7 (range 1-32) days were studied. The clinical diagnoses of the infants were respiratory distress syndrome (n=14), congenital pneumonia (n=1), congenital diaphragmatic hernia (n=4) and gastroschisis (n=1). The infants with surgically correctable anomalies were studied postoperatively. As per the neonatal unit’s policy, all sedation had been discontinued once infants entered the weaning phase of ventilation. Fifteen infants were receiving caffeine when studied. The mean SIMV rate at the time of study was 40 (range 20 – 45) breaths per minute.

4.3.2 Outcomes
The mean PTPdi of infants when receiving PS with SIMV was 20% lower than that when receiving SIMV alone (p< 0.001), (figure 4.1) (table 4.1). The infants’ spontaneous respiratory rate was significantly lower on PS with SIMV than SIMV alone (p= 0.001). No significant differences were found in the mean pH (p = 0.9), arterial carbon dioxide (p = 0.55) or oxygen (p= 0.78) tensions between the two modes (table 4.1).
Table 4.1: PTPdi and blood gas results by ventilation mode, presented as mean (SD).

<table>
<thead>
<tr>
<th></th>
<th>SIMV</th>
<th>PS with SIMV</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PTPdi (cmH(_2)O.sec/min)</strong></td>
<td>141 (93)</td>
<td>112 (85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Infant respiratory rate (bpm)</strong></td>
<td>64 (13)</td>
<td>55 (10.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>(supported and unsupported)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td>7.32 (0.05)</td>
<td>7.32 (0.07)</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>PaCO(_2) (kPa)</strong></td>
<td>5.9 (1.3)</td>
<td>6.0 (1.6)</td>
<td>0.55</td>
</tr>
<tr>
<td><strong>PaO(_2) (kPa)</strong></td>
<td>8.6 (2.6)</td>
<td>8.5 (1.8)</td>
<td>0.78</td>
</tr>
</tbody>
</table>

Figure 4.1: PTPdi of each infant when supported by both SIMV and PS with SIMV.

Linked data points show individual patients. Red linked data point illustrates the mean PTPdi for each mode.
4.4 Discussion

The results show that the addition of PS to SIMV compared to SIMV alone significantly reduced the WOB in infants being weaned from the ventilator. Infants with a wide range of gestational ages and a number of diagnoses were assessed, yet addition of PS to SIMV reduced the work of breathing in all (figure 4.1). The WOB was assessed by measuring the PTPdi, which reflects energy expenditure of the diaphragm muscle during isometric and non-isometric contractions. A potential problem in measuring the PTPdi is transmission of positive pressure by the ventilator to the oesophagus. During triggered ventilation, however, the infant’s inspiratory effort precedes the positive pressure inflation and there is a trigger delay. In addition, as in the neonatal period the chest wall is much more compliant than the lung, any effect regarding transmission is likely to be small.

An increased level of flow cycling or termination sensitivity during PSV delivered by the SLE ventilator results in decreased asynchrony. However, as the flow level is increased the inflation is terminated at higher levels of inspiratory flow resulting in progressively shorter inflation times and lower mean airway pressures, which may adversely affect oxygenation. As a consequence, the flow cycling level was set individually for each patient in this study such that an inflation time of at least 0.25 seconds was delivered.

Supporting an increased number of infant efforts with positive pressure inflation as with the addition of PS to SIMV compared to SMV alone might potentially result in hyperventilation. Yet on comparison of blood gases there was no significant difference in carbon dioxide levels between the modes. It has been previously demonstrated that infants supported on SIMV compared to assist control ventilation have greater spontaneous respiratory activity such that similar total minute volumes (i.e.
spontaneous plus mechanical) were achieved on both modes. It could therefore be conjectured that total minute volume is likely to have been similar in this study on PS with SIMV as on SIMV alone, hence explaining the lack of significant difference in carbon dioxide levels between modes. This is supported by the finding that the infants’ respiratory rates were significantly lower on PS with SIMV compared to SIMV alone. In a previous study by Gupta et al., although a reduction in total respiratory rate was noted when PS was added to SIMV, the minute ventilation was shown to increase. Two levels of PS were used; one which was targeted to deliver an expired tidal volume of 5-8 ml/kg and a second which was adjusted to deliver an expired tidal volume of 2.5-4 ml/kg. The SIMV rate was set lower at 20 breaths per minute; the difference in set rate as compared to the current study may explain the disparity between the effects of the addition of PS on minute ventilation between the two studies. In the current study a mean SIMV rate of 40bpm was used to avoid a potential increase in the work of breathing, as a reduction in SIMV rate of below 20bpm has been shown to prolong the duration of weaning.

PS with SIMV has been compared to SIMV alone in a randomised trial including 107 extremely low birthweight infants. Fewer infants were still ventilated at 28 days when supported by PS with SIMV compared to SIMV alone and infants with birthweight of 700g to 1000g supported by SIMV with PS required significantly fewer days of supplementary oxygen. The results presented in this chapter suggest that the positive results of PS with SIMV in that study may be explained by a lower WOB.

The WOB was reduced by approximately 20% when PS was added to SIMV. There was no significant difference in the mean pH between the two periods suggesting the infants were not more fatigued when supported by SIMV alone, but the infants were only studied on each mode for one hour. PS was applied at 50% of the difference in
the peak inflating pressure minus the PEEP, as that PS level was used in the randomised trial. A greater level of pressure support may have further reduced the WOB. That hypothesis is supported by the study by Osorio et al., demonstrating a lower spontaneous inspiratory effort per minute when PS was added at 6 cmH₂O rather than 3 cmH₂O in prematurely born infants being weaned from the ventilator.

In conclusion, the addition of PS to SIMV compared to SIMV alone reduced the work of breathing as assessed by measurement of the pressure time product. This may be beneficial since an increased WOB may lead to muscle fatigue and is associated with failed extubation. The results further support the concept that weaning is better achieved by modes providing positive pressure support to every breath.
Chapter 5: Randomised controlled trial comparing PSV and ACV**

5.1 Introduction

Patient triggered ventilation or synchronised ventilation has been shown to be advantageous in reducing the duration of mechanical ventilation. In a survey of U.K. neonatal units synchronised ventilation (either ACV or SIMV) was used as the primary weaning mode by 88% of responders. During SIMV and ACV, the initiation of inflation is determined by the infant’s inspiratory effort. During pressure support ventilation (PSV), not only is the initiation of inflation determined by the infant’s inspiratory effort, but termination of inflation occurs when the inspiratory flow is reduced to a certain level. PSV compared to SIMV has been associated with superior breathing rhythmicity. In another study, as the level of termination sensitivity was increased, the occurrence of asynchrony was decreased, but at the expense of shortened inflation times. Despite the lower level of peak inflating pressure provided by the ventilator during PSV compared to ACV or SIMV, blood gases, at least in short term studies, were maintained. The reduced level of ventilator support however, could lead to an increase in the work of breathing and muscle fatigue, adversely affecting respiratory muscle strength. Thus the raised hypothesis is that, even if a minimum inflation time was used during PSV, the work of breathing would be lower and respiratory muscle strength greater on ACV compared to PSV and, although the level of asynchrony would be higher on ACV, the duration of weaning would be shorter on ACV.

The aims of this study, therefore, were in a randomized trial to undertake physiological measurements to determine if there were any differences in the work of breathing, the rate of asynchrony or the level of respiratory muscle strength during weaning by ACV or PSV. In addition, the study aimed to assess if any such differences were associated with a difference in the duration of weaning between the two modes. The results from this trial have been published.
5.2 Methods

5.2.1 Design

A prospective randomised clinical trial (Clinical Trial Registration number: NCT01376544) was carried out at King’s College Hospital, London between September 2008 and February 2010. Ventilated infants less than fourteen days old regardless of gestation who were inborn were eligible for entry into the trial during the weaning phase of ventilation. Exclusion criteria included infants receiving neuromuscular blocking agents, those with congenital heart disease and those with neurological problems including hypoxic-ischaemic encephalopathy. Infants were enrolled into the study if their parents gave informed written consent.

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, but the block size was six. All infants were entered into the study if they had a supplemental oxygen requirement of less than 40% and were receiving peak inspiratory pressures of ≤ 20cmH₂O for infants >29 weeks gestation, ≤17cmH₂O for infants over 26 completed weeks and less than 29 weeks gestation and ≤ 15cmH₂O for infants of 26 weeks or less. Until entry into the study, the unit protocol of pressure and rate weaning (minimum of 40 breaths per minute) was employed.

All infants were ventilated using an SLE 5000 ventilator (version 4.1 software). Upon entry into the study, all infants followed the same protocol. Once entered into the study, sedation was stopped and caffeine (20mg/kg loading dose followed by 5mg/kg once daily) administered to infants <34 weeks and to those who had had a surgical correction for congenital diaphragmatic hernia. All infants had a ventilator backup rate
of 40bpm and trigger sensitivity set at 0.6 to 1.0 L/minute to avoid auto triggering. Volume targeted ventilation was not utilised.

For those infants randomised to PSV, the termination sensitivity was set initially at 5% and increased in steps of 5% if the inspiratory time (Ti) was persistently above 0.3 seconds in order to reduce the likelihood of asynchrony. If subsequent Ti were less than 0.25 seconds then the termination sensitivity was decreased again to avoid inadequate support. Maximum Ti set for patient in the PSV arm was 0.45 seconds. For infants randomised to ACV the Ti was set at 0.35 to 0.4 seconds as deemed appropriate by the attending clinical team. Arterial carbon dioxide levels were maintained in predetermined ranges: between 4.5 and 5.5 kPa on days 1 and 2, between 5 and 7 kPa from day 3 to 7, and after day seven permissive hypercapnia was employed providing the pH was greater than or equal to 7.25. Weaning from ventilation in both arms was achieved only by reducing the peak inflating pressures. The decision to extubate was made by the attending neonatologist following the unit’s routine policy, that is, the infant was making respiratory efforts and maintaining a pH greater than 7.25 on peak inflating pressures of less than 16 cm H₂O and with FiO₂ less than 0.4. Following extubation, infants were placed on nasal continuous positive airways pressure (nCPAP) if they had a birth weight less than 1000g; infants of greater birthweight were nursed with an appropriate level of supplementary oxygen being delivered into the incubator.

5.2.2 Failure criteria
Infants failed the study mode if after entry: high frequency oscillatory ventilation (HFOV) was required; neuromuscular blocking agent was used; peak inspiratory pressures rose to greater than 26cmH₂O or if in the PSV arm the delivered Ti was <0.2seconds for four hours despite a minimum termination sensitivity of 5%. Failure of
extubation was defined as the need for re-intubation and ventilation within 48 hours of the primary extubation, regardless of need for nCPAP. The indications for re-intubation were the development of a respiratory acidosis (pH < 7.25) which persisted for more than four hours, the occurrence of frequent troublesome apnoeas or one major apnoea and/or increased inspired oxygen requirements (FiO₂ ≥ 0.6).

5.2.3 Outcome measures
Measurements of the work of breathing as assessed by PTPdi over a five minute period, level of thoraco-abdominal asynchrony (TAA) assessed using uncalibrated respiratory inductive plethysmography in AC coupled mode and respiratory muscle strength (Pimax and Pemax) were attempted at study entry (baseline), 24 hours later and immediately prior to extubation. Additionally, the level of active expiration and magnitude of TTdi and Pdi_max was determined prior to extubation. The numbers of active expiratory efforts were expressed as a percentage of the mechanical inflations during the last five minutes of the recording.

The inflation time delivered at each time of measurement was determined from the airway pressure recordings. Blood gases were taken from infants for appropriate routine analysis only and no additional gases were taken for the study; all gases taken were documented. The nurses recorded hourly the need and level of respiratory support and supplemental oxygen requirement. The duration of weaning was the time from randomisation to first extubation and the time to first successful extubation was when the infant remained extubated for at least 48 hours. The infants’ demographics and pre-extubation levels of respiratory support were determined from the medical records and intensive care observation charts.
5.2.4 Analysis

A sample size of 36 infants allowed detection of a difference between the groups in the results of the physiological measurements equivalent to one standard deviation, as well as a 24 hour difference in duration of weaning, with 80% power at the 5% level.

Analysis was on an intention to treat basis. Differences were assessed for statistical significance using the Pearson Chi-Square, Fisher’s Exact (where expected values were <5) or Mann Whitney U test as appropriate.

5.3 Results

Sixty seven patients were eligible to be recruited into the trial; 36 were successfully recruited (figure 5.1).

---

**Figure 5.1:** Diagram of recruitment.

# - researcher non availability
The recruited infants compared to the non-recruited infants were more mature with a median gestational age of 29 (range 24 to 39) weeks versus 28 (range 23 to 41) weeks (p=0.044) and had higher birth weights, median 1.49 (0.65 to 3.69) kg versus 1.03 (0.59 to 2.86) kg (p=0.044). Twenty nine preterm infants with respiratory distress syndrome were enrolled into the trial, 16 in the ACV arm and 13 in the PSV arm. There were no significant differences in the demographics of the ACV and PSV groups (table 5.1).

<table>
<thead>
<tr>
<th></th>
<th>ACV</th>
<th>PSV</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (male)</td>
<td>18 (11)</td>
<td>18 (11)</td>
<td>0.17</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>29 (24 – 35)</td>
<td>31 (24 – 39)</td>
<td>0.42</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>1.155 (0.65-2.6)</td>
<td>1.72 (0.67-3.69)</td>
<td>0.48</td>
</tr>
<tr>
<td>Antenatal steroids</td>
<td>13</td>
<td>10</td>
<td>0.49</td>
</tr>
<tr>
<td>Surfactant</td>
<td>15</td>
<td>14</td>
<td>0.49</td>
</tr>
<tr>
<td>Postnatal age at randomization (days)</td>
<td>2.5 (1-10)</td>
<td>3 (1-14)</td>
<td>0.2</td>
</tr>
<tr>
<td>Caffeine</td>
<td>16</td>
<td>15</td>
<td>1.0</td>
</tr>
<tr>
<td>PDA</td>
<td>5</td>
<td>4</td>
<td>1.0</td>
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<tr>
<td>IVH grade:</td>
<td></td>
<td></td>
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<td>1-2</td>
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<td>1.0</td>
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<tr>
<td>ARDS</td>
<td>0</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>PIP (cmH2O):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at pre-extubation</td>
<td>15 (10-17)</td>
<td>15.5 (13-18)</td>
<td>0.51</td>
</tr>
<tr>
<td>MAP (cmH2O):</td>
<td>7 (5-9)</td>
<td>7 (5-10)</td>
<td>0.94</td>
</tr>
<tr>
<td>FiO2</td>
<td>0.22 (0.21-0.4)</td>
<td>0.25 (0.21-0.4)</td>
<td>0.14</td>
</tr>
</tbody>
</table>
In the PSV group, 14 of the 18 infants were maintained on a termination sensitivity level set at 5%, as attempts to increase the sensitivity above 5% resulted in too short inflation times. In three infants, termination sensitivities of 10% were initially tolerated, but later in the study the termination sensitivity had to be reduced to 5% so an adequate inflation time could be achieved. The remaining infant temporarily tolerated a termination sensitivity of 15%, however, for the majority of the study the termination sensitivity was required to be reduced to 10% to achieve an adequate inflation time of more than 0.25 seconds. The median inflation times did not differ significantly between the two groups at any of the measurement times (table 5.2).

Table 5.2: Time to extubation, results of PTPdi, P_{i,\text{max}} generated against an occlusion and inflation times by mode of weaning. Results are demonstrated as median (range).

* n = number of infants for whom results were available.

<table>
<thead>
<tr>
<th></th>
<th>n*</th>
<th>ACV</th>
<th>n*</th>
<th>PSV</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of weaning (hours)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>34 (7-100)</td>
<td>27 (10-169)</td>
<td></td>
<td></td>
<td>0.88</td>
</tr>
<tr>
<td>Final extubation (hours)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>35 (7-334)</td>
<td>27 (10-818)</td>
<td></td>
<td></td>
<td>0.88</td>
</tr>
<tr>
<td>PTPdi (cmH_2O.s/min):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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</tr>
<tr>
<td>at baseline</td>
<td>14</td>
<td>116 (39-353)</td>
<td>7</td>
<td>179 (101-265)</td>
<td>0.14</td>
</tr>
<tr>
<td>at 24 hours</td>
<td>7</td>
<td>117 (37-319)</td>
<td>6</td>
<td>102 (51-216)</td>
<td>1.0</td>
</tr>
<tr>
<td>pre extubation</td>
<td>9</td>
<td>119 (79-288)</td>
<td>13</td>
<td>150(66-303)</td>
<td>0.87</td>
</tr>
<tr>
<td>P_{i,\text{max}} (cmH_2O):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at baseline</td>
<td>15</td>
<td>22 (10-52)</td>
<td>8</td>
<td>20.5 (7-41)</td>
<td>0.38</td>
</tr>
<tr>
<td>at 24 hours</td>
<td>8</td>
<td>30 (9-60)</td>
<td>6</td>
<td>14 (8-30)</td>
<td>0.06</td>
</tr>
<tr>
<td>at pre extubation</td>
<td>9</td>
<td>30 (16-67)</td>
<td>14</td>
<td>24 (15-71)</td>
<td>0.8</td>
</tr>
<tr>
<td>Inflation times (seconds)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at baseline</td>
<td>18</td>
<td>0.36 (0.34-0.4)</td>
<td>12</td>
<td>0.37 (0.23-0.44)</td>
<td>0.11</td>
</tr>
<tr>
<td>at 24 hours</td>
<td>18</td>
<td>0.36 (0.34-0.4)</td>
<td>10</td>
<td>0.29 (0.26-0.45)</td>
<td>0.16</td>
</tr>
<tr>
<td>at pre-extubation</td>
<td>18</td>
<td>0.36 (0.34-0.4)</td>
<td>14</td>
<td>0.36 (0.23-0.45)</td>
<td>0.91</td>
</tr>
</tbody>
</table>
It was not possible to measure all infants at all study times, but there were no significant differences at any of the measurement times in the results of the physiological measurements except the baseline $P_{max}$ (tables 5.2 and 5.3). There were no significant differences in the level of active expiration between the two groups (table 5.3). The duration of weaning was similar in the two groups, as was the time to successful extubation (table 5.2 and figure 5.2).

**Figure 5.2:** Kaplan Meier for time to final extubation

Two infants in the ACV group failed weaning, one because of a protocol violation as the infant was switched to SIMV and the other required peak inflating pressures in excess of 26 cm H$_2$O. In the PSV arm, one infant failed weaning due to very short inflation times. In the ACV group, two infants failed initial extubation and one died.
having never been extubated. Three infants in the PSV group failed initial extubation, one of whom died thereafter. Three infants in both the PSV and ACV groups developed BPD (as defined by supplemental oxygen requirement or respiratory support at 28 days or 36 weeks corrected gestation (whichever was later). In either group no infant developed an airleak.

Table 5.3: Results of TAA, active expiration and TTdi and Pdi_{max}.

Results are demonstrated as median (range).

* n = number of infants for whom results were available.

<table>
<thead>
<tr>
<th></th>
<th>*n</th>
<th>ACV</th>
<th>P value</th>
<th>*n</th>
<th>PSV</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pe_{max} (cmH_{2}O)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at baseline</td>
<td>14</td>
<td>11  (4-38)</td>
<td>0.03</td>
<td>6</td>
<td>6   (1-16)</td>
<td>0.03</td>
</tr>
<tr>
<td>at 24 hours</td>
<td>8</td>
<td>13  (4-54)</td>
<td>0.66</td>
<td>6</td>
<td>10  (4-21)</td>
<td>0.66</td>
</tr>
<tr>
<td>at pre extubation</td>
<td>9</td>
<td>15  (7-28)</td>
<td>0.98</td>
<td>14</td>
<td>14  (4-39)</td>
<td>0.98</td>
</tr>
<tr>
<td>TAA (degrees)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at baseline</td>
<td>16</td>
<td>25  (5.8-38.7)</td>
<td>0.33</td>
<td>8</td>
<td>8   (5.1-35.8)</td>
<td>0.33</td>
</tr>
<tr>
<td>at 24 hours</td>
<td>9</td>
<td>24  (3.9-37.5)</td>
<td>0.41</td>
<td>6</td>
<td>27  (11.2-34.2)</td>
<td>0.41</td>
</tr>
<tr>
<td>at pre extubation</td>
<td>9</td>
<td>7   (3.3-34.3)</td>
<td>0.78</td>
<td>12</td>
<td>27  (4.7-36.6)</td>
<td>0.78</td>
</tr>
<tr>
<td>Active expiration (%)</td>
<td>15</td>
<td>0.28 (0-10)</td>
<td>0.35</td>
<td>17</td>
<td>0   (0-3.3)</td>
<td>0.35</td>
</tr>
<tr>
<td>TTdi</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at pre extubation</td>
<td>9</td>
<td>0.069 (0.031-0.14)</td>
<td>0.75</td>
<td>12</td>
<td>0.07 (0.022-0.16)</td>
<td>0.75</td>
</tr>
<tr>
<td>Pdi_{max}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at pre extubation</td>
<td>10</td>
<td>34  (20-99)</td>
<td>0.97</td>
<td>11</td>
<td>35  (20-80)</td>
<td>0.97</td>
</tr>
</tbody>
</table>
5.4 Discussion

This study has demonstrated that weaning by ACV or PCV was equally efficacious in that there were no significant differences in either the duration of weaning or the time to successful extubation between the two groups. In addition, similar numbers in each group failed the first attempt at extubation and there were no significant differences at any of the time points in the results of the physiological measurements. These results suggest weaning by any method that supports all of the patient’s respiratory efforts will be equally efficacious. In support of that hypothesis, a secondary analysis of an observational study of 349 adult intensive care units in 23 countries highlighted that there were no significant differences in clinical outcomes between patients ventilated with PS with SIMV or ACV.\textsuperscript{242}

Prior to the study it had been postulated that the work of breathing would be higher in the PSV compared to the ACV group as those infants would be exposed to shorter inflation times. The hypothesis was not proven as the median inflation times in the two groups were similar. This likely also explains for the lack of difference in the results of measurements of asynchrony and respiratory muscle strength. The results highlight if clinicians operate within a protocol which emphasizes the importance of attention to inflation time duration, the efficacy of PSV and ACV are similar.

A termination sensitivity of 15\% was only tolerated by one infant during the study and that only temporarily. In all the other infants, termination sensitivities of either 5\% or 10\% had to be used to ensure the inflation times were at least 0.25 seconds. In a study of adults recovering from acute lung injury, the lowest cycling off criteria (5\%) was associated with a reduced respiratory rate and higher tidal volumes.\textsuperscript{243} The work of breathing was not increased by increasing the cycling off criteria to 40\% of the peak inspiratory flow, but the comparison periods were of only 20 minutes duration.\textsuperscript{243}
another study,\textsuperscript{165} however, the flow termination sensitivity during PSV has been shown to affect the work of breathing.\textsuperscript{165} Increasing the sensitivity from one to 45\% of the peak inspiratory flow was associated with a decrease in tidal volume, an increase in breathing frequency and a more than 50\% increase in the work of breathing.\textsuperscript{165} It is important to note that the patients were only exposed to each termination criteria for 10 to 15 minutes and the differences were seen only with a large change in termination criteria from one to 35\% and 45\%. Although both these studies,\textsuperscript{165, 243} were of adults it is possible that lower termination sensitivities for longer periods would increase the work of breathing in neonates, particularly in those ventilated with small endotracheal tubes, which have a high resistance.\textsuperscript{244}

Strengths of the study were the randomisation of consecutive infants and the use of the same ventilator model and software for each infant in both arms of the study. The study compares methods of weaning from the ventilator that supports all the infants' inspiratory effort above trigger threshold. The study described in chapter 4 of this thesis demonstrates that the work of breathing is increased during weaning when only a proportion of the infant's breaths are supported by mechanical inflations compared to when all the infants' breaths were supported.

The study has some limitations. The sample size allowed confident detection of a difference equivalent to one standard deviation in the results of the physiological measurements, but to detect only a difference of 24 hours in the duration of weaning between the groups. However, such a difference was chosen as it would be clinically important. A further limitation was that the duration of intervention was relatively short, approximately 30 hours, but this reflects the duration of weaning and hence the study tested the efficacy of two weaning modes. Randomisation was not stratified according to gestation; there were more infants of greater than 29 weeks of gestation in the PSV
group, but there was no significant difference in the median gestational age of the two groups. The study participants included both term and prematurely born infants and infants with a variety of underlying conditions. It is possible that in certain group(s), benefit of one of the modes of weaning might have been greater; the study, however, was of a pragmatic design and reflects that the weaning policy at KCH NICU is not different according to gestational age or diagnosis. The study was not powered to detect a significant difference in the subgroup of 29 premature infants. Infants received caffeine if they were \( \leq 34 \) weeks of gestational age\textsuperscript{245} or if they had a CDH. The latter policy was adopted at KCH NICU, as administration of caffeine in a non-randomised trial was associated with increased respiratory muscle strength.\textsuperscript{246} The numbers of infants born prematurely or who had had a CDH did not differ significantly between the two groups.

In conclusion, the work of breathing, respiratory muscle strength, rate of synchrony, duration of weaning and time to successful extubation by ACV and PSV did not differ significantly. The results suggest that weaning by ventilatory techniques that support all of the infant’s respiratory efforts are equally efficacious when emphasis is placed on ensuring an adequate inflation time.
Chapter 6: Assessment of proportional assist ventilation

6.1 Introduction

Proportional assist ventilation (PAV), a more sophisticated form of PTV, has been introduced as a form of ventilation that may enable clinicians to deliver precise amounts of compensation for abnormal work load.\textsuperscript{171} During mechanical ventilation three factors impede gas flow into the lung. The first is inertia, which is very small unless using high frequency oscillatory ventilation and thus can be ignored. Second is the compliance of the respiratory system, which is directly in phase with the volume change. The third factor is resistance of the respiratory system largely due to the resistance to inspiratory gas flow in the airways. The resistance is in phase with flow and so approximately leads the volume change by 90 degrees. Therefore, resistance peaks when inspiratory flow is maximal and has no impeding effect when flow is at zero i.e. the beginning and end of inspiration. During PAV, the ventilator has the facility to provide inflation pressure in phase with the change in tidal volume and in phase with the change in flow or a combination of the two. This is defined as elastic and resistive unloading respectively.\textsuperscript{247} Support is normally only required during inflation, as the elastic recoil of the respiratory system drives expiration; however a negative pressure can be provided in phase with expiratory flow if the resistance with delayed lung emptying. Although the ventilator measures both the compliance and resistance when in conventional modes, it is necessary for the clinician to select the level of elastic and resistive unloading to be provided. Theoretically, during the PAV, inflation pressures will be in phase with the infant’s breathing and the infant’s respiratory efforts so harnessed that lower inflation pressures will be required during PAV compared to conventional modes and hence ventilator induced lung damage minimised. Indeed in infants with acute respiratory distress, significantly lower mean airway pressures were used during PAV compared to ACV or IMV, yet with similar carbon dioxide levels and oxygen requirements.\textsuperscript{171} Only a small number of infants, however, were studied and a crossover design employed and thus no long term outcomes were reported.\textsuperscript{171}
Despite the availability of PAV for neonates for over ten years, neonatologists have been slow to adopt the mode. This may reflect the fact that there have been only a few studies in neonates, but also that technical problems have emerged. Overcompensation for load has been shown to result in high pressures and oscillatory waveforms.\textsuperscript{174} The use of pressure limits to prevent high pressures was shown to result in abnormal waveforms.\textsuperscript{175} The behaviour and accuracy of this form of ventilation has yet to be tested objectively in a variety of disease states common to the newborn infant and to date, \textit{in vitro} experiments have only been carried out using static models. In addition, although various methods have been proposed to calculate the ideal unloading settings these all have problems as discussed in \textit{chapter 1 section 1.9.2.3}. The Stephanie\textsuperscript{®} neonatal ventilator (F. Stephan GmbH, Medizintechnik, Kirchstrasse, Germany) displays compliance and resistance measurements when used in conventional ventilation modes; this display could be used to calculate unloading settings.

Infants with evolving chronic lung disease may be ideal candidates for PAV as they have abnormal resistive and elastic loads.\textsuperscript{70, 248-249} They are also less likely to be sedated and have fewer apnoea episodes, which is important as during PAV the inflation time and degree of support is dependent on the infant effort.\textsuperscript{169} Data available from a two centre crossover study of PTV (SIMV or ACV) and PAV in twenty-two chronically ventilated prematurely born infants demonstrated that the mean airway pressure (MAP) was significantly lower when infants were ventilated on PAV, with similar inspired oxygen fractions and transcutaneous PCO\textsubscript{2} levels at four hours. The infants on PAV, however, experienced significantly longer desaturations despite the apnoea back up support that provided mandatory breaths after a ten second apnoea. That result emphasises the need for a more effective backup ventilation during this mode.\textsuperscript{172}
Two studies have been undertaken, an *in vitro* assessment of PAV and a pilot *in vivo* study using data gathered from the *in vitro* study to inform protocols. The aims of the *in vitro* study were to explore how the neonatal ventilator functioned in dynamic situations using lung models that mimicked the lung function abnormality of respiratory diseases. The aim of the pilot *in vivo* study was to compare PAV to ACV in infants with evolving or established BPD by determining levels of work and thoracoabdominal synchrony using data from the *in vitro* studies to inform unloading settings. The methods and results of the *in vitro* study have been published.\(^{170}\)

### 6.2 *In Vitro* study methods

Dynamic lung models were developed and used to assess the PAV ventilator (Stephanie® neonatal ventilator, F. Stephan GmbH, Medizintechnik, Kirchstrasse, Germany). All experiments were undertaken with two Stephanie® neonatal ventilators.

#### 6.2.1 Lung Models

Lung models were developed to closely represent the infant’s respiratory system in that they incorporated a synthetic diaphragm and a ‘pleural space’.

#### 6.2.1.1 Model design and construction

The dynamic lung models each contained a commercial ‘lung’ model (type 1: SLE Silicon test lung part number N6647; type 2: SmartLung Infant™, imtmedical, Gewerbestrasse, Switzerland) mounted in the base of plastic container (type 1- figure 6.1, type 2- figure 6.2). The lung model inlet for the type 1 model was externalised through the base of the container and for the type 2 model via the side of the container, and was attached to a ventilator circuit. Airflow was measured using a pneumotachograph inserted between the airway opening of the lung model and
ventilator manifold. Airway pressure was measured from a side arm on the pneumotachograph. The open ends of the both containers were covered by a latex rubber film; this represented the ‘diaphragm’. Repeated inward and outward movement of the rubber film was used to simulate the diaphragmatic movements. The pressure changes within the outer container were monitored from an outlet on the side by a second pressure transducer, this was described as ‘pleural pressure’ (Ppl). Unlike the type 1 lung model, the type 2 lung model was adjustable allowing various compliance levels to be set and additional tubing was added to the airway port to increase resistance.

6.2.1.2 Model characteristics

Five different models were developed with different compliance and resistance characteristics (table 6.1). In order to assess the effect of decreased work for the infant with increasing unloading, tidal volume was maintained at approximately 3ml (i.e. 6ml/kg for a 500g baby) for models A and B and 12ml (i.e. 6ml/kg for 2kg baby) for models C to E using the measurement of tidal volume displayed on the ventilator to guide the extent of the retraction of the rubber film.
Figure 6.1: Diagram of a type 1 lung model.

Figure 6.2: Photographic example of a type 2 model.
### Table 6.1: Table showing the type and characteristics of the internal lung in the five different lung models used. Commercial compliance is the compliance of model as stated by manufacturer. Actual compliance of the internal lung is that measured when outside the completed model. (MAS: meconium aspiration syndrome).

<table>
<thead>
<tr>
<th>Model</th>
<th>Compliance</th>
<th>Applied Resistance</th>
<th>Condition represented</th>
<th>Weight approximation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ml/cmH₂O</td>
<td>cmH₂O/l/s</td>
<td>Ventilator displayed</td>
<td></td>
</tr>
<tr>
<td>Internal lung</td>
<td>Commercial</td>
<td>Actual</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>0.5</td>
<td>0.5</td>
<td>0.4</td>
<td>50</td>
</tr>
<tr>
<td>Type 1</td>
<td></td>
<td></td>
<td></td>
<td>500g</td>
</tr>
<tr>
<td>B</td>
<td>0.5</td>
<td>0.5</td>
<td>0.4</td>
<td>135</td>
</tr>
<tr>
<td>Type 1</td>
<td></td>
<td></td>
<td></td>
<td>500g</td>
</tr>
<tr>
<td>C</td>
<td>5</td>
<td>4.9</td>
<td>3.5</td>
<td>150</td>
</tr>
<tr>
<td>Type 2</td>
<td></td>
<td></td>
<td></td>
<td>2kg</td>
</tr>
<tr>
<td>D</td>
<td>3</td>
<td>2.8</td>
<td>2</td>
<td>150</td>
</tr>
<tr>
<td>Type 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>2</td>
<td>1.6</td>
<td>1.5</td>
<td>150</td>
</tr>
<tr>
<td>Type 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
6.2.2 Evaluation of lung model

6.2.2.1 Evaluation of linearity of the compliance of the lung models
Each model was assessed for linearity of compliance at a range of inflation pressures appropriate for use in a newborn infant. The inflation pressures ranged from five to 30 cmH$_2$O. Results showed that each model had a linear relationship of change in volume related to change in pressure with an R squared of 0.99 for each lung model (Appendix A2).

6.2.2.2 Evaluation of reliability
Model A was selected for the evaluation as it most closely matched the mechanical respiratory load encountered by an infant with RDS, the condition most likely to be helped by PAV in the neonatal period. The model was connected to the Stephanie® ventilator, set in SIMV mode, with peak inspiratory and end expiratory pressures of 25/5 cmH$_2$O, a back-up rate of 60 breaths/min and inspiratory time of 0.5 s. The inflation pressure and Ppl and delivered volumes were recorded over five breaths. The compliance of the lung was calculated by dividing the delivered volume by the transpulmonary pressure swing, derived from the difference between the airway pressure and the Ppl after positive end expiratory pressure (PEEP) had been deducted, over the respiratory cycle. The SIMV back-up rate was then reduced to 5 breaths/min and the ventilator breaths stimulated by pulling on a tab attached to the outer surface of the latex ‘diaphragm' which simulated an infant's breath. The results of eight simulated breaths were averaged (mean). If the model functioned appropriately, the ratio of delivered volume to transpulmonary pressure would remain constant and so the lung compliance results should also remain constant despite varying Ppl. The baseline compliance result was 0.22 ml/cmH$_2$O. The mean compliance of the eight simulated breaths with negative Ppl ranging from 6.6 to
11.3 cmH₂O was 0.21 ml/cmH₂O with a SD of 0.033, demonstrating the reliability of the model.

6.2.3 Experiment protocol

The compliance and resistance of each lung model were assessed using the ventilator in pressure limited mode. The ventilator was then changed to PAV mode with an airway pressure limit of 25 cmH₂O and PEEP of four cmH₂O. An airway pressure limit was imposed to avoid 'runaway pressures', the progressive increase in inflation pressure with every breath due to positive feedback that can occur with overcompensation for elastic unloading. During PAV, the 'diaphragm' was retracted manually to simulate breathing efforts, generating tidal volumes as close as possible to 3 ml for model A and B and 6 ml for models C to E. The tidal volume displayed on the ventilator was used to guide the extent of the retraction of the rubber film.

6.2.4 Outcomes

A. Inflation pressures during increasing elastic and resistive unloading

Baseline assessment was made with elastic unloading (EU) and resistive unloading (RU) at zero. Recordings were repeated with the resistive unloading at zero and the elastic unloading increased in increments of 0.25 cmH₂O/ml until the elastic unloading was equivalent to the elastance of the model. Following this, increasing levels of resistive unloading were applied with elastic unloading set at zero. The resistive unloading was increased from zero in increments of 25 cmH₂O/L/s to 150 cmH₂O/L/s. The effect of resistive unloading was not examined for model A, as the resistance of that model was within the normal range. The delivered inflation pressures (PIP-PEEP) were compared with those expected which were calculated using the following equations.
Equation 6.1  Expected inflating pressures during elastic unloading

\[ \text{expected inflating pressure} = \text{elastic unloading} \times \text{tidal volume} \]

Equation 6.2  Expected inflating pressure during resistance unloading

\[ \text{expected inflating pressure} = \text{resistance unloading} \times \text{peak inspiratory flow} \]

At each setting, the mean of 10 inflations was used in the calculation.

B. Airway pressure wave forms

The highest level of unloading which was not associated with either wave form abnormalities (oscillations) or too high pressures (defined as a peak pressure 5cmH₂O greater than that expected) was determined. At that unloading setting, the pleural pressure waveform was compared with the inflation pressure waveform during elastic and resistive unloading.

C. Time delay between pleural and airway pressure changes

The traces were assessed to determine if there was a time delay between the onset of the change in pleural pressure and the change in airway pressure during elastic or resistive unloading. The maximum level of unloading which was not associated with wave form abnormalities was used.

D. Effect of elastic and resistive unloading on the inspiratory load

During increasing elastic and resistive unloading, the airway pressures were compared to the pleural pressures.
6.2.5 Analysis

Analysis was performed over ten breaths to account for variations secondary to waveform differences of individual manual retractions/relaxations of the rubber film. Data was reported as a mean with standard deviation. To ensure results were not specific to one Stephanie® machine, studies on one model were repeated on two different ventilators.

6.3. In vitro study results

The two Stephanie® ventilators gave results within 10% of one another as assessed during resistive unloading on models B and C (see Appendix section A3).

6.3.1 Delivered inflation pressures during elastic unloading

During exclusively inspiratory elastic unloading of all five models the delivered airway pressure exceeded the expected calculated pressure. Ventilator inflation pressures exceeded the expected pressures by a mean of 4.3 cmH₂O (SD 0.78) for model A, 2.3 cmH₂O (SD 1.0) for model B, 1.1 cmH₂O (SD 0.21) for model C, 1.9 cmH₂O (SD 0.4) for model D and 1.1 cmH₂O (SD 0.6) for model E (figure 6.3 A to E).
Figure 6.3 A and B: Observed (delivered) versus expected inflation pressure during elastic unloading model A and B respectively.
Figure 6.3 C and D: Observed (delivered) versus expected inflation pressure during elastic unloading model C and D respectively.
6.3.2 Delivered inflation pressures during resistive unloading

During resistive unloading, the delivered inflation pressures exceeded the expected pressures by a mean of 1.8 cmH\textsubscript{2}O (SD 0.8) for model B and by 2.1 cmH\textsubscript{2}O (SD 1.6) for model C (figures 6.4a and b). For model D the inflation pressures exceeded expected by a mean of 2.1 cmH\textsubscript{2}O (SD 1.7) and by a mean of 1.5 cmH\textsubscript{2}O (SD 1.0) for model E (figures 6.4 c and d).

Figure 6.3 E: Observed (delivered) versus expected inflation pressure during elastic unloading model E.
Figure 6.4a and b: Observed (delivered) versus expected inflation pressure during resistive unloading model B and C respectively.
Figure 6.4c and d: Observed (delivered) versus expected inflation pressure during resistive unloading of model D and E.
6.3.3 Airway pressure wave forms

During elastic unloading, the airway pressure wave form differed in shape from the Ppl wave form (figure 6.5), but the two wave forms were similar during resistive unloading. Oscillations in the airway pressure wave form (figure 6.6) were noted with each model at certain levels of elastic or resistive unloading. For model A an elastic unloading of 0.5cmH₂O, for model B an elastic unloading of 1.5 cmH₂O/ml and a resistive unloading of 100cmH₂O/L/s, and for models C, D and E a resistive unloading of 100cmH₂O/L/s. Oscillations were either reduced or eliminated by reducing the trigger sensitivity. High pressures were delivered when an elastic unloading of 3cmH₂O/ml was used with model A, that is, the elastic unloading required to reduce the elastance to zero (figure 6.7).

**Figure 6.5:** Spectra® trace showing airway and ‘pleural’ pressures during elastic unloading of model B.
Figure 6.6: Oscillations in the airway pressure waveform seen in the Spectra® trace of model A during elastic unloading of 2.0cmH₂O/ml.

Figure 6.7: Acceptable pressures (a) and excessive high pressures (b) during elastic unloading of model B.
6.3.4 Delay between airway and pleural pressure changes

There was a time lag of 100ms at all levels of elastic unloading (figure 6.8) and 60ms at all levels of resistive unloading between the start of the Ppl change and the airway pressure change. Inflation, however, did not extend into expiration in any model regardless of the level of unloading. There was no delay between the start of the Ppl change and the onset of airway flow.

**Figure 6.8:** Actual Spectra® trace showing time delay during EU between onset Ppl and airway pressure (Pa).
6.3.5 Effect of elastic and resistive unloading on inspiratory effort

For model A to E as the elastic unloading was increased, the Ppl decreased (figures 6.9a-e). The rise in airway pressure was closely matched by the fall in Ppl during elastic unloading in model A but the fall in Ppl was less than the increase in airway pressure in models B to E. For models B to E during progressive resistive unloading, the fall in Ppl more closely matched the increase in airway pressure (figures 6.10a-d).

**Figure 6.9a:** Model A changes in Pa (●) and in Ppl (○) with increased elastic unloading.
Figure 6.9b: Model B changes in Pa (●) and in Ppl (○) with increased elastic unloading.

Figure 6.9c: Model C changes in Pa (●) and in Ppl (○) with increased elastic unloading.
Figure 6.9d: Model D changes in Pa (•) and in Ppl (○) with increased elastic unloading.

Figure 6.9e: Model E changes in Pa (•) and in Ppl (○) with increased elastic unloading.
Figure 6.10a: Model B changes in Pa (●) and in Ppl (○) with increased resistive unloading.

Figure 6.10b: Model C, changes in Pa (●) and in Ppl (○) with increased resistive unloading.
Figure 6.10c: Model D, changes in Pa (●) and in Ppl (○) with increased resistive unloading.

Figure 6.10d: Model E, changes in Pa (●) and in Ppl (○) with increased resistive unloading.
6.4 In vivo study methods

6.4.1 Design and eligibility
A pilot crossover study was carried out at King’s College Hospital, London. Infants ventilated since birth and more than two weeks old were eligible for entry. Exclusion criteria were congenital cardiac disease, neuromuscular disorders and neuromuscular blockade. Parents gave written informed consent for their infant to take part in the study.

6.4.2 Study methodology
Infants were ventilated using the Stephanie® neonatal ventilator, (F. Stephan GmbH, Medizintechnik, Kirchstrasse, Germany). If the infant was ventilated on a different type of ventilator prior to entry, the ventilator was changed. A period of not less than one hour was allowed for the infant to settle post handling before the study commenced. Infants were only studied if their endotracheal tube leak was less than 30%, as demonstrated by the ventilator display as the difference between VTi and VTe immediately prior to enrolment. Each mode was delivered for one hour and the order in which the modes were studied was randomised between infants.

A flow sensor (pneumotachograph) inserted between the endotracheal tube and the ventilator manifold was used in both modes to trigger inflation initiation. The backup ventilator rate was set at 40 breaths per minute for both modes. During PAV, the pressure limit was increased to 5 cmH2O above the pre-study setting, as has been done in previous studies,172 to allow for the a proportional increase in support if infant effort was increased. During ACV, the peak pressure was set at the same level as the pre-study setting on which the infant had had stable gas exchange results. During PAV, the apnoea limit was set to five seconds. The FiO2 was altered as required to maintain saturations within prescribed normal limits according to unit protocol i.e.
saturations of 92 to 94% for infants <34 weeks and >94% for infants ≥ 34 weeks gestational age. The same trigger threshold was used in both modes.

PAV unloading was calculated from the compliance and resistance values displayed on the ventilator in the baseline pressure limited mode. Full unloading, was defined as that required to decrease the respiratory load to normal. Normal respiratory loads were deemed to be an elastance of 1cmH$_2$O/ml and a resistance of 50cmH$_2$O/L/s. Full (100%) elastic unloading was calculated as:

\[
\text{Equation 6.3:} \quad \frac{1}{\text{patient compliance}} - \text{(normal elastance)}
\]

The infant’s compliance was calculated by dividing the displayed compliance by the patient weight. Seventy five percent of full unloading was applied initially and increased to full unloading providing no abnormalities in waveform were detected by the observing researcher during the epoch.

6.4.3 Outcome measures

Blood gases were taken immediately prior to commencing the study and at the end of each one hour epoch. The numbers of hypoxic episodes were recorded, defined as desaturations to a value of < 80%. Comparisons were made of WOB as measured by PTPdi, respiratory muscle strength measured by $P_{i_{\text{max}}}$, asynchrony as measured by TAA and episodes of active expiration during the last five minutes of each one hour epoch. The numbers of active expiratory efforts were expressed as a percentage of the mechanical inflations during the last five minutes of the recording. Assessment was also made of the time delays between onset of the infant’s effort (negative deflection of Pes) and onset of ventilator inflation (airway pressure).
6.5 *In vivo* study results

Three patients were studied; two patients were infants born prematurely with evolving bronchopulmonary dysplasia (BPD), the third infant was a term infant ventilated for many weeks following meconium aspiration; hence also had evolving BPD (table 6.2). All three infants when studied were not receiving any sedative or analgesic medication and had received caffeine.

Each infant required lower mean airway, peak inspiratory pressures and inflation times during the hour of PAV than when ventilated on ACV (table 6.3). In two of the three infants the FiO$_2$ required to keep saturations within limits as described by the unit policy was higher when supported by PAV compared to ACV. The number of episodes of desaturation to <80% also tended to be higher during the PAV epochs. Physiological measurements were similar on both modes (table 6.4). Minute ventilation and blood gas parameters were similar in all three patients (table 6.3 and 6.4). Each infant had a lower percentage of active exhalation events, calculated from all breaths over a five minute period, when supported by PAV than when supported with ACV (table 6.4 and figure 6.11). Untriggered infant efforts were also more common when supported on ACV than when supported on PAV.
### Table 6.2: Demographics

<table>
<thead>
<tr>
<th>Patient</th>
<th>GA (weeks)</th>
<th>Age (days)</th>
<th>PMA (Weeks)</th>
<th>Birth weight (g)</th>
<th>Weight at measurement (g)</th>
<th>Antenatal steroids</th>
<th>Surfactant (doses)</th>
<th>Postnatal steroids</th>
<th>% PAV unloading</th>
<th>Resistance (cmH₂O/L/s)</th>
<th>Compliance (ml/cmH₂O/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>23</td>
<td>31</td>
<td>28</td>
<td>588</td>
<td>831</td>
<td>Incomplete</td>
<td>2</td>
<td>No</td>
<td>75</td>
<td>85</td>
<td>0.5</td>
</tr>
<tr>
<td>B</td>
<td>23</td>
<td>45</td>
<td>30</td>
<td>534</td>
<td>920</td>
<td>Incomplete</td>
<td>1</td>
<td>Yes</td>
<td>100</td>
<td>80</td>
<td>0.5</td>
</tr>
<tr>
<td>C</td>
<td>41</td>
<td>63</td>
<td>50</td>
<td>2999</td>
<td>4570</td>
<td>No</td>
<td>0</td>
<td>Yes</td>
<td>100</td>
<td>100</td>
<td>0.44</td>
</tr>
</tbody>
</table>

### Table 6.3: Ventilation requirements and blood gas results on each mode.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Mean airway pressure (cmH₂O)</th>
<th>Peak inspiratory pressure (cmH₂O)</th>
<th>Inspiratory time (s)</th>
<th>FiO₂</th>
<th>Episodes of desaturations (n)</th>
<th>pH</th>
<th>PCO₂ (kPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PAV</td>
<td>ACV</td>
<td>PAV</td>
<td>ACV</td>
<td>PAV</td>
<td>ACV</td>
<td>PAV</td>
</tr>
<tr>
<td>A</td>
<td>4.5</td>
<td>6.7</td>
<td>7.3</td>
<td>16</td>
<td>0.41</td>
<td>0.35</td>
<td>0.6</td>
</tr>
<tr>
<td>B</td>
<td>7.3</td>
<td>9.1</td>
<td>11.8</td>
<td>17</td>
<td>0.30</td>
<td>0.35</td>
<td>0.38</td>
</tr>
<tr>
<td>C</td>
<td>8.6</td>
<td>12.2</td>
<td>20.49</td>
<td>22</td>
<td>0.27</td>
<td>0.40</td>
<td>0.5</td>
</tr>
</tbody>
</table>
Table 6.4: Results of physiological outcome measures according to ventilator modes.

<table>
<thead>
<tr>
<th>Patient</th>
<th>PTPdi (cmH₂O.s/min)</th>
<th>TAA angle (Degrees)</th>
<th>Piₘₐₓ (cmH₂O)</th>
<th>Active exhalation events (%)</th>
<th>Untriggered efforts (%)</th>
<th>Time delay (secs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PAV</td>
<td>ACV</td>
<td>PAV</td>
<td>ACV</td>
<td>PAV</td>
<td>ACV</td>
</tr>
<tr>
<td>A</td>
<td>205</td>
<td>212</td>
<td>7.6</td>
<td>3.6</td>
<td>19</td>
<td>23</td>
</tr>
<tr>
<td>B</td>
<td>184</td>
<td>234</td>
<td>3.7</td>
<td>5.8</td>
<td>37</td>
<td>26</td>
</tr>
<tr>
<td>C</td>
<td>398</td>
<td>361</td>
<td>34.6</td>
<td>33.1</td>
<td>43</td>
<td>34</td>
</tr>
</tbody>
</table>

Table 6.5: Tidal breathing parameters. *Total rate = supported + unsupported breaths.

<table>
<thead>
<tr>
<th>Tidal volume (ml)</th>
<th>Total Rate (bpm)</th>
<th>Total minute ventilation (L/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>PAV</td>
<td>ACV</td>
</tr>
<tr>
<td>A</td>
<td>6.8</td>
<td>8.4</td>
</tr>
<tr>
<td>B</td>
<td>8.3</td>
<td>8.1</td>
</tr>
<tr>
<td>C</td>
<td>28.0</td>
<td>23.2</td>
</tr>
</tbody>
</table>
**Figure 6.11**: Trace during ACV, showing active exhalation during inflation 1 resulting in zero flow and tidal volume.

6.6 Discussion

6.6.1 *In vitro* study

The results of the *in vitro* study showed that, during PAV using dynamic lung models, unloading did reduce the inspiratory load, but there were discrepancies between the theoretical and actual delivery of PAV. During PAV, it has been assumed that the airway pressure and Ppl wave forms would be similar, but this was found not to be the case during elastic unloading. It is also assumed that there would be no delay between the onset of the Ppl change and the onset of increase in airway pressure, but a delay of 100 ms for elastic unloading and 60 ms for resistive unloading was demonstrated. The consequent effect of the delay is that during elastic unloading, no support would be provided for up to 33% of the infant’s inspiratory effort assuming this to be 0.3s in duration.\(^{251}\) It has been demonstrated that the longer the ‘trigger’ delay the greater the
increase in the work of breathing; this is undesirable as an increased work of breathing can lead to muscle fatigue and has been associated with failed extubation in prematurely born infants. In adults, there has been an additional anxiety that a long delay will prolong inspiration into expiration. This is of particular concern in infants, in whom extension of inflation into expiration during conventional ventilation provokes active expiration, which is a cause of pneumothorax. In the *in vitro* study, inflation was not demonstrated to extend into expiration, but it would be important to assess this *in vivo*. The delivered pressures, during both elastic and resistive unloading, were greater than expected, but the deviations were relatively small.

Oscillations in the airway pressure wave form have previously been reported when resistive unloading levels were set above that needed to reduce the resistance to normal. The data currently reported highlight that practitioners need to be aware oscillations may also occur during elastic unloading. The oscillations occurred with an elastic unloading level of 1.5 cm H₂O/ml in the high resistance model B and 0.5 cm H₂O/ml in the low resistance model A. These oscillations are due to auto-triggering and were reduced or eliminated by decreasing the trigger sensitivity. This explains why higher levels of unloading can be achieved before oscillations develop when the airways resistance is high and the response therefore damped. Reducing the trigger sensitivity, however, may lead to non-triggered breaths and increase in trigger delay, thus trigger delay was studied in the *in vivo* pilot study.

The excessive high inflation pressures seen with full elastic unloading in model B were associated with short inspiratory times (figure 6.7) and appear to be due to the design of the ventilator. If, however, the lung model had an inertance which was significantly higher than that of the neonatal lung, this would alter the pressure wave form. Inertance, however, is directly related to mass and as the lung model was lighter than
the lungs of an infant with RDS, any inertial effect would be lower rather than greater than in the clinical situation. In addition, there was no delay between the onset in the fall of the Ppl and the onset of airflow.

A strength of the in vitro study was the successful assessment of the function of the ventilator in different mechanical situations mimicking common neonatal respiratory disorders and with a wide range of elastic and resistive unloading. The study demonstrated that the efficacy of unloading depended on the mechanical characteristics of the lung model. Elastic unloading produced a proportional reduction in load in model A, which had a high elastic and low resistive load, but was less effective in models B, C, D and E, where the resistive load was high. In models B to E resistive unloading produced appropriate inspiratory pressures to compensate for the resistive load.

The selection of the most appropriate unloading settings in clinical practice has been a problem and though various methods have been proposed, as discussed at section 1.9.2.3, many are not ideal. Resistance of the ETT is dependent on the size of tube used, but factoring purely for this may underestimate the respiratory system resistance of an infant with BPD. The level of elastic unloading has been determined by the effect on the oesophageal pressure per unit inspiratory volume. Oesophageal manometry, however, is invasive and the accuracy of this measurement may be questionable in the presence of chest wall distortion. Increasing elastic unloading gain has been shown to reduce chest wall distortion in preterm infants as assessed by respiratory inductive plethysmography. It has, therefore, been suggested that an alternative method for setting the level of unloading would be to observe the patient on continuous positive airway pressure (CPAP). The elastic unloading would then be gradually increased until the chest wall deformity reduced and breathing became
Such criteria, however, are subjective and infants may not tolerate significant periods on CPAP. These results highlight the importance of factoring in the degree of compliance and resistive abnormalities of the infant if the appropriate level of unloading is to be set.

6.6.2 In vivo study

Data from the three patients showed that it might feasible to utilise the compliance and resistance data from the Stephanie® neonatal ventilator as displayed when in a conventional mode to inform unloading settings in infants with chronic lung disease for a future larger crossover study. A statistical comparison of PTPdi and TAA data were not performed due to the small number of patients recruited in the time frame.

The problems of translating a bench study to the clinical arena related to complications of ventilation and the non-uniform nature of patients and disease. The frequent desaturations during PAV may have been due to secretions and potential partial obstruction of the endotracheal tube. During PAV the delivered airway pressure is dependent on the instantaneous generated flow and tidal volume of the patient. In the circumstance of a partially blocked endotracheal tube, detected flow at the level of the pneumotachograph may be low despite increased infant effort to overcome the blockage. However, the lower pressure generation due to a ‘detected’ low effort may result in a clinical deterioration. In such a case the apnoea backup inflations may not engage as infant effort could continue with a perceived low flow generation and without an apnoea of >5 seconds. A low tidal volume alarm could be set to a minimum specified expired tidal volume to alert medical staff to insufficient efforts or blocked tubes. Alternatively the ‘minimal volume guarantee’ function, a new option from 2006 on the Stephanie®, could be utilised. When engaged if tidal volumes fall below the set value the ventilation pressure for each subsequent breath is increased above the PAV.
generated pressure until tidal volume is achieved. Volume safety options were not explored in the current study.

The trigger delay seen during the dynamic lung model studies was up to 100ms. Whilst for all three patients the trigger delay was shorter during PAV (calculated from an average over 250 breaths per epoch), no conclusions can be drawn from this pilot. However, the mechanism by which a shorter trigger delay may be delivered is not clear. One hypothesis may be that PAV results in less cycle off (or expiration) asynchrony, leading to less extension of inflation into expiration, hence the infant is immediately free to trigger the ventilator with the next effort. The use of ventilator calculated respiratory mechanics to ascertain baseline unloading gain/values proved successful in these three patients. Settings of unloading must be less than the total respiratory system resistance or elastance in order to avoid runaway phenomena. The use of a peak pressure set 5 cmH₂O above the ACV PIP and unloading settings less than total load prevented the abnormal runaway pressures previously seen.

6.6.3 Conclusions
In conclusion, on in vitro assessment PAV provided by the Stephanie® neonatal ventilator delivered pressures in excess of those expected, had airway pressure wave forms which deviate from the Ppl wave forms and had a delay in pressure delivery of up to 100 ms. It did, however, provide appropriate levels of elastic and resistive unloading. Data obtained from the pilot study further highlights the need for adaptive backup systems and the use of the minimum volume alarm or minimum volume guarantee function. However, the pilot data does show that it is feasible to utilise the ventilator calculated values of compliance and resistance to set unloading, therefore be larger studies of PAV can be undertaken using this method.
Chapter 7: Relationship of PTPdi to gestational age and birthweight
7.1 Introduction

Assessment of work of breathing (WOB) has been used in both the paediatric and neonatal population in the intensive care setting to compare the efficacy of the support provided by both invasive and non-invasive forms of ventilation. One method of assessing work of breathing is to measure the pressure time product of the diaphragm (PTPdi). Prematurely born infants may have poorly developed respiratory muscles which may adversely influence their ability to increase their work of breathing in response to an increased load. The diaphragm changes structurally with development and therefore may result in higher PTPdi with maturity at birth and postnatal age. Birthweight and resultant increased muscle mass may also impact on the force generation capacity of the diaphragm and therefore ability to increase work of breathing. Thus, the aim of this study was to determine if maturity at birth or postnatally and birthweight affected the work of breathing as assessed by measurement of the diaphragm pressure time product (PTPdi).

7.2 Methods

The results of infants who had been recruited for short term ventilation studies, described in chapters 3 and 4, who had PTPdi measurements performed during a baseline period on a pressure limited mode were analyzed. The results of PTPdi over 20 consecutive breaths from infants were assessed on time cycled, pressure limited ventilation using SLE 5000 ventilators were used. The studies were approved by the King’s College Hospital Research Ethics Committee and parents gave informed written consent for their infants to take part in the studies.
7.2.1 Patients
Patients that had been recruited for the acute respiratory distress study or the weaning crossover study was eligible for the study. For infants who had been recruited into both studies, data from the acute respiratory distress study only were used, this being the first set of measurements for that infant. Data were analysed from 23 infants who had been recruited to the acute respiratory distress study including five infants who had measurements undertaken later than 48 hours after birth. Twenty patients were recruited to the weaning study, of which ten infants had been recruited to both studies; hence weaning study data from those ten infants were not included giving a total of thirty three infants included in this analysis.

7.2.2 Analysis
Data were tested for normality using the Kolmogorov-Smirnov test and were found to be normally distributed. The relationships between PTPdi and gestational age at birth (GA), postmenstrual age at measurement (PMA), postnatal age at measurement (PNA) and birthweight were examined using linear regression analysis. Forward entry multiple regression analysis was used to determine which factors independently related to PTPdi results.

7.3 Results
7.3.1 Demographics
Thirty three infants (17 male, 16 female) whose results were included in this analysis had a median (range) GA of 29 (24 to 38) weeks, PMA of 29 (24 - 40) weeks, birthweight of 1.42 (0.61-3.8) kilograms and PNA of 2 (1-14) days. Six infants were receiving caffeine and seventeen infants were receiving morphine. Four infants were supported by ACV, ten with IPPV and the remaining 19 infants supported by SIMV.
One infant was fully enterally fed, ten were receiving parenteral nutrition and the remaining 22 were receiving dextrose intravenously at the time of measurement.

7.3.2 Regression analysis

A significant positive correlation was found between PTPdi and GA at birth \((r = 0.624\) and \(p < 0.001\)) (figure 7.1) and also PMA at measurement \((r = 0.621\) and \(p < 0.001\)). Exclusion of the outlier did not alter the significance of the results. There were also positive correlations with birthweight \((r = 0.47\) and \(p = 0.003\)), PNA \((r = 0.308, p = 0.042\)) and the administration of morphine \((r_{k-b}=-0.4, p=0.03\)). Caffeine was not found to have a significant correlation with PTPdi. When the predictor variables were modelled together, only birthweight and birth GA remained significant. Removing each variable in a stepwise fashion until all remaining variables remained significant resulted in a model in which birthweight was no longer a significant independent predictor. The final model resulted in GA alone as an independent predictor of PTPdi with coefficient \((B) = 26, p = 0.001\).
Figure 7.1: Correlation between GA at birth and PTPdi in 33 infants.
7.4 Discussion

The results demonstrate that maturity at birth affects infant work of breathing as assessed by PTPdi. Those results are consistent with gestational age being correlated with crying maximal transdiaphragmatic pressure (cPdi_max), as a measure of diaphragmatic strength, in term and preterm infants. In that study, the positive correlation of cPdi_max and GA were shown to be specifically related to changes in changes in Pes but not Pgas and was therefore ascribed to maturational influences on chest wall compliance. Caffeine has been shown to affect diaphragm contractility and inspiratory muscle strength in premature infants. Only six of the infants in the cohort were receiving caffeine at the time of measurement and as such were unlikely to have affected the overall trend.

The increased force generation capacity of the diaphragm and ability to increase work of breathing in response to a stimulus may be related to structural changes that occur with development. Watcho et al, determined that, in piglets, Pdi on phrenic nerve stimulation increased with diaphragm body weight. This may be related to muscle fibre cross sectional area increasing with body growth. Keens et al, demonstrated that the human neonatal diaphragm has fewer high oxidative fibres than the adult which may render the infant prone to fatigue. Fatigue of the neonatal diaphragm has not been consistently demonstrated in studies, however infants do have a lower proportion of fatigue resistant type 1 fibres which gradually increases during postnatal development. Thus more mature infants may have a greater capacity for sustained increased work of breathing in comparison to less mature infants.

The lack of correlation between PTPdi and PNA may be explained by either growth arrest of the diaphragm and/or ventilation related diaphragmatic muscle atrophy. A
study of prematurely delivered baboons showed persistent growth arrest of the diaphragm even at ten days following premature delivery. All the infants currently studied had been ventilated since birth, and diaphragm muscle atrophy may occur as early as eighteen hours after commencing mechanical ventilation. The impact on nutritional status and potential resultant decreased diaphragmatic force generation due to lack of growth may also have contributed to the lack of correlation with PNA. Growth and weight gain were not assessed in this study.

In conclusion the significant correlation of gestational age at birth and PTPdi suggests that when using PTPdi to assess work of breathing, gestational age should be considered when comparing the results of interventions.
Chapter 8: Discussion
8.1 Summary of results and current literature

8.1.1 Volume ventilation

In *chapter 3*, it was reported that prematurely born infants with acute respiratory distress when ventilated with targeted tidal volume of four ml/kg had a significantly higher PTPdi than when ventilated on a baseline mode without a tidal volume target (VT) or at a target level of 6ml/kg. At a targeted volume of four ml/kg the PIP decreased though the minute volumes were similar when compared to no VT or a VT of 6 ml/kg, due to an increase in the spontaneous respiratory rate of the infant which likely accounted for the increased WOB. These findings are supported by other evidence in the literature that a low level of VT will result in an increased work of breathing. A tidal volume of 4ml/kg was shown to significantly increase work of breathing in comparison to 6ml/kg and baseline pressure limited ventilation in premature infants weaning from the ventilator as well as specific cohort of near term and term infants. Indeed, in the term and near term cohort with a VT of 4ml/kg ventilator pressure support was reduced to PEEP such that the produced tidal volume was a result of spontaneous effort only.

A European survey undertaken between 2007 and 2008 found that only 11% of the 73 units included used a volume strategy when ventilating neonates, despite the findings of the 2005 Cochrane review which reported that the duration of ventilation was found to be shorter on VTV than pressure limited ventilation. With additional evidence from later literature supporting the avoidance of very low (≤ 4.5ml/kg) tidal volumes and the findings of the more recent Cochrane review, volume targeted ventilation may be a more attractive proposition. The most recent Cochrane review of VTV, included meta-analysis of nine RCTs and three crossover studies. Despite initial intentions, the authors were unable to separate out the different VTV modes due to a high heterogeneity of different ventilators used. Nevertheless, the
relative risk (RR) of the combined outcome of BPD or death was 0.73 (95% confidence interval (CI) of 0.5-0.93) and the number needed to treat (NNT) was 8. Days of ventilation were also lower for those ventilated with volume targeting (MD -2.36 (95% CI -3.1 to -0.8). There, however, remains a concern that not all volume targeted ventilation has the same effect. For example, in one study, infants ventilated with PRVC had an increase in the duration of ventilation and no reduction in the rates of BPD. The differences in control and cycling characteristics of the various ventilators and specific volume modes available are likely to result in subtle clinical and physiological variances in for example mean and peak airway pressures affecting oxygenation, inspiratory time, waveform and potentially alveolar recruitment. As a result a particular form of VTV may engender a different outcome within a study than another form. It therefore remains to be elucidated as to whether any particular type of volume targeting is more beneficial. Within the meta-analysis there was also variation of targeted volumes used in the studies included; for example, Herrera et al, used a fixed VG of 4.5ml, Polimeni et al, used two different VG levels of 4.5 and 6ml/kg, others used a fixed VG of 5ml/kg and some used targets that extended their upper limit to 8ml/kg or above. Different tidal volumes may be needed at different stages of disease or with evolving chronic lung disease. An Australian study underway is recruiting infants less than 30 weeks of gestation and will compare a moderate targeted volume of 5ml/kg to IPPV as delivery room interventions in those requiring respiratory support and intubation. An observational study of infants <800g reported that mild permissive hypercapnia was maintained with 5ml/kg, but that tidal volumes required to achieve acceptable carbon dioxide levels increased over the first three weeks. The gradual increase in the VT level was attributed to complications of positive pressure ventilation with the evolution of increased alveolar dead space associated with chronic lung disease.
Targeting a tidal volume at the expiratory limb and therefore treating the lungs as a single compartment, however, may not be a complete solution to avoiding volutrauma, as in the diseased lung of prematurely born infant, tidal ventilation shows regional variation. Electrical impedance tomography (EIT) assessed in a cohort of 27 stable VT ventilated premature infants less than 32 weeks gestation ventilation was found to be greatest in the middle third of the chest. Where lung disease is non-homogeneous, regional variation in lung mechanics may result in local volutrauma and thus VILI.

Studies of ventilated animal models and adult patients would support the notion that providing a targeted minute volume (with avoidance of excessive injurious tidal volumes) and thereby allowing a variation in tidal volume will provide adequate support in a more physiological manner than a ‘fixed’ VT. In a crossover study of 14 intensive care patients being weaned from mechanical ventilation, the effect of additional dead space was assessed when ventilated by a volume targeted mode, PSV and an adaptive support minute ventilation mode (ASV). In ASV, the minute ventilation was controlled by a respiratory rate-VT combination with adjustments based on breath by breath respiratory mechanics assessment. When dead space was added, and patient effort increased due to increased ventilatory demand, the ASV and PSV modes provided increased pressure support in contrast to the VTV mode where decreased inspiratory pressure support resulted. Therefore, during VT the patient contribution was greater than in the other two modes when inspiratory load was added; this may be detrimental in the long term. In an experimental animal study using the Dräger Babylog® interfaced with a computer, six juvenile rabbits were ventilated with SIMV, VT, target minute ventilation ($V'_E$) and combined VT+$V'_E$. The combined VT+$V'_E$ mode attenuated the increased PaCO$_2$ in comparison to the other modes when apnoea with reduced compliance and lung volume was induced. The use of
mandatory minute ventilation has been studied in near term infants,\textsuperscript{272} but the combined VT+$V'_E$ mode has not yet been fully evaluated in premature infants in comparison to a VT mode.

8.1.2 Pressure support ventilation

In chapter 4, results of 20 newborn infants that were being weaned from ventilation demonstrated that when supported with PS at 50\% in addition to SIMV as compared to SIMV alone that their PTPdi was significantly lower, by 20\% with a corresponding lower total respiratory rate. Those results suggest that the mechanism of the shorter duration of ventilation in the randomised trial by Reyes \textit{et al.}\textsuperscript{6} for infants ventilated on PS with SIMV as opposed to SIMV alone was related to decreased work of breathing.

\textit{Chapter five} reported the results of a randomised trial of PSV and ACV in newborn infants being weaned from the ventilator. No significant differences were demonstrated in the duration of weaning, the results of physiological assessments or in episodes of active exhalation. The similarity of the inflation times may explain the lack of differences seen. Thille \textit{et al.}\textsuperscript{273} reported in consecutive adult intensive care patients a higher incidence of asynchrony, as assessed by both inspiratory and expiratory events, for patients supported by ACV rather than PSV (p=0.04).\textsuperscript{273} They also reported that a high incidence of asynchrony, was associated with a longer duration of mechanical ventilation (7.5 days IQR 3-20 versus 25.5 days IQR 9.5-42.5).\textsuperscript{273} The authors’ hypothesis for this result was that in patients with asynchrony there may be wasted diaphragmatic energy expenditure which may promote injurious diaphragmatic patterns and lead to a deleterious effect on weaning.\textsuperscript{273} The RCT in chapter 5 reported only active exhalation, (expiratory asynchrony event) it is therefore conceivable that assessment of other asynchrony events may have yielded differences between the two
modes, though this seems unlikely in view of the similar inflation times of the two modes within the study.

In the studies reported in chapters 4 and 5, termination sensitivities between 5 and 10% were used in the majority of infants. This potentially resulted in higher expiratory asynchrony than if higher termination sensitivities were used;\textsuperscript{162} but the termination sensitivities were manipulated to specifically avoid too low inflation times. Evidence suggests that the ideal termination sensitivity, at least in adult patients, is dependent on the disease process itself.\textsuperscript{165, 243} In patients recovering from acute lung injury, i.e. those with a reduced compliance and a low resistance (thus a short time constant) lower termination sensitivities of 1 and 5% resulted in a lower respiratory rate, higher tidal volume and reduced work of breathing with the same level of pressure support as compared to a termination sensitivity of 40 to 45%.\textsuperscript{165, 243} Conversely in patients with obstructive disease, i.e. a high resistance and increased time constant, it has been suggested that a higher termination sensitivity may be more beneficial.\textsuperscript{274} The patients within the studies reported in chapters 4 and 5 of this thesis were recovering from acute lung disease and more likely to have a lower resistance. For infants with evolving chronic lung disease i.e. a condition with high resistance, termination sensitivities may need to be higher to compensate for the long time constant.

\subsection*{8.1.3 Proportional assist ventilation}

In chapter 6, dynamic lung models were successfully devised and utilised to examine the effects of PAV. The results demonstrated that unloading during PAV reduced inspiratory load, but that there were discrepancies between the theoretical and actual delivery of inspiratory pressure. Airway pressure waveforms were shown to be different from Ppl waveforms and a delay in pressure delivery of 100ms was also
demonstrated. Oscillations were seen in the *in vitro* study, but to a lesser extent when higher resistances were present.

Results presented from a pilot crossover study established the feasibility of using the displayed compliance and resistance data from the Stephanie® neonatal ventilator to inform unloading settings in infants with evolving BPD. The results also highlighted the need for adaptive backup systems to prevent desaturations. The use of adaptive backup systems have been previously described,\textsuperscript{172-173} early studies demonstrated desaturations during PAV were longer in duration than during ACV.\textsuperscript{172}

No recent studies examining PAV in premature infants have been published. An inherent problem of the use of PAV is the need for reliable neuromuscular coupling. Ventilation designed to improve patient-ventilator ‘interaction’ of which PAV is an example, has continued to evolve. These modes aim to increase ventilatory support in response to increased work of breathing or effort. Neurally adjusted ventilatory assist (NAVA), utilises the diaphragmatic electrical activity (EAdi) to trigger both the initiation and the termination of inflation. This therefore allows a bypass of inherent trigger delays in a pneumatic circuit. Additionally, the pressure support delivered is coupled with the magnitude of the EAdi. The EAdi is measured using a nasogastric EMG catheter. In the neonatal population this mode has been compared in a number of crossover trials to date with promising results compared to modes such as PSV and ACV.\textsuperscript{275-278} Data from these studies suggest an improved patient ventilator synchrony,\textsuperscript{275,277} lower peak pressures\textsuperscript{278} with a lower work of breathing.\textsuperscript{276} 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 ventilator support regardless of leak around the endotracheal tube.\textsuperscript{279}
8.1.4 PTPdi

The data in chapter 7 demonstrated that maturity at birth correlates with PTPdi. This result is biologically plausible with evidence from animal models that structural changes occur with development and maturity.\textsuperscript{129, 255, 258} Lavin et al,\textsuperscript{280} examined developmental changes in contractile function of the costal diaphragm of prematurely born lambs. Fetal development was characterised by an increase in maximum force generation; postnatal development was characterised by a reduced susceptibility to fatigue.\textsuperscript{280}

8.2 Strengths and weaknesses of the studies

8.2.1 Recruitment and study population

A strength of the studies in this thesis was the assessment of each ventilation mode in patients most likely to benefit. Thus, three different groups of infant were studied: those with acute respiratory distress; those during weaning and those with evolving chronic lung disease, acknowledging that no one form of ventilation may suit all infants at all times.

Infants enrolled in the SIMV versus PS with SIMV study were of a mixed gestational range; the majority (80\%) were less than 34 weeks gestation. A sub-analysis of term compared to premature infants was not feasible. This may have been able to demonstrate whether more mature (near term/term) infants respond similarly to the different support provided by the addition PSV. However, the wide gestational range was chosen specifically in order to be able to generalise results to the whole inpatient groups of other neonatal units.

8.2.2 Study protocols

A possible limitation of the VTV study may be perceived to be the short epochs (20 minutes) of targeted tidal volume. A longer period of each VTV may have allowed
further adaption and consequently changes in arterial blood carbon dioxide tension may have been detected. Nevertheless, significant changes in the WOB were demonstrated.

There was heterogeneity in the baseline ventilator modes with the VTV study with two infants receiving ACV, two SIMV and the remainder CMV. Despite this, overall low VT was associated with significantly worse WOB. In a previous study, infants weaning from the mechanical ventilator where ten infants were supported with SIMV and ten with ACV, a VT of 4ml/kg resulted in an increased PTPdi in comparison to both 6ml/kg and the baseline mode without volume targeting. The study was not powered to reflect whether a difference could be demonstrated between 4ml/kg during SIMV as compared to ACV.

Adjustment of the pressure support termination sensitivity in the RCT resulted in very similar inflation times for those supported by PSV and ACV. The similar inflation times may account for the lack of differences seen between the modes. The option of altering the termination sensitivity is not available on all ventilators and for example is set at 15% on all Dräger Babylog® machines. Use of a set termination sensitivity may have resulted in differences being demonstrated, very short inspiratory times, however, have adverse effects and thus it was deemed necessary to alter the termination sensitivity to avoid inspiratory times of less than 0.2 seconds.

A backup ventilator rate of 30 breaths per minute (bpm) has been shown to result in 85% of all inflations being triggered as opposed to 75% when back up rate is set at 40 bpm (p <0.01) without effecting carbon dioxide clearance. In the RCT of ACV and PSV, the minimum backup rate employed was 40 bpm in both arms of the study. This
may have resulted in a lower proportion of triggered inflations associated with asynchrony; however this would be applicable to both arms of the study.

8.2.3 Physiological measurements

All *in vivo* studies within the thesis utilised PTPdi as a measure of WOB. PTPdi reflects the energy expenditure of the diaphragm during both isometric and non-isometric contractions. Crucially, the PTPdi of spontaneous inspiratory efforts not supported by ventilator inflations can also be calculated in order to assess the total WOB. The relationship of the oxygen cost of breathing and the inspiratory PTP is linear when mean inspiratory flow is constant and thus reflects energy expenditure and has been shown to increase with increasing mean inspiratory flow. Therefore the use of PTPdi as a measure of work of breathing is a strength of the studies. A single measurement of PTPdi, however, is difficult to interpret, and may need to contextualised with muscle strength and endurance. As such infants in the RCT of ACV and PSV had measurements of TTdi taken pre-extubation as a comparator.

8.2.4 *In vitro* study

Dynamic lung models were designed to simulate various compliance resistance states of the lungs. A rubber film was inserted and manually retracted to simulate diaphragmatic movement and infant effort. This resulted in variation of ‘efforts’ and depth of a simulated breath. Pleural pressure waveforms were therefore not uniform or identical to each other. The use of an automated or mechanical device to retract the diaphragm could have provided uniformity and allowed shaping of the waveform. A positive aspect of the approach employed was the variation in efforts and volumes produced more closely reflect the nature of breathing *in vivo*.
8.3 Clinical implications

1. Low tidal volumes of 4ml/kg significantly increased the WOB and this may be detrimental if sustained at this level over a long time period. Thus in infants with acute respiratory distress where ventilation is required to provide full support whilst allowing recovery, weaning a VT to 4ml/kg may not be appropriate.

2. A mode of ventilation that supports all breaths rather than a preset number will result in a lower work of breathing. The decreased work of breathing is a consequence of lower spontaneous respiratory rate where minute volumes are preserved by additional ventilator support. Thus using the combined PS with SIMV mode during weaning and decreasing the pressure support level may allow a more gradual weaning allowing an infant to regain inspiratory muscle strength and therefore reducing likelihood of extubation failure.

3. When ensuring adequate inflation times of greater than 0.2s are delivered, modes of ventilation supporting all breaths equally are similar in their efficacy.

4. PTPdi results are influenced by the infants’ gestational age at birth. This measurement is therefore a useful indicator of changes in WOB for an individual but may be less useful as a direct comparison between, non gestational age matched patients or as a stand-alone measurement.

5. Initial PAV settings can be informed by the compliance and resistance data displayed when in a time cycled mode. A delay of 100 ms for elastic unloading was demonstrated, this may result in no support being provided for up to 33% of the infant’s inspiratory effort, which could possibly both increase work of breathing and result in extension of inflation into expiration.
8.4 Future directions

Prevention of premature birth remains a key focus in perinatal research. However, at present respiratory failure and the need for respiratory support of the neonate remains common. The focus of ventilatory based research will continue to be on reducing damage and improving synchronicity. A greater focus on physiology and interactions is likely to be possible with more sophisticated monitoring such as electrical impedance tomography and more accurate end tidal CO$_2$ monitoring. Whilst non-invasive respiratory support techniques such as CPAP and high flow humidified nasal cannulae oxygen (HHNC) are popular, non-invasive ventilation has been limited by inefficient triggering systems until recently. The advent of small neonatal EMG probes may allow this development to be more successful.

8.5 Future studies

8.5.1 Acute respiratory distress
A study comparing the different types of VTV would help to inform a randomised controlled trial of time cycled pressure limited ventilation versus volume targeted ventilation. Ideally a future trial would employ a volume target of not less than 5ml/kg. When comparing the two modes obtaining tracheal aspirate samples for analysis of inflammatory cytokine concentrations in the first week may yield information about any differences of the modes on ventilator induced lung injury.

8.5.2 Weaning
Providing support to all infant breaths reduces the work of breathing. A comparison of PS with SIMV and ACV on the duration of ventilation and successful extubation may be warranted. Weaning in ACV with an infant who is triggering above the backup rate can only be achieved by decreasing the inflation pressure, but by doing so the tidal volume
may be compromised. However, during PS with SIMV decreasing pressure support on the additional PS breaths and maintaining adequate tidal volumes on the SIMV breaths may allow the shift in effort to the patient without either compromising tidal volumes or extubating precipitately.

8.5.3 Chronic disease
In infants with evolving or established chronic lung disease, the use of PAV needs further evaluation. Work from the research group is underway to examine the effects of elastic unloading in infants with evolving BPD. The findings from the study, if positive, may prompt a randomised trial, to evaluate if any benefit is appreciable in the long term before the routine use of the modality.

New adaptive modes of ventilation such as NAVA and adaptive support minute ventilation have yet to be fully tested in the neonate. With the advent of EMG probes suitable for the neonate and the evolution of neonatal ventilators incorporating these algorithms in the last two years these studies are now feasible.

8.5.4 Physiological measurements
Measurements such as TTdi and TTmus have been shown to predict successful extubation in paediatric patients. Initial data from twenty neonatal patients would suggest a similar sensitivity and specificity for neonatal patients. That data however were from a very heterogeneous population with a time of measurement of up to six hours before extubation. More extensive, immediately pre-extubation data collected in specific populations, for example, infants <30 weeks gestation may yield more meaningful data. The invasive nature of the TTdi measurement due to the need for an oesophageal probe does not lend itself to routine use; measurement of the non-
invasive TTmus however, may be useful and has the advantage of reflecting the function of all the inspiratory muscles not just the diaphragm.

8.6 Conclusions

The studies have shown that low levels of volume targeting even within the deemed ‘physiological’ range will significantly increase work of breathing, additional spontaneous effort supported by PSV when ventilated with SIMV will decrease work of breathing and that PSV and ACV are equally efficacious in the weaning phase. A delay in pressure delivery of up to 100 ms was demonstrated with PAV. In addition, utilising the ventilator calculated compliance and resistance values to inform unloading settings in a neonate is feasible, though further investigation is required in vivo to test the efficacy of PAV.
References


259. Maxwell LC, Kuehl TJ, McCarter RJM, Robotham JL. Regional distribution of fiber types in developing baboon diaphragm muscles. The Anatomical Record 1989;224:66-78.


279. Kacmarek RM. Proportional assist ventilation and neurally adjusted ventilatory assist. Respir Care 2011;56:140-8; discussion 9-52.


Appendices
### A.1 Control and cycling characteristics of common neonatal modalities

<table>
<thead>
<tr>
<th>MODE</th>
<th>Control</th>
<th>Trigger</th>
<th>Limit</th>
<th>Cycle</th>
<th>Notes</th>
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<tr>
<td>PC-IMV</td>
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<td>Time</td>
<td>Pressure</td>
<td>Time</td>
<td>IPPV in this thesis</td>
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<td>Flow* or pressure</td>
<td>Pressure</td>
<td>Time</td>
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<td></td>
<td>(time for mandatory breath)</td>
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<td></td>
<td>(SIPPV - Dräger/PTV - SLE 5000) (*)</td>
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<td>Pressure</td>
<td>Time</td>
<td>SIMV in this thesis</td>
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<tr>
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<td>(time for mandatory breath)</td>
<td></td>
<td></td>
<td>Limited number of supported breaths</td>
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The characteristics of the volume targeted modes are discussed in the relevant sections of chapter 1 as is the concept of proportional assist ventilation.
A.2 Linearity of compliance of lung models

Each model was assessed for linearity of compliance at a range of inflation pressures appropriate for use in a newborn infant. Results showed that each model had a linear relationship of change in volume related to change in pressure with an R squared of 0.99 for each lung model (figures A.1 to A.4).

**Figure A1:** Compliance of Type 1 lung model.
Figure A2: Compliance of Type 2 model set at ‘compliance 2’ level.

\[ y = 1.6x + 17.233 \]
\[ R^2 = 0.9907 \]

Figure A3: Compliance of Type 2 model set at ‘compliance 3’ level.

\[ y = 2.8x + 11.9 \]
\[ R^2 = 0.9895 \]
Figure A4: Compliance of Type 2 model set at 'compliance 5' level.
A.3 Comparison of two Stephanie® ventilators

The two Stephanie ventilators gave results within 10% of one another as assessed during resistive unloading on models B and C (figure A5 and A6) and elastic unloading with model C (figure A7).

**Figure A5:** Observed and expected inflation pressure using Model B on two different Stephanie ventilators (machine 1 and machine 2) during resistive unloading.
Figure A6: Observed and expected inflation pressure using Model C on two different Stephanie ventilators (machine 1 and machine 2) during resistive unloading.
**Figure A7:** Observed and expected inflation pressure using Model C on two different Stephanie ventilators (machine 1 and machine 2) during elastic unloading.
A.4 Publications

URLs for the publications produced associated with this thesis are detailed below:

1. http://adc.bmj.com/content/94/6/434.full.pdf+html


2. http://fn.bmj.com/content/95/5/F331.full.pdf+html


3. http://fn.bmj.com/content/95/6/F443.full.pdf+html


4. http://fn.bmj.com/content/96/4/F265.full.pdf+html


5. http://fn.bmj.com/content/97/6/F429.full.pdf+html