Pressure Support Ventilation or Synchronised Intermittent Mandatory Ventilation for weaning premature babies on mechanical ventilation: A multi centre randomised controlled trial.

A thesis submitted in partial fulfilment of the requirements for the degree of

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Abstract

Mechanical ventilation is life saving as a respiratory support for preterm infants with respiratory distress syndrome. There is good evidence now that any form of volume-targeted modality of mechanical ventilation is superior over pressure-targeted modality to reduce chronic lung disease and death. It is perceived by minimising the duration of mechanical ventilation would reduce the exposure to positive pressure breaths and thereby could reduce long term morbidities such as chronic lung disease.

An area of lacunae is defining what is weaning on mechanical ventilation. Whilst most clinicians will agree when to commence mechanical ventilation there is paucity of consensus on when to commence weaning on mechanical ventilation and the best way for weaning to prevent extubation failure.

Pressure support ventilation (PSV) is pressure-targeted modality of ventilation designed to support spontaneous breathing. It was designed as a weaning mode to facilitate extubation. Pure PSV has no back up rate. Currently, PSV is used in combination with other modes such as SIMV to provide some back up respiratory rate for the unreliable respiratory drive due to apnoea in preterm infants. However, there is inadequate understanding of the appropriate PSV level for weaning

preterm infants on mechanical ventilation. Clinicians routinely use 50%-70% of peak inflation pressures used prior to commencing the weaning mode.

Use of Pressure support ventilation (PSV) could be variable- with one extreme utilising minimal pressure to just overcome the tube resistance (PS_{min}) with the aim to prevent fatigue and avoid extubation failure. The other extreme is augmenting spontaneous breathing effort to provide a full tidal volume breath (PS_{max}). Features of flow triggering and flow cycling aid synchrony at inspiration and expiration and this allows greater autonomy to the infant to control all aspects of its breathing cycle. Addition of some PSV to aid spontaneous breaths has shown to reduce the duration of weaning.

A randomised controlled study was designed to compare duration of weaning using PS_{max} and SIMV. Infants less than 32 weeks gestation at birth with respiratory distress syndrome from surfactant deficiency were eligible to participate.

93 infants stratified in three groups based on their gestation at birth were randomised over 30-month period. Weaning was commenced in the randomised mode when infants reached a set priori of MAP<10 cm H_2O, FiO_2 <40% and had a reliable respiratory drive for at least 2 consecutive hours.

In the control arm (SIMV with PS_{min})– clinicians reduced the back up rate to wean. In the intervention arm (PS_{max} with ten SIMV breaths)- clinicians reduced the PSV_{max} to PSV_{min} for weaning. A minute ventilation test was performed to assess readiness to extubation when both arms reached PS_{min} with ten back up SIMV breaths.

Primary outcome for the study was duration of weaning on mechanical ventilation.

Our study suggests there is no difference between the two groups but there is a trend towards faster extubation in the PSV arm (the median time to extubate in the SIMV arm was 42 (95%CI, 28.23 to 55.76) hours and the median time to achieve the primary outcome in the PSV arm was 31 (95% CI, 12.59 to 49.40) hours). The survival distribution between the interventions was statistically not significant, Chi-square 0.768, p 0.381. This effect was more evident in bigger infants weighing at least 1500 grams.

There was no difference in the secondary outcomes between the two groups and common preterm morbidities were equally balanced. There were no adverse events during the study period to report.

Contrary to the general belief, infants are not disadvantaged by weaning on PSV_{max}. Clinical outcomes were comparable with the traditional SIMV method of weaning on mechanical ventilation.

Dedication

I dedicate this thesis to my parents who always instilled thirst for knowledge and enthused me with their hard work, to my wife Trupti who supported me patiently during my MD studentship and to my daughters Trisha and Tanisha who brought tremendous happiness during difficult times.

Acknowledgements

Declaration

I declare that no portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or institution of learning.

Prashant Moodabidri Mallya

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1 Introduction to Newborn Respiratory Physiology

Oxygenation in the newborn lungs is driven by the oxygen pressure gradient. Thus the lungs must be well expanded and perfused. Deficiencies in either, lead to imbalance in perfusion to ventilation efficiency and impair gas exchange. The expansion of lungs depends upon the stage of lung development and thus the limiting factor in premature infants.

1.1 Lung development

Phases of lung development (Agrons et al., 2005)

- Embryonic phase (3-6 weeks)

- Pseduoglandular phase (6-16 weeks)

- Acinar or Canalicular phase (16-26 weeks)

- Terminal sac phase (26-36 weeks)

- Alveolar phase (36 weeks- up to 5 years)

It is during the canalicular phase that type II cells capable of producing surfactant appear first. Towards the end of this stage primitive distal saccules (primitive alveoli) begin to form through a process known as primary septation. It is the primitive alveoli that help in maintaining gas exchange. With the development of pulmonary capillaries effective gas exchange is dependent upon the degree of acinus capillary coupling.

1.2 Mechanics of respiratory physiology

Inspiration- is an active energy-expending act. The diaphragm and the intercostal muscles expand the lungs through its insertion on the chest wall. Diaphragmatic contraction leads to an increase in the chest volume. This causes drop in the intra-pleural pressures and causes gas flow into the chest.

Expiration- is a passive state. The elastic recoil of the muscles and the high surface tension due to lack of surfactant in premature infant aid expiration. During tidal exhalation, abdominal muscles play little role in expiration.

Compliant chest wall leading to easy deformation, atelectasis at end expiration resulting into lower functional residual capacity provide little structural support for ventilation. The shape of the chest wall (more cylindrical) and the ribs insertion (more horizontal) lead to mechanical disadvantage of the inspiratory muscles not getting enough fulcrum to lift the chest when compared to the adults.

1.2.1 Compliance

Compliance is a measure of the change in the volume resulting from unit change in the pressure.

Compliance = Change in volume (ΔV)/ change in pressure (ΔP)

Compliance measured during active expiration is called as dynamic compliance. This reflects the elastic recoil of the lungs. This underestimates the static compliance especially in infants who are breathing rapidly.

The pressure volume loop (compliance curve) is sigmoidal. Hence at both the ends of the loops, the compliance is low, i.e. for the unit change in the pressure there is very limited change in the volume. The compliance curve also help in identifying the necessary residual distending pressure to establish an appropriate functional residual capacity (residual lung volume). Without this distending pressure, there is progressive atelectasis of the alveoli and cause atelectotrauma. The level of PEEP at which the static lung compliance is maximised is called the optimum PEEP.

1.2.2 Resistance

Resistance (R) could be differentiated into

a. Viscous resistance- by the tissues surrounding them
b. Airway resistance – by the moving molecules in the gas stream and between the respiratory system
c. Imposed resistance – from the ventilator circuit when the infant needs respiratory support

Resistance is defined as pressure gradient between two points to move the gas at a constant flow rate.

R= Pressure/ flow

1.2.3 Time constant

Time constant is the measure of how quickly the lungs inflate or deflate. This is directly related to the compliance of the respiratory system and the resistance of the airways system. Thus in a mathematical formula this is represented as

Kt=Compliance (CL) X Resistance (Raw)

where Kt represents expiratory time constant

CL =Lung compliance

Raw = Airway Resistance

One time constant is defined as the time it takes the alveoli to discharge 63% of the tidal volume. This is important when commencing mechanical ventilation to appropriately set expiratory time. Five time constants are required to exhale 99% of tidal volume in normal lung.

1.2.4 Work of breathing

Breathing requires expenditure of energy. This energy is required to overcome the elastic and the resistive forces. Thus work of breathing in a mathematical model is represented as

Pressure (force) X Volume (displacement)

The work of breathing can closely correlate to oxygen consumption. Mechanical ventilation reduces oxygen consumption by decreasing the pressure generated by the inspiratory muscles. Kanak & Roze have nicely elucidated this point in adults and in neonates respectively (Kanak et al., 1985), (Roze et al., 1997).

1.3 Treatment options

In the acute phase, the treatment option in a neonate with surfactant deficiency is surfactant replacement and supporting spontaneous breathing. Spontaneous breathing could be supported by:

   a. Non invasive respiratory support
   b. Mechanical ventilation

1.3.1 Non invasive respiratory support

Non invasive respiratory support could be provided by using a nasal interface (i.e. a nasal prong or mask) and keeping the mouth free to provide respiratory support for spontaenously breathing newborn. More

recently use of laryngeal masks that bypasses the need to intubate has also come into practice but the evidence so far is limited.

High surface tension from surfactant deficiency and a tendency to develop atelectasis from alveolar collapse increases risk of respiratory failure. It is well known, use of constant distending pressure from CPAP mitigated this problem and subsequent effort at breathing. CPAP also improved oxygenation and achieved better gas exchange by improved alveolar recruitment also known as 'open lung approach'. The clinical application being to mimick the normal physiologic reflex of grunting as seen in infants with respiratory distress. Grunting is expiratory braking against closed glottis and diaphragmatic contraction which limits the airflow during exhalation to help maintain end expiratory volume i.e. avaoid alveolar collapse.

Continuous distending pressure is applied throughout the breathing cycle. Since its successful application in infants with respiratory distress by gregory (Gregory GA, 1971) in 1970s CPAP delivery systems have undergone rapid transformation in its ability to deliver the set positive pressure, minimise work of breathing. Tremendous interest in the early years has also enhanced our understanding of pulmonary mechanics and fine tuned the CPAP delivery based on well designed research.

CPAP systems could be classified by the technique used to control gas flow.

1. Constant flow device such as Bubble CPAP and the older generation of ventilator CPAP.

Ventilator CPAP- This traditionally has been a constant flow device with flow rate set by the clinician. Advances in technology has added features of demand flow. Bubble CPAP is another example of constant flow and variable pressure device.

2. Variable Flow device are so called because they use fludic control to maintain CPAP. Fluidic Control mechanisms provides adequate inspiratory flow and maintain stable pressue (Bernoulli effect). The other adavantage of providing CPAP with this flow driver is satisfying patient demand by Coanda effect should patient demand more flow than that provided by the constant background flow. Expiration is easiier compared to constant flow system from 'fluidic flip' principle which reverses gas flow to the expiratory limb.

CPAP as a respiratory support could be provided early in the respiratory distress- termed as 'Prophylactic' or subsequently for post extubation care. The earlier approach of supplemental oxygen and 'rescue' CPAP for signs of respiratory distress is no longer favoured with good evidence suggesting reduced need for mechanical ventilation and surfactant with decreased incidence of BPD and death(Subramaniam,

2016). Post extubation, CPAP has shown to reduce the incidence of extubation failure and needing further mechanical ventilation (Davis, 2003).

1.3.2 Mechanical ventilation

Mechanical ventilation could be provided by either pressure-controlled modality or volume controlled modality. There is good evidence to suggest volume targeted ventilation in any form is superior to pressure targeted ventilation (Wheeler et al., 2010). Although there is emerging consensus to practice volume targeted ventilation, there is lack of agreement amongst clinicians of the best practice for weaning on mechanical ventilation. These issues and modes of mechanical ventilation would be highlighted in the subsequent chapters.

Along with mechanical ventilation come associated problems of ventilation- Ventilator induced lung injury (VILI). The etiology is multifactorial. Surfactant deficiency, premature antioxidant systems, premature lung structures and compliant chest wall are the qualities of premature lung that lead to VILI (Donn and Sinha, 2006).

Lung injury from mechanical ventilation could be attributed to:

a. Volutrauma – damage caused by overdistention
b. Barotrauma- caused by excessive pressure
c. Atelectotrauma- shearing forces that lead to continual opening and closing of the alveoli
d. Biotrauma- injury from infection and inflammation

e. Rheotrauma- injury from inappropriate airflow leading to turbulence, inefficient gas exchange and inadvertent positive end expiratory pressure leading to lung overdistention.

Lung protective strategies aims to mitigate these issues and minimise the damaging effects of these components. This could be use of patient triggered ventilation modes, volume targeted ventilation and use of pulmonary graphics to optimise ventilation.

Preventing VILI starts with use of antenatal steroids along with surfactant therapy.

Other contributing factors include preventing hypocapnia. Anecdotal report of use of CPAP and preventing hypocarbia led to lower incidence of chronic lung disease (Avery ME, 1987) was further supported in a retrospective multicentre cohort analysis of 235 infants of birth weight less than 1000 grams (Kraybill EN). They concluded hypocapnia in the first 48 hours was a predictor for developing chronic lung disease. Further evidence of hypocarbia and adverse neurodevelopmental outcome (Graziani LJ, 1992) led to permissive hypercarbia as a strategy for preventing chronic lung disease. However in a controlled study (Mariani G, 1999) suggested there is no evidence to support this approach.

2 Introduction to respiratory support in neonates

2.1 Non invasive respiratory support

Non-invasive respiratory support is a positive pressure delivery through a nasal interface. This could be CPAP or bi-level CPAP delivered either in synchronised or non-synchronised form. Most studies have investigated the use and benefits in post extubation state. The primary use of CPAP versus Bi-level CPAP in respiratory distress syndrome as primary mode of respiratory support is very limited. In a recent study of 120 infants born between 28-32 weeks gestation, choice of CPAP or SiPAP for respiratory distress from surfactant deficiency at birth did not show any significant difference in need for intubation and ventilation in the first 72 hours of life. There was no significant difference in the rates of pneumothorax or chronic lung disease (Wood FE, 2013).

 In another study (Lista et al., 2010) comparing Bi-level CPAP to CPAP, 40 newborn infants born between 28-34 weeks gestation were randomised to receive either form of respiratory form within 1 hour of life. A quarter of infants received surfactant in delivery suite. They investigated the clinical course, respiratory outcomes and markers of inflammation in the two groups. They concluded infants cared for in the bi level CPAP group required shorter duration of respiratory support and

shorter duration of oxygen requirement. There were no significant differences in other outcomes. The only limitation of this study was this included more mature infants (mean gestation 30 weeks in both the groups) and small cohort.

The other forms of non-invasive respiratory support include Humidified High Flow Nasal Cannula Oxygen (HHFNC). In a more recent Cochrane review, HHFNC when compared to CPAP either as first line support after birth (total of 439 infants) showed no difference in the rates of chronic lung disease or death. However infants in the HHFNC treatment group needed longer duration of respiratory support. When HHFNC therapy was used after a period of mechanical ventilation (total of 934 infants), there was no difference in the rates of treatment failure, chronic lung disease or death (Wilkinson et al., 2016).

The only form of non-invasive respiratory support extensively studied is CPAP. Ever since Gregory et al. established the use of CPAP for RDS (Gregory GA, 1971), this has been the most well studied for its safety and efficacy as a mode of respiratory support for use in newborn and preterm neonates.

But despite considered as a gentle and perceived to prevent lung damage seen in mechanical ventilation, three large trials COIN (Morley et al., 2008), SUPPORT(2010) and Vermont Oxford Network(Dunn et al., 2011) concluded there was no difference in the clinical outcomes such as death or bronchopulmonary dysplasia. Although the incidence

of pneumothorax was reported higher in the CPAP group in COIN trial, this has not been reported in the other two large trials. Although the trials show that preterm infants could be supported by non-invasive support, at least 50% infants in the CPAP group required mechanical ventilation in COIN trial and the same noted in the SUPPORT trial and VON trial. Study by Sandri et al(Sandri et al., 2010) also showed there was no difference in the need for mechanical ventilation in infants managed with surfactant followed by CPAP versus rescue treatment with surfactant. Thus whatever the approach mechanical ventilation is the default mode of supporting such infants who fail non-invasive respiratory support or are not suitable to receive non-invasive respiratory support.

2.2 Invasive respiratory support

Mechanical ventilation of the neonate could be defined as movement of gas into and out of the lung by an external source connected directly to the patient via an endotracheal tube or tracheostomy.

The origins to the modern day ventilation can be traced to the Old Testament(Goldsmith JP, 2011) with description of the mouth to mouth resuscitation technique. Description of endotracheal intubation by Hippocrates in 400BC is one of the earliest evidence to support artificial breathing support. This was followed by report from Paracelsus after 2000 years using bellows and oral tube.

In 1879, a simple rubber bulb connected to a tube inserted into the upper airway 'aerophore pulmonaire', was the first device specifically designed for suction and short-term ventilation of newborn infants. Alternate compression and suction provided fresh air and ventilation achieved by passive exhalation.

Later foot compression of the bellows to provide longer term positive pressure ventilation was published by O'Dwyer in 1887 (O'Dwyer, 1885).

Bloxsom (Bloxsom, 1950) in 1950, suggested it was the oxygen uptake in the respiratory tract which was the most important mechanism to initiate respiration. However, he felt that change of pressures aided this mechanism. He believed that positive pressure is the only mechanism

to overcome the respiratory resistance. He argued that tracheal intubation was fraught with danger of lung perforation and suggested use of positive pressure air lock. This machine produced alternate positive and negative pressure in a tightly sealed cylindrical steel chamber.

The earliest use of servo controlled ventilator is reported by Donald & Lord (Donald and Lord, 1953). Their case series reported a device that actively assisted lung expansion and rapid oxygenation. They reported success by means of achieving lung expansion. This was an apt inference and not merely limiting to success to survival or death. In an era when there was high infant mortality in the first month of life, largely due to prematurity, atelectasis and intracranial haemorrhage and health care largely 'laisser-faire or let them be', good nursing, airway clearance and oxygen supplementation was a breakthrough. They used clinical spirometry to assess respiratory efficiency in babies with atelectasis, a photoelectric pick up mechanism to trigger the respirator and synchronise to the infant's spontaneous breathing to 'amplify' spontaneous breathing efforts. The infant thus controlled the machine with feeble respiratory efforts. Solenoid operated valves reduced the inertia of the cranks, bellows and pistons.

The Kennedy tragedy in 1963 boosted research and development in the field of premature care and respiratory support. Atelectasis of the alveoli was a recognised problem. Hence in an attempt to keep them

open, CPAP was delivered via endotracheal tube with remarkable improvement. Until then most of the respiratory support was provided by adult machines, modified for use in babies, and utilised intermittent gas flow delivered by the ventilator.

In 1971, using continuous gas flow Kirby and co-workers developed a new generation neonatal ventilator. This device not only helped in spontaneous breathing between the mandatory breaths, but also helped prevent dead space breathing noted in the intermittent gas flow types. Spontaneous breathing also overcame the need for paralysis and the problem of babies 'fighting the ventilator'. This combination of spontaneous breathing under constant flow and intermittent mechanical breaths was termed Intermittent Mandatory Ventilation (IMV) and became the standard method of neonatal ventilation(KIRBY et al., 1972)

Over the decades the technology to support newborn breathing has seen an exponential progression. Current generation of neonatal ventilators have undergone series of modifications and refinements. This includes improving response times and delivering accurate tidal volume consistently, a problem with the old generation ventilators. Now the microprocessor technology with complex computer algorithms has replaced the use of solenoid activated switch for delivery of gas and accurate mixing and stopwatch to control inspiratory time. The new generation ventilators utilise computer based safety mechanisms and

have replaced spring-loaded manometer for monitoring peak inspiratory pressure used in the first generation ventilators.

With increasing survival of premature babies and technological advances, the survival of premature babies has increased. This has resulted into a new complication of prematurity, bronchopulmonary dysplasia (BPD). BPD was first described by Northway et.al (Northway WH, 1967), seen in moderate premature babies and related to the iatrogenic reason of ventilation induced lung injury from the ventilation practices. Designs to minimise this led to alternate forms of respiratory support- High Frequency Ventilation and patient triggered ventilation modalities. The current generations of ventilators allow synchronising infant's breath with ventilator and allow infant to control the ventilation. The use of pulmonary graphics and judicious use of lung distension through breath to breath monitoring allow minimising iatrogenic lung injury through artificial ventilation(Donn and Sinha, 2006).

For respiratory management of premature babies the discovery of exogenous surfactant complemented the advances in ventilation strategies. The pioneering work of Avery and Mead (Avery, 1959) reported surfactant deficiency was critical for development of lung atelectasis. This breakthrough has clearly shown to have a significant impact on newborn survival along with antenatal steroid treatment to prevent surfactant deficiency.

Although improved technology and their availability has led to newer ventilation techniques, this has not led to a significant change in the neonatal outcomes (Costeloe et al., 2012). Mechanical ventilation though is the mainstay in treatment of preterm infants with surfactant deficiency; it still remains a major contributor to adverse neonatal outcomes related to iatrogenic lung injury.

Thus, it is not only important to recognise who to ventilate and how to ventilate, but an important part of jigsaw is to recognise when to commence weaning and the best mode of weaning infants from mechanical ventilation. Early weaning could facilitate earlier extubation and perhaps reduce the extent of ventilation induced lung injury. At present clinicians continue to have differences in practices and our study attempts to explore if pressure support ventilation can assist in faster weaning of preterm infants from mechanical ventilation.

2.3 Conventional Ventilation

Neonatal mechanical ventilation for respiratory distress due to surfactant deficiency was first described in their works in 1953 & 1958 (Donald and Lord, 1953, Donald et al., 1958). The aim of mechanical ventilation was to normalise acid base balance for preventing death. Mechanical ventilation methods have improved over the years with the introduction of microprocessor technology and servo control methods for better patient ventilator interaction and to prevent Ventilator Induced Lung Injury (VILI).

With clinicians advice technological advances have enabled biomedical engineering to introduce newer modes of ventilation in babies. But this has introduced new terminology specific to parent companies and has caused much confusion. The confusion in the literature limits understanding and generalisability of ventilation functions.

To simply this confusion, neonatal ventilators could be classified as below (Donn, 2009) Table 1:

Conventional (Tidal Ventilation)
Modes: Intermittent mandatory ventilation (IMV) Synchronised Intermittent Mandatory ventilation (SIMV) Assist/Control (A/C) Pressure support ventilation (PSV)
Modalities: Pressure targeted Pressure limited Pressure control Volume targeted Hybrid
High Frequency ventilation
High frequency jet ventilation (HFJV) High frequency oscillatory ventilation (HFOV) Hybrids

Table 1 Classification of neonatal ventilators

2.3.1 What is conventional ventilation?

Conventional ventilation is based on tidal ventilation. It aims to deliver air or air and oxygen mixture for gas exchange. The clinicians usually target a physiological range of 4-8 ml/kg/breath.

2.3.2 Classification of conventional ventilation

Description of mechanical ventilator has historically been devised according to the patient physiology rather than the machine function. This has led to many commercial manufacturers to devise individual nomenclature leading to much confusion. Conventional mechanical ventilators can be classified (Donn, 2009) using target or limit modality (pressure or volume) and by the cycling mechanism or mode Table 1.

Modes of ventilation:
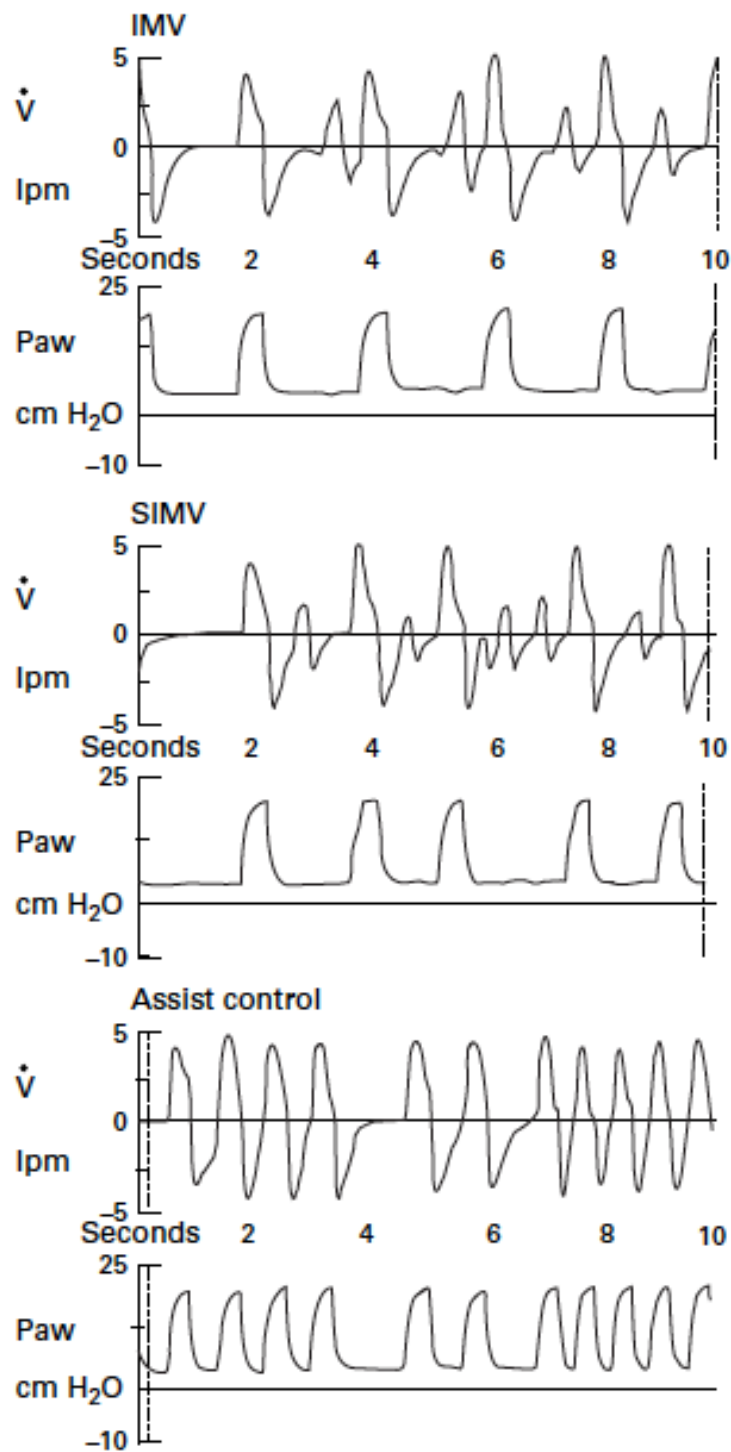
Figure 1: Comparison of IMV, SIMV and A/C modes

Intermittent Mandatory Ventilation (IMV)- all mechanical breaths are delivered at regular intervals chosen by the clinician. This result in significant asynchrony in an infant with active respiratory drive sees Figure 1.

Synchronised Intermittent Mandatory Ventilation (SIMV)-

In this form of triggered mode of ventilation, the ventilator algorithm uses fixed time windows to achieve synchrony in a spontaneously breathing infant. When the infant breathes over the set back up rate then the set PEEP supports spontaneous breathing.

In Assist-Control (A/C) mode –

All spontaneous breaths are supported provided the infants' spontaneous breath exceeds the set trigger sensitivity. The set back up breath (control mode) only comes to play if the infant has inadequate respiratory drive. Hence this is fail-safe mode of ventilation which clinician most often chooses to commence in acute illness. The key difference between SIMV and A/C mode is that the timing mechanism is reset after every mechanical breath in A/C mode and therefore the back up rate is not truly mandatory.

Modalities of Ventilation:

Modality refers to the target or the limit variable of the mechanical breath.

Generally this refers to Pressure Modality or Volume Modality. Until

recently, clinicians could only regulate or target one form of the

modality. In pressure-targeted modality, clinician set pressure variables

and volume variable was dependent on lung mechanics. If, on the other

hand, clinician targeted volumes, pressure was variable and with

improved lung compliance, for the same volume there was 'auto

weaning' of pressures see Figure 2. On the same corollary, note change

of pressure delivery 'auto weaning' in volume ventilation.
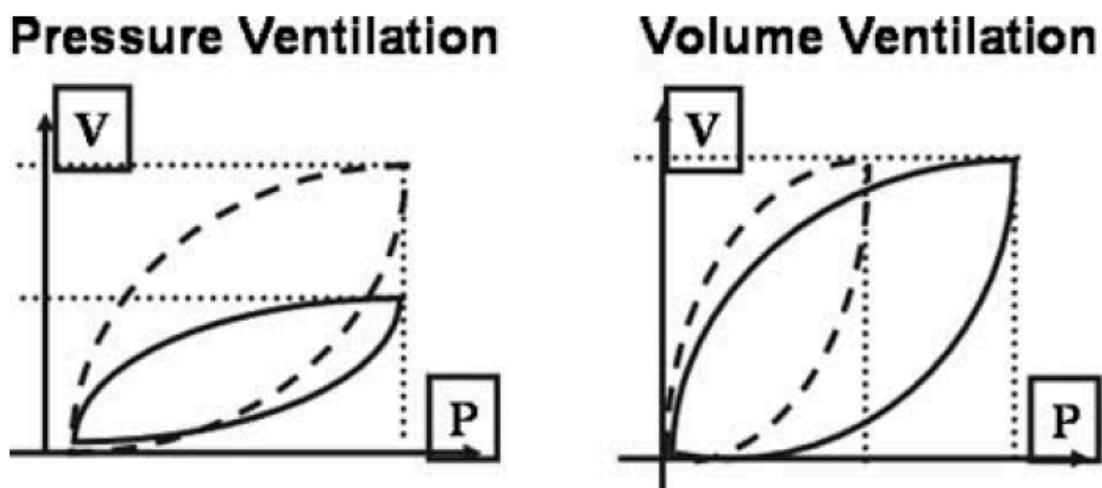
Figure 2 Change of volume achieved in pressure-targeted ventilation as compliance improves.

In newer generation of ventilators, although breath form will target one of the two modalities, it can however switch from one variable type to other during single inspiration using "dual control". This form is utilised in newer hybrid form of ventilation such as

Volume Assured Pressure Support (VAPS)

Pressure Regulated Volume Control (PRVC)

A mechanical breath can therefore be classified according to the three features:

a. Trigger variable- mechanism used to initiate the breath and also to terminate the breath. This could be:

   a. Time i.e. when the ventilator cycles into inspiration and expiration based on pre set time limit for each component. This is the oldest mechanism to achieve mechanical ventilation.

   b. Pressure: Pressure changes near to the patients' wye piece could also be used to trigger a mechanical breath. Negative intra thoracic pressure generated 'patient pull' could be used a trigger for towards the patient

   c. Flow: Similar to pressure flow of gases near to the patient wye piece could also be utilised to achieve synchrony for inspiration and expiration. This is also called as flow cycling. In flow cycling, the decelerating inspiratory flow is the trigger for the ventilator to cycle into expiration. The advantage is that the infant is in complete control of achieving synchrony for inspiration and expiration.

b. Limit Variable: refers to the targeted modality, volume or pressure

c. Cycle: The trigger mechanism as described above also allows cycling mechanism to enable ventilator to flip between inspiration and expiration.

Although, the clinical evidence (Greenough et al., 2008) suggests there is no clear benefit of synchronised versus non synchronised mode of ventilation to prevent death and other long term adverse outcomes, current neonatal mechanical ventilation strategies have evolved using synchronised form of ventilation and current ventilator manufacturers continue to produce newer triggered modes of ventilation. Synchronised form of ventilation is preferred perhaps from comparison of A/C mode to SIMV with a trend towards shorted duration of weaning (Chan and Greenough, 1994, Dimitriou et al., 1995).

Many variables in triggered modes of ventilation such as optimising trigger function, optimising flow rates and individual ventilator mechanics preclude generalisability of the trial results for declaring superiority of triggered mode of ventilation. More importantly, lack of data from adequately powered randomised controlled studies on long-term outcomes limits applicability of the newer modes of patient triggered ventilation despite advances on servo control technology.

3 Pressure Support Ventilation

Although ventilators in the 80s used assisted mode of ventilation, randomised trials conducted failed to show any benefit over conventional ventilation methods for short term outcomes such as duration of weaning and other common neonatal outcomes (Baumer, 2000). However clinicians caring for preterm infants were aware of the problems to achieve ideal synchrony. This was mainly: need for complete synchrony: both at inspiration and expiration thus preventing 'fighting the ventilator' scenario and need for sedation and paralysis.

For a period of time, various trials tried establishing superiority of various trigger types (Hird and Greenough, 1991a), (De Luca et al., 2009). However to date there is no conclusive evidence that any one form is better over the other. It is perceived that flow cycled mode of ventilation offers the infant better control over its breathing cycle by allowing greater synchrony for the full breathing cycle over the traditional time cycled ventilators (De Luca et al., 2009),

A form of partial ventilation support that could bypass the problems of patient ventilator asynchrony, using flow cycling as a means to prevent 'fighting the ventilator' scenario and matching the patient demand with demand flow features is available with Pressure Support Ventilation (PSV).

Pressure support ventilation is a pressure controlled spontaneous breathing mode of ventilation, where all breaths are triggered by the infant and synchronised during inspiration and expiration.

By definition, PSV is

- Patient triggered
- Pressure limited
- Flow cycled mode of assisted mechanical ventilation

Hence, for every patient effort that is above the set trigger threshold, the patient is rewarded with a predetermined level of pressure support (set point decided by the clinician). Flow cycling gives the infant the ability to determine the duration of the inspiratory and the expiratory portion of the breathing cycle and thereby manage the frequency. This ability to control the depth of the breathing cycle allows sigh breaths. This feature is available from variable flow feature that allows meeting the patient demand. Ability to develop sigh breaths has shown to be beneficial for lung recruitment and for oxygenation (Poets et al., 1997)

Thus, the equation of motion for PSV would be

$$Paw + Pmus = VT/C + V/R$$

Where Paw is ventilator airway pressure applied, Pmus is pressure generated by respiratory muscles. The elastic property of the system is determined by the tidal volume (VT) and compliance (C). The resistive

property of the lungs is determined by airways resistance (R) and flow (V).

Therefore if the Paw is fixed, tidal volume can be increased by greater muscle power by increasing the flow and the volume. An increase in PSV will not affect flow and tidal volume if there is a decrease in respiratory drive.
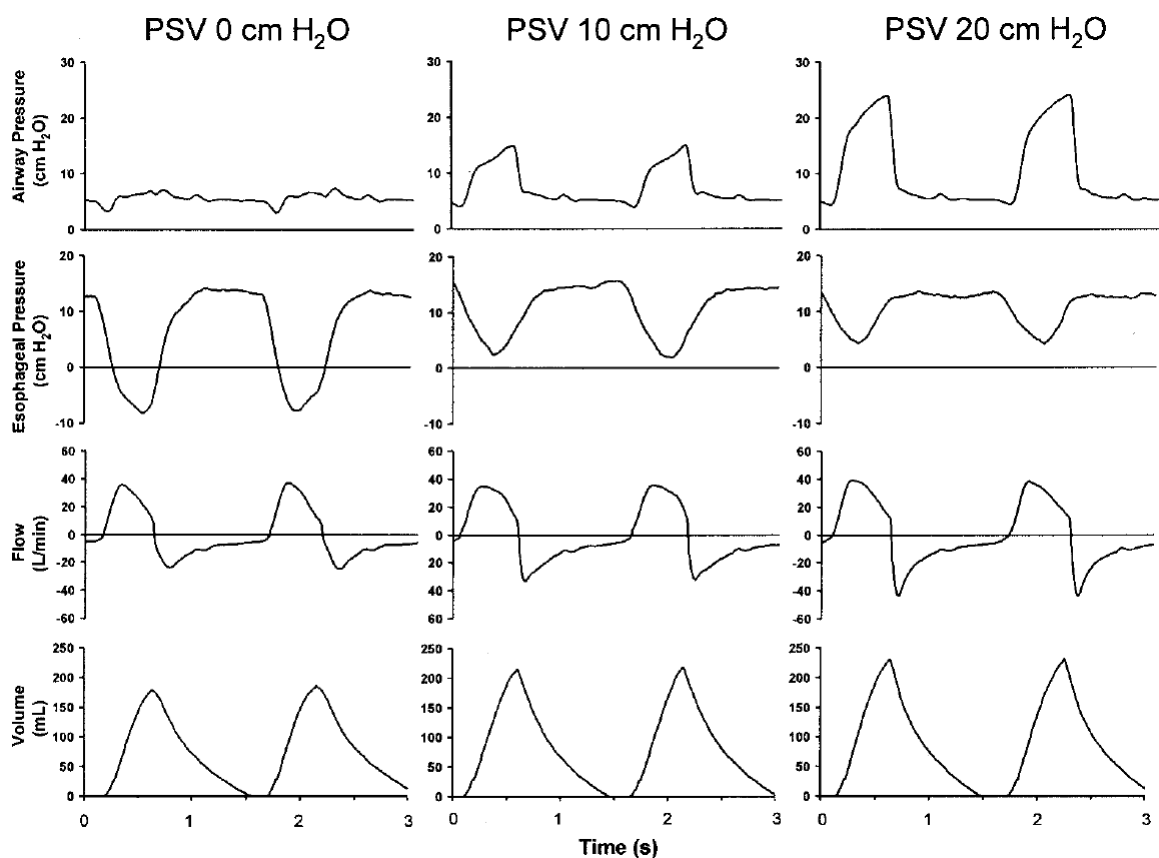
Figure 3 shows relation of Paw and Pmus to tidal volume delivery.

Figure 3 (Adapted from Hess RD, Respiratory Care 2005; 50(2) 166-183) shows airway pressure, oesophageal pressure, flow and tidal volume in a patient with 0, 10 and 20 cm H_2O of pressure applied to the

airway. Note the decrease in oesophageal pressure as airway pressure is increased. There is only a small increase in tidal volume with the increase in pressure support. In this case the principal effect of pressure support is to provide respiratory muscle unloading.

Thus PSV has three features (Gupta et al., 2009a):

1. Identification of the trigger

2. Pressurisation in the circuit

3. Breath termination
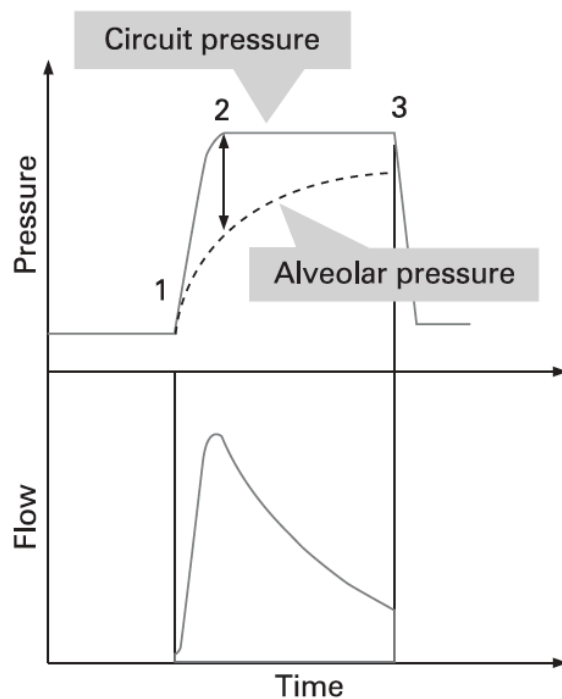
Figure 4 Schematic diagram-showing features of pressure support ventilation

1- Triggering

Recognising patients' inspiratory effort

2- Pressurisation

Rapid inspiratory flow to maintain constant inspiratory pressure with
variable decelerating inspiratory flow

3- Breath termination or cycling to expiration

Recognition of the end of spontaneous inspiration

With the trigger, PSV increases exponentially and stays at that level until the termination of the inspiratory phase. However this delivery is affected by ventilator time constant, which in turn is affected by the inspiratory rise time. In the old generation PSV mode this was constant but advancement in microprocessor technology has enabled to variable rise time depending on patient condition.

3.1 Optimal Patient Ventilator Interactions

PSV must have following characteristics to match the patient demand:

a. Inspiratory pressure support to commence with patient effort without trigger delay

b. Provide flow in synchrony with the patient effort

c. Provide level of pressure support during the inspiratory effort sufficient to unload the muscles and prevent fatigue

d. Terminate with breath in synchrony with the patient effort.

These characteristics are illustrated in the next page see Figure 5 Design characteristics of Pressure Support Ventilation breath.
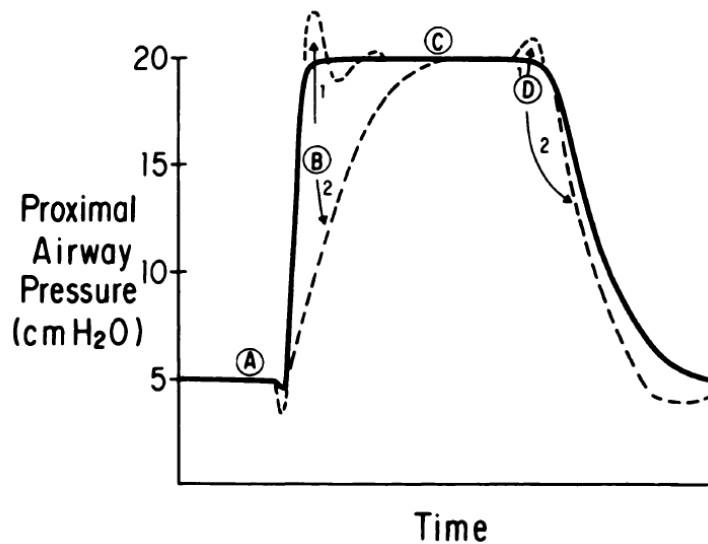
Figure 5 Design characteristics of Pressure Support Ventilation breath.

A= Inspiratory pressure triggered by the patient. Responsiveness and demand valve sensitivity are characterised by the depth of the negative pressure

B= The pressure rise is characterised by high initial flow delivery into the airways. B1= "ringing" if the initial flow exceeds patient demand, B2= if flow less than the patient demand.

C= Plateau maintained by the servo control to match the patient demand. A smooth plateau suggests appropriate responsiveness to patient demand; fluctuation would reflect less responsiveness of the servomechanism.

D= Breath termination should coincide with patient effort. D1= delayed termination with patient actively exhaling. D2= premature termination with continued patient effort.

(Adapted from The Nagoya Conference on system design and patient ventilator interactions during PSV, Chest 1990; 97: 1990)

Since its inception in the adult ITU, system design and delivery of PSV has been fine tuned (MacIntyre N, 1990, Kacmarek RM, 1991) in its ability to triggering and system design.

3.1.1 Identification of the trigger (patient effort)

This can be usually achieved by detecting either a change in the pressure (negative pressure drop reflecting active inspiration) or a change in the flow or both. Both the methods need an additional demand valve to open and close during inspiration and expiration potentially increasing the work of breathing and cause an inspiratory delay for the machine to support the breath causing asynchrony. In the Avea®, a 'flow-by' system is introduced. A constant flow (bias flow) is available in the circuit. With the spontaneous breathing effort, the ventilator detects a difference in the flow between the inspiratory and expiratory limb. Flow triggering avoids the need for a demand valve and gives the benefit of producing a continuous positive airway pressure. The flow trigger is usually set between 0.2L/min to 0.5L/min in neonatal ventilation, i.e. for every 0.2L displacement of air or oxygen in the circuit the ventilator identifies there is a demand and supports the breath. This is an improvement from previous design in that the trigger monitoring is closer to the patient at the Wye piece. Despite attempts to best achieve synchrony there is no major improvement since the last design modification in the 90s.

3.1.2 Pressurisation in the circuit

A high inspiratory flow is provided initially which rapidly decelerates throughout inspiration. Servo control provides the infant with an ability to interact with the flow delivery and the ventilator adjusts to the infant demand. The ventilator works as a pressurised demand flow system at the predetermined level. The rate of pressurisation can be altered. In the Avea, this can vary from slow rise to sharp rise (0 to 9 respectively) with 5 being default position. The modifications to the pressure delivery comes from the fact that although high initial flow rate rapidly achieves the required pressure this could be too fast and cause overshoot "ringing" and in others be too slow and lead to excessive patient effort in the initial phase (MacIntyre N, 1990) see Figure 5.

3.1.3 Breath termination

Ideally inspiratory pressure assist should cease with patients' inspiratory respiratory effort. Currently this is achieved by flow cycling. This can be either an absolute value of flow but more usually a fixed percentage of the peak inspiratory flow is reached (5% and 15% of the peak flow). As most neonatal endotracheal tubes are uncuffed, a leak in the circuit is inadvertent. Therefore an inspiratory time limit is also set up for safety backup. This prevents prolonged inspiration and exposure to high inspiratory pressures.

3.1.4 Flow and tidal volume delivery during PSV

During PSV, inspiratory flow and volume is determined by interplay of the pressure applied to the airway (Paw), the respiratory muscle pressure (Pmus), the airways resistance (R) and the time constant (resistance×compliance). Mathematically this is represented (Hess, 2005) by

Flow= (Paw+Pmus)/R ×log10-t/time constant

And volume is the integral of flow time curve.

The above characteristics help in deciding how the PSV is delivered and maintained.

PSV can be utilised for either total unloading of the respiratory muscles during spontaneous breaths or partial unloading. Total unloading occurs when muscle contraction is just enough to trigger the breath beyond which the positive airway pressure and machine flow cause zero mechanical work of breathing and virtually no ventilatory muscle oxygen consumption (Brochard et al., 1989). This is also called PSmax.

Partial unloading occurs when levels less than PSmax are used. When PSV is just enough to overcome the tube resistance this is called PSmin. Here the patient contributes to the volume delivery by active contraction of the respiratory muscle whilst being assisted by the PSV. The characteristics of PSV delivery such as flow synchrony and servo

control of the flow delivery to match the patient demand make it a favourable method to wean the patient off mechanical ventilation.

In many aspects the PSV resembles flow cycled assist control ventilation except in PSV there is no backup rate. Therefore this mode of ventilation is often coupled with partial modes of ventilation such as SIMV.

Another feature that has been introduced in PSV mode is an adjustable inspiratory rise time. An increase in the rise time slows the pressure and flow rates and this may be useful in neonates with very short inspiratory times that can interfere with adequate tidal volume delivery. However this feature has not been studied in infants.

3.2 Effect of Pressure support ventilation

Benefits of PSV include:

A. Patient comfort (MacIntyre, 1986) – from demand flow feature

B. Better synchrony- both at inspiration and expiration using flow cycling therefore less patient agitation and need for sedation

C. Decreased patient work of breathing (MacIntyre, 1986, Patel et al., 2009)

D. Muscle reconditioning and possibly lower extubation failure (MacIntyre, 1986)

Disadvantages of PSV

A. Varying tidal volume depending upon the patient's condition,

B. Varying minute ventilation due to unstable/unreliable respiratory drive

C. Atelectasis from smaller tidal volumes

D. Unstable pressure assist with varying baseline PEEP in presence of a leak in the circuit leading to prolonged inspiration exposing the infant to inadvertent high airway pressure.

In a bench study comparing the available commercial ventilators in a laboratory based study (Thille et al., 2009) concluded that despite advancements in technology there was large variation between different ventilators in terms of trigger function and pressurisation quality. This

could affect patient ventilator interaction and contribute to increased

work of breathing.

3.3 Clinical studies using PSV in neonates

In the first ever randomised controlled trial comparing volume controlled ventilation to pressure limited ventilation in preterm infants with RDS (Sinha et al., 1997), 50 preterm infants (mean gestation 31.2 in both the groups) weighing 1200g or more were consecutively assigned to either volume control or pressure limited ventilation. Weaning in SIMV with added PSV of 10-12 cms H_2O was commenced in the volume-controlled arm when back up rate was ≤40 per minute. Weaning in the TCPL was continued in Assist Control mode aiming similar tidal volumes. Infants in the volume-controlled mode met the success criteria (mean airway pressure less than 8cm H_2O and/or alveolar –arterial oxygen difference less than 13 kPa for more than 12 hours) earlier than TCPL mode of ventilation. (mean 65 hours Vs. 125 hours), and had a shorter duration of ventilation (mean 122 hours Vs. 161 hours). The authors concluded that the type of flow delivery (presence of demand flow system to augment the continuous flow in volume ventilation over the continuous flow in the TCPL mode) along with better alveolar recruitment from square wave form, consistent tidal volume delivery and better ventilation perfusion mismatch helped in faster weaning process. However an important attribute that could have led to faster weaning process in the volume controlled ventilation could be the addition of PSV to augment spontaneous breathing. The authors

highlight use of PSV was due to its striking similarity with flow synchronised A/C mode.

Subsequent study investigated the same mode in a randomised controlled study (Singh et al., 2006) in smaller and more immature infants (less than 32 weeks and less than 1500 grams) with surfactant deficient lung disease. The ventilation strategy and the success criteria was the same as in the previous study. Infants were stratified into two groups based on the birth weight (600-1000g and 1001-1500 grams). They were randomly assigned by permutated block algorithm with block sizes of 2, 4, and 6. Infants were commenced on SIMV with PSV for weaning when PIP <16cm H_2O and FiO_2 <0.3) PSV (10-12 cms) was added to the volume SIMV arm whilst weaning. Infants were extubated if they tolerated low SIMV rate (20) and their mean airway pressure was less than 8 cm H_2O. The study did not show significant difference (mean 23 hours Vs. 33 hours) between the two groups to achieve success criteria (mean airway pressure less than 8cm H_2O and/or alveolar –arterial oxygen difference less than 13 kPa for more than 12 hours). However post hoc analysis showed significant difference in the smaller babies weighing less than 1000 g (21 hours Vs. 58 hours). Although the results echo the previous study the overall difference between the two groups could be related to the steroid up take (95% to 44%). Addition of PSV in the two studies could also have contributed to the study results.

A pressure support setting of 10-12 cm H_2O as a blanket approach could deliver a Peak inspiratory pressure of up to 17 cm H_2O depending on the level of PEEP. This level of pressure support in the smaller infants especially <1000g could deliver full tidal delivery and help in conditioning of the respiratory muscles thereby benefitting them with weaning process.

There are three randomised controlled studies investigating PSV as a weaning mode. Two studies compare fixed PSV level along with variable SIMV with other modes (Reyes et al., 2006) (Patel et al., 2012) and a more recent study compared two levels of pure PSV (Farhadi Roya, 2016).

In the randomised controlled trial comparing SIMV and SIMV +PSV (Reyes et al., 2006), preterm infants weighing less than 1000g were randomised into two strata (500-699g) and (700- 1000g) using block randomisation method in a sequential sealed envelope from a computer generated randomisation list. Their mean gestational age was 25.0+/-1.4 and 25.4 +/- 1.3 weeks. SIMV was also their primary mode of ventilation. The level of PSV was determined at 30-50% difference of the PIP and PEEP.

The success criteria were manifold:

a. Time to reach minimal ventilator settings defined as PIP≤16cm H_2O, FiO_2 ≤0.30, PEEP ≤5cm H_2O and SIMV rate ≤ 15 breaths per minute for ≥ 48 hours.

b. Time to reach extubation (inadvertent or planned by clinician) and maintained for ≥48 hours

c. Age of final discontinuation of mechanical ventilation

d. Total duration of mechanical ventilation

e. Ventilator requirement at day 28

f. Total duration of supplemental oxygen

g. Oxygen requirement at day 28 and at 36 weeks postmenstrual age.

They reported that addition of PSV to SIMV reduced the duration of mechanical ventilation and could lead to decreased oxygen dependency. This effect was observed even with lower ventilator rate in the SIMV+PSV group. $PaCO_2$ values were same in both the groups.

This study however has many limitations in the design:

a. The management of the infants in the SIMV group was left to the clinicians and this could bring clinician bias.

b. The infants in the SIMV+PSV group on commencing the randomised mode further had a reduction in the back up rate in anticipation of increase in mean airway pressure and possible hyperventilation. This could have helped in their faster weaning process.

c. Infants in the SIMV were disadvantaged by very low SIMV rates (rate of 15 or less) maintained for 48 hours possibly by fatigue.

The second study compared weaning by assist control (A/C) mode of ventilation to PSV (Patel et al., 2012). The study recruited 36 infants with median gestation of 29 (range 24 to 39) weeks. Infants were randomised when FiO_2 was <40%, PIP for infants' ≥29 weeks of ≤20 cm H_2O, ≤17 cm H_2O in infants between 26 and 29 weeks, and ≤15cm H_2O in infants' ≤26 weeks' gestation. Block randomisation using opaque sealed envelope was used for randomisation. Permissive hypercapnia was allowed after 7 days provided pH was ≥7.25. A/C mode was delivered by time cycle with inflation time up to 0.4 seconds as determined by the clinical team. Flow cycling aided complete synchrony in the PSV mode. The researchers changed the termination sensitivity depending on the inspiratory time to maintain at least 0.25 seconds. Extubation was as per unit policy when the infant needed <16 cm PIP and FiO_2 <0.3. Failure criteria was defined as infants needing HFOV, PIP >26 cm H_2O and in the PSV arm if inspiratory time was <0.2 seconds despite 5% termination sensitivity. Most infants required a termination sensitivity of 5% to maintain an inflation time of at least 0.25 seconds. Peak inspiratory pressures were reduced for weaning in both the arms. Primary outcome of the study was to determine if the work of breathing, respiratory muscle strength, and degree of asynchrony and duration of weaning was different in the two modes. The authors

concluded that there was no significant difference between the two modes and PSV was equally efficacious.

This study has some limitations. The trial was based on concept of sufficient inflation time as perceived appropriate by the clinician. This negates the advantage conferred by flow cycling mechanism where the infant determines the respiratory rate and the depth of the breathing according to its requirement. Instead the authors could have related the observed inspiratory time with tidal volume delivery and verified if this met the physiological demands. Although the authors measured the transdiaphragmatic pressure time product to assess the work of breathing we do not know if the oxygen cost of breathing was significantly different between the two modes (Roze et al., 1997).

The most recent study by (Farhadi Roya, 2016) comparing two levels of PSV 10 and 14 cms. The study recruited 50 preterm infants between 24 and 37 weeks gestation (mean gestation- 31 weeks in group weaned on 10 cms and 32 weeks in group weaned on 14 cms PSV). The two groups received flow triggered SIMV for initial respiratory support during acute phase. Weaning on PSV commenced when Peak inspiratory pressure was <16 cms, PEEP 4 cms, and oxygen supplementation of less than 30% with a back up rate less than 20 per minute. During PSV mode they received 15 SIMV breaths. After 24 hours they were extubated without further weaning if they were deemed clinically stable (respiratory rate more than 80/minute were excluded). They concluded

PSV of 10 cms favoured extubation and facilitated shorter weaning duration. The findings of this study need to be interpreted with caution due to methodological limitations. The choice of two levels of PSV (10 and 14 cms H_2O) is purely arbitrary with no physiological data to support this. It is therefore difficult to establish what level of PSV is adequate for weaning. They excluded infants with respiratory rate of more than 80 indicating non-resolution of lung disease perhaps. But this could also be from 'unsettledness' from extubation readiness and inadequate respiratory support, thereby increasing the duration of mechanical ventilation.

Current literature reviews on PSV confirm safety, practicability and feasibility in neonatal medicine.

In a small quasi experimental crossover study (Gupta et al., 2009a) breath to breath analysis of the pulmonary mechanics data was analysed in 10 preterm infants (<32 weeks gestation) during the weaning stages of ventilation (when MAP was <10 cm H_2O and FiO_2 <0.4). At the time entry into the trial they were on low rate SIMV (20 breaths/min) with some PSV. PIP in SIMV was between 12 and 16 cm H_2O. The three modes of ventilation: SIMV alone, SIMV with partial PSV (PSmin) (delivering 2.5-4ml/kg tidal volume) and SIMV with full PSV (PSmax delivering 4-8 ml/kg). The study showed that respiratory rate settled (72 Vs. 65 Vs. 59 $p<0.05$ by ANOVA) with increasing PSV and tidal volume improved with increasing PSV (3.9 vs. 5.2 vs. 6.7 $p<0.05$

by ANOVA) with no significant change in the CO_2 levels between the three groups before and after the study. There were no major episodes of desaturation during the study period in any of the cohorts. These results are in agreement with studies by Tokioka (Tokioka et al., 1997). They studied three levels of PSV (0, 5, and 10cm H_2O) in neonates with congenital heart disease post operatively. They also investigated thoracoabdominal synchrony through use of respiratory inductance plethysmography and measured phase angle differences between rib cage and abdomen to measure asynchrony. They concluded with increasing PSV level led to more synchronous breathing effort.

This study highlighted that preterm infants could maintain adequate gas exchange without risk of hypo/hypercarbia with varying PSV level. The likely explanation is self-regulation of the spontaneous breaths. In addition the study also showed appropriate tidal volume delivery by regulating the PSV level and efficient respiratory mechanics.

Similar results were observed in another cross over randomised study (Osorio et al., 2005). This study recruited 15 infants mean gestational age 26+/-1.5 weeks. The study objective was to evaluate the effect of two levels of PSV (3 cm and 6 cm H_2O over PEEP) when added to low rate SIMV breath with acute reduction of the ventilator rate (by 10 breaths per minute lower than the clinical setting). All aspects of ventilator including PIP, PEEP and inspiratory time of the SIMV breaths remained same Incidentally, all infants were intubated by 2.5mm

endotracheal tube thus results between the two groups varied from the level of the PSV. The authors reported that spontaneous breaths were ably supported by addition of PSV. Gas exchange was maintained with both levels of PSV over SIMV. The study also suggested with 6 cm PSV (93% elastic unloading) stabilised breathing with reduced respiratory effort. There was no change in oxygen requirement whilst maintaining minute ventilation. The study reported no adverse events during the study.

The above studies investigated feasibility of PSV as a weaning mode and reported no adverse outcomes whilst maintaining gas exchange perhaps with improved respiratory mechanics.

However the above studies reported an increased mean airway pressure over conventional SIMV mode. This is expected as flow and subsequent pressure delivery is dependent on the infant effort rather than iatrogenic.

In a RCT comparing PSV to A/C (Patel et al., 2012) the MAP observed in the two groups was identical. This is likely from flow cycling technique used in both the groups suggesting similar gas flow. The drawback of this study being PSV was provided with fixed flow (instead of the variable flow) as determined by the manufacturer. So in a true sense there was no difference between the two arms of the study.

In a randomised controlled pilot study comparing PSV+VG and SIMV (Nafday et al., 2005) during the acute phase of RDS, use of PSV+VG did not decrease duration of weaning nor reduced incidence of chronic lung disease. The VG was limited to deliver 5ml/kg/breath. The mean gestation in both the group was 27 weeks. The authors argued that despite volume guarantee delivering a stable tidal volume and synchrony achieved by the PSV did not translate into reduction of time to weaning compared to SIMV in the first 24 hours during the study period. The observed higher MAP in PSV group is related to the flow delivery. PSV is a pressure triggered continuous spontaneous breathing mode with decelerating inspiratory peak flow early. It is likely that its use early in the disease with surfactant deficiency in an infant with inadequate respiratory drive would lead to converting a decelerating flow to continuous flow type to achieve the desired tidal volume (volume guarantee). This phenomenon has been reported in the volume controlled ventilation trial (Sinha et al., 1997). Whilst this may be a cause for anxiety, the observed effect has now proven not to be counterproductive in the long-term outcomes. The trial was underpowered to report any strong conclusions, which the authors also acknowledge.

In another randomised cross over trial (Olsen SL, 2002)recruited 14 preterm infants (32 to 37 weeks) all diagnosed with RDS and received surfactant. The mode allocation was random using sealed opaque envelopes to determine the sequence. The study commenced after 6

hours of the last dose of surfactant administration. Both modes targeted about 5ml/kg breath delivery. At the end of each mode helium dilution technique was used to assess the end expiratory volume. The primary outcome measure was minute ventilation. Secondary outcome measures were arterial alveolar oxygen tension (a/A) ratio, end expiratory volume and specific dynamic compliance (dynamic compliance/EEV). The authors concluded no advantage in pulmonary oxygen exchange with PSV+VG based on the lower end expiratory volume and higher minute ventilation in the PSV+VG group.

Despite volume guarantee set at 5ml/kg in this more mature group of infants, there was tachypnoea noted (respiratory rate 60±20 vs. 31±10 in the SIMV group). There was no difference in the $PaCO_2$. One explanation could be the level of PSV offered was inadequate leading to "pulling the ventilator" to satisfy the need thereby causing increase in spontaneous contribution to the tidal volume. This explanation could explain the decrease in the EEV due to progressive atelectasis. Another explanation could be the difference in the PEEP level setting in the ventilator. The methodology of this study has been critiqued (Keszler et al., 2003).

Another short term crossover study of 23 infants of gestational age 31±6 weeks during the recovery phase of the RDS, reported a reduction in PIP and mean airway pressure(Abubakar and Keszler, 2001) with PSV and PSV+VG. The observed difference was greater

when compared with SIMV than with A/C. This was attributed due to shorter inspiratory time from flow cycling. Although there was no difference in the tidal volume delivery this was less variable with VG mode (set to deliver 5ml/kg).

A cross over study comparing Mandatory Minute Ventilation (MMV) to SIMV (Guthrie et al., 2005) showed feasibility of using PSV in infants >33 weeks receiving mechanical ventilation for medical or surgical procedures. A preset minute volume (150- 240mls/kg/min) was used. Continuous online CO_2 monitoring was in place. Minute ventilation is essentially PSV but ventilator algorithm monitors the minute volume over a specified times (usually 7- 10 seconds) and determines the mandatory breath rate to meet the targeted minute volume. In the best case scenario the ventilator will trigger none and in case of apnoea the ventilator will do most part of the breathing. The machine delivered breaths are time cycled pressure limited breaths. The authors concluded whilst PSV maintained gas exchange effectively, an issue of hypoventilation from fast shallow breathing as seen very preterm infants could pose a risk for hypoventilation period. This would need further investigation.

In another cross over trial (Migliori et al., 2003) compared SIMV and PSV on the effects on respiratory function in preterm infants (<37 weeks). They used continuous flow ventilator for this study and volume limitation to restrict tidal volume delivery to 6 ml/kg in both study

modality to restrict higher than usual peak inspiratory pressure. They recruited 20 infants (mean gestation 29 weeks, mean weight 1354g). Each infant was studied in four study epochs of four-hour duration. They concluded a significant reduction in respiratory rate and an increase in tidal volume and minute ventilation during the PSV study period as compared to SIMV mode of ventilation. This reflects pressure support ventilation improves respiratory function and given a good respiratory drive the infant can control its respiration. However this study has some limitation. Volume limitation could have detrimental effect on the complex patient ventilator interaction. The advantage of PSV is to achieve higher tidal volume for similar effort and this is dependent on the flow delivery that is controlled by the patient. Thus limiting tidal volumes, it could significantly affect patient comfort and cause air hunger. Although the study concluded the advantage of PSV and improved respiratory function the results could have been different in smaller infants with volume limitation.

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4 Weaning on Mechanical ventilation

Mechanical ventilation is one of the major advances in neonatal medicine. Despite newer non-invasive respiratory support strategies being developed to provide 'gentler' alternative approach, intubation and mechanical ventilation still remains the mainstay of supporting preterm respiratory system. Despite best attempts, extubation success is approximately 70% (Gupta et al., 2009b) with one third requiring mechanical ventilation. The significant high number in need for re intubation and commencing mechanical ventilation reflects limited understanding of appropriate weaning strategies from mechanical ventilation.

A dynamic process of reducing support on ventilator after achieving the desired gas exchange progressing to extubation is called 'weaning on mechanical ventilation'. This process can also be interpreted as transferring the work of breathing from the ventilator to the patient in a gradual phased manner ensuring at all times the infant is able to cope with the imposed work of breathing. This is generally monitored by infant condition at the bedside by either an increase in respiratory rate, oxygen requirement and increase in breathing effort. These observed parameters are often supported by blood gas biochemistry i.e. increase in CO_2 retention, fall in pH and decreased alveolar arterial oxygen tension. These changes can also be seen in the ventilator graphics such as decrease in tidal volume and minute ventilation.

Early weaning on mechanical ventilation is important to decrease the complications of mechanical ventilation. Whilst most clinicians agree on this and agree on how to approach and initiate mechanical ventilation, there is very little data to confirm best method of weaning on mechanical ventilation.

Weaning commences when the clinician reduces the ventilation in response to infant's 'clinically stable' condition and blood gas supporting adequate gas exchange. It is therefore important to acknowledge, that weaning on mechanical ventilation is commenced the moment the clinician reduces any degree of ventilatory support.

This ability to cope with the changes depends on a delicate balance between 'loads' imposed on the respiratory system and its 'capacity' see Table 2 Causes of weaning and extubation failure (Sinha and Donn, 2002).

↑ Respiratory Load	↓ Respiratory Capacity
Increased elastic load • Unresolved lung disease • Secondary pneumonia • Left to right shunting (e.g. PDA) • Abdominal distension • Hyperinflated lungs	Decreased respiratory drive • Sedation • CNS infection • PVH /PVL • Hypocapnia/alkalosis
Increased resistive load • Think copious airway secretions • Narrow/ occluded ET tube • Upper airway obstruction	Muscular dysfunction • Malnutrition • Electrolyte imbalance • Chronic pulmonary hyperinflation
Increased minute ventilation • Pain and irritability • Sepsis/hyperthermia • Metabolic acidosis	Neuromuscular disorders • Diaphragmatic dysfunction • Prolonged neuromuscular blockade • Myotonic dystrophy • Cervical spinal injury

Table 2 Causes of weaning and extubation failure

Weaning on mechanical ventilation involves tackling two issues:

a. Identifying the right patients through appropriate objective assessment.

b. In infant failing this assessment regular assessments to identify their readiness must be instituted.

The ventilator management in patients needing mechanical ventilation include

a. Normalising the loading conditions

b. Optimising the patient comfort by increasing synchrony.

Excessive loading predisposes to muscle fatigue and total unloading leads to muscle atrophy (MacIntyre, 2005). The goal is therefore to set the ventilator such that the patient generates some work of breathing to maintain and build muscle tone and at the same time prevent fatigue. This is well depicted in Figure 6 (MacIntyre, 2005).
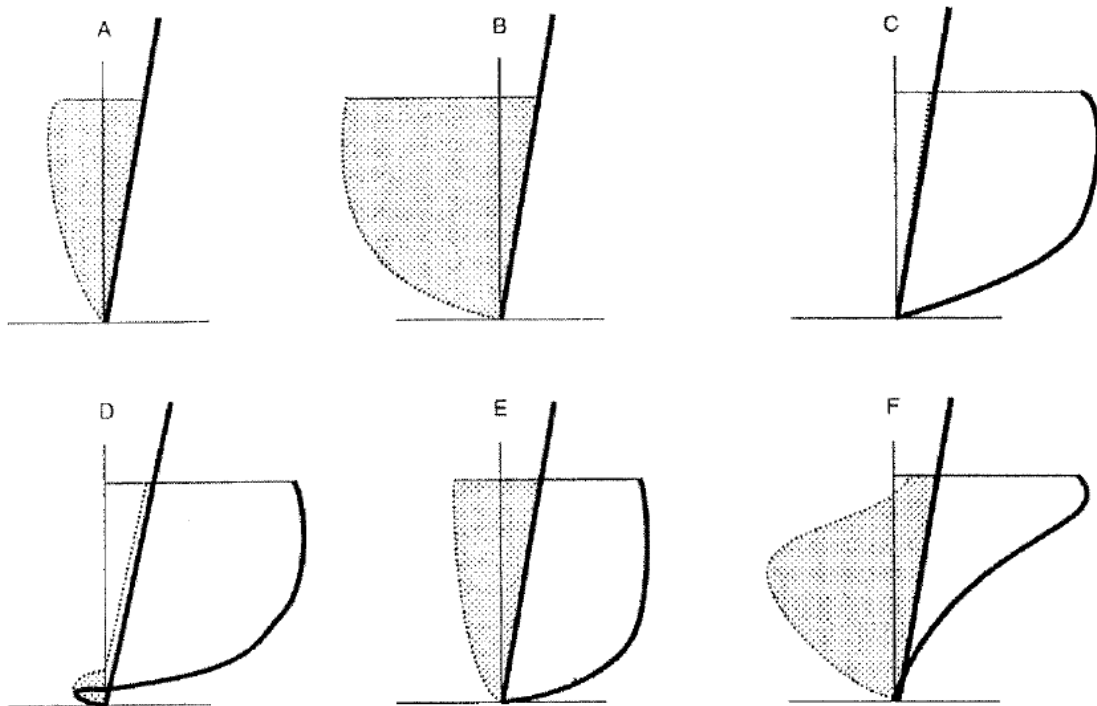
Figure 6 Pressure volume curve depicting various patient ventilator interactions with constant tidal volume.

In each curve, volume is on the vertical axis and pressure is on the horizontal axis. Airway pressure is depicted by solid lines, Oesophageal pressure is depicted by dashed lines. The bold angled line directed upward and to the right from the origin reflects passive inflation oesophageal pressure (chest wall compliance). The shaded area reflects patient work.

A. A normally loaded spontaneous (unsupported) breath

B. An abnormally loaded spontaneous breath

C. A ventilator controlled breath in an abnormal patient

D. A synchronous assisted breath designed to virtually unload an abnormal patient (only triggering is evident)

E. A synchronous assisted breath designed to partially unload an abnormal patient

F. A dyssynchronous assisted breath in an abnormal patient; high-pressure patient load exists through much of this breath from inappropriate ventilator flow delivery.

4.1 Misconceptions about the impact of endotracheal tubes on weaning mechanical ventilation

The notion that breathing through the small ETT imposes a significant work of breathing is conflicting. Data from observational study (Keidan et al., 2000) in children needing general anaesthesia, conclude that work of breathing through an endotracheal tube was half that of mask and oropharyngeal airway. They suggest this could be due to relatively larger proportion of subglottic area to the body size (20 times greater in proportion to adults)(Eckenhoff, 1951). Thus due to use of short endotracheal tube and flow rates less than that needed in adult intensive care, the infant is benefitted with endotracheal tube contrary to popular belief.

In another observational study (Argent et al., 2008) the mid and peak inspiratory flow in humans is approximately 0.5L/kg/min. This finding is important when applied in the smallest infants ventilating through small endotracheal tubes for example flow limitation occurred with flow of 24L/min or 8L/kg/min in a 3 kg infant.

Another notion is an increase in flow rate changes the laminar flow to turbulent flow. Jarreau and colleagues (Jarreau et al., 1999) found that flows even in the smaller endotracheal tubes of 2.5 to 3.5 mm was laminar and therefore does not change increase the pressure drop.

These findings are helpful when planning weaning on mechanical ventilation.

To assess pressure drop at fixed flow rates as used in volume controlled ventilation we performed an in-vitro experiment to investigate pressure drop to enhance our understanding at common flow rates used in volume controlled ventilation see Appendix 7.

4.2 Estimation of Neonatal Endotracheal Tube (ETT) Resistance by Water Manometer

(Mallya et al., 2012). (See also Appendix 7)

Aim of the study: to Assess in vitro the pressure drop using varying sizes of ETT commonly used in preterm infants at different lengths, flow rates with medical air and 100% oxygen.

Methods: We used Portex tubes for this in vitro study. Portex tubes were chosen as similar make was used for intubation in our study. A water manometer (scale 0-300mm) was used to measure the pressure drop across the ETT. We used two different lengths (7 and 14 cms) and different sizes (2.5, 3.0, 3.5 and 4.0 mm). We assessed pressure drop across a range of flow rates from 4 L/min up to 11L/min.

Flow (L/min)	Pressure drop with medical air (cms H_2O) Mean (SD)	Pressure drop with 100% Oxygen (cms H_2O) Mean (SD)
4	4.34 (6.4)	5.5 (26.3)
5	5.81 (8.3)	7.45 (20.3)
6	7.99 (10.8)	9.77 (16)

7	10.16 (13.5)	12.9 (14.6)
8	12.59 (16)	16.21 (18.9)
9	15.67 (20)	19.8 (25.6)
10	19.79 (25.7)	23.62 (33)
11	22.77 (59.3)	18.24 (129)

Table 3 Comparison of pressure drop with medical air and 100% oxygen

Results: There was no difference in the pressure drop using medical air at 7 and 14cms ETT [(120.6 (66.12) vs. 127.3 (68.7) cm H_2O; p=0.29] and there was statistically significant pressure drop with 100% oxygen at 14 cm compared to 7 cm ETT length [146.73 (72.94) vs. 130.48 (72.94) cms H_2O; p=0.015]. Difference in the ETT diameter did not seem to contribute to significant difference in the pressure drop across all the flow range. As expected there was a statistically significant increase in pressure drop at flow rates increasing from 4L/min to 11L/min.

Conclusion: Although, the results of this study could not be studied in vivo, the results of the study highlighted how the infant contributes to achieving the desired tidal volume with weaning the ventilator at a given flow rate in volume controlled ventilation.

4.3 Current evidence in weaning on mechanical ventilation

With the advent of synchronised modes of mechanical ventilation, Intermittent Mechanical Ventilation (IMV) is now rarely practiced. Several studies (Chan and Greenough, 1993, Chan and Greenough, 1994, Bernstein et al., 1996) even though were performed when surfactant uptake was about 50-60% confirmed some form of synchronisation was helpful than none. It was thought that patients 'fighting the ventilator' had active expiration and the cause for air leak syndrome. Several studies conferred various advantages of synchronised ventilation which include improved oxygenation, improved CO_2 elimination, increased minute ventilation, and decreased blood pressure fluctuations (Hummler et al., 1996).

4.4 Historic studies comparing various ventilation practices for weaning preterm infants.

In a large international randomised controlled trial (Baumer, 2000) compared patient triggered ventilation (A/C mode)with IMV. He concluded there was no benefit in view of higher than usual pneumothorax rate in the assisted group (<28 weeks gestation). In addition, there was no difference in other secondary outcomes of interest. The study methods were criticised due to a large number of infants deviating to the conventional IMV instead of using HFOV as a rescue mode. This study also highlighted how previous experience in using a particular ventilation strategy, particularly in triggered mode of ventilation is important to use a relatively new mode of ventilation. This could be the reason for the findings of the study.

In another randomised controlled trial (Beresford et al., 2000) comparing SIMV with conventional fast rate ventilation in preterm infants (mean gestation 29 weeks) were randomised within two hours (range 0-24 hours) of decision to commence mechanical ventilation. SLE 2000 was used in this trial. No crossover was allowed. Respiratory rate of the infant was counted prior to intubation. Infants in the conventional fast rate started at the same rate or higher than resting rate and in the trigger group 20 breaths less than the resting rate. Weaning was performed reducing pressures until acceptable blood

gases were obtained and ventilator rate reduced down to 5-10 breaths per minute. The researchers concluded that there was no difference in the rate of chronic lung disease. The results of the trial could be influenced from the fact that infants in the conventional group got the benefit due to short time constants due to the nature of the disease (poor compliance and high resistance from surfactant deficiency). The back-up rate in the SIMV group was not clear. 13% infants in the trigger group 'failed' in assigned mode and were changed to conventional high rate mechanical ventilation. Interestingly 1/6th of the infants needed bagging and in up to 1/3rd of the infants there was no specific reason. The rest failed due to inadequate oxygenation, needing high peak pressures, poor respiratory effort, all indicating inadequate respiratory support rather than failed mode. Although this was not strictly a weaning trial, the results highlighted that SIMV was at least efficacious in managing preterm infants.

In a two part randomised controlled trial, (Dimitriou et al., 1995) investigated PTV to SIMV. (N=40). They concluded PTV was a better mode of weaning on mechanical ventilation compared to SIMV. In addition, they also added concept of a minimum (critical number of breaths) 20 breaths/minute that is necessary to prevent failing on weaning. The major limitation of the study was obvious disadvantage in the SIMV group when the backup rate was reduced to 5 breaths per minute before commencing ET CPAP for 1 hour to demonstrate readiness to extubation. This phenomenon was not observed in the

second part of the study when the infants were extubated when SIMV back up rate was 20 breaths /minute. These results would be different in current practice with use of PSV (Reyes et al., 2006) favouring use of PSV with SIMV to reduce weaning duration.

In a randomised controlled trial comparing duration of weaning and efficacy of weaning by patient triggered ventilation (A/C mode) and conventional ventilation, it was concluded, that PTV was more advantageous with mean duration of 39 hours (range 3-186) versus 65 hours (range 15-262 hours) p<0.02. This study was performed after the authors acknowledged the studies previous to this were limited either due to triggering capabilities (Hird and Greenough, 1991b), or due to technological limitations. A purpose built neonatal ventilator (SLE 2000 HV) was used in this study. Infants were weaned either by PTV or conventional route once their back up rate was 40/min and had received a loading dose of aminophylline. Weaning on PTV was achieved by reducing the pressure and rate reduction in the conventional mode. Duration of weaning was defined as the time from entering the trial to extubation. The study reported A/C mode failed in three infants (25, 26 and 27 weeks gestation and labelled them as the most immature infants in the intervention arm). However this study is limited in current context due to better antenatal care, antenatal steroids and liberal use of surfactant. In their study, less than 15% infants received surfactants. But despite these limitations the study showed PTV was superior to the conventional methods.

In another RCT comparing A/C mode of ventilation with SIMV in 1994 (Chan and Greenough, 1994), mean gestation 29 weeks and only 50% recruited infants received surfactant, found no difference between the two groups. However, 15% of the infants in both the arms who failed weaning methods were <27 weeks gestation. The results of the study is limited in applying to current practice for the following reasons- the use of inadequate PEEP (limited to only 3cm H_2O), use of airway pressure for trigger, and post extubation management (use of head box oxygen and or CPAP) which was not clearly described in this study. Despite no statistically significant results, there was a trend towards shorter duration of weaning in infants randomised to A/C mode [median 22 (range 4-339) vs. median 36 (range 8-647)]. This suggests it is better to support spontaneous breaths in infants receiving mechanical ventilation with positive pressure inflations above PEEP. Whether PSV offers that advantage has been described before in section 4.3.

In a randomised controlled trial comparing A/C mode to PSV (Patel et al., 2012) concluded that PSV has similar characteristics to weaning on A/C mode and was equally efficacious. The details of the study has been discussed in section 4.3

Clinicians world over prefer SIMV for weaning from mechanical ventilation (Van Kaam et al., 2010). Thus study results from this research could be generalised in its application to wider population.

4.5 What is currently known?

- The pressure-volume loop is altered by the infant effort and infant assumes greater role with weaning of ventilator support.

- There is as yet lack of clear consensus as to superiority of one mode of ventilation to reduce the duration of mechanical ventilator days.

- Pressure Support Ventilation seems to 'mimic' natural spontaneous breathing.

These points are well illustrated in Figure 7 Schematic diagram depicting how patient effort alters pressure volume loop.(MacIntyre, 1986)
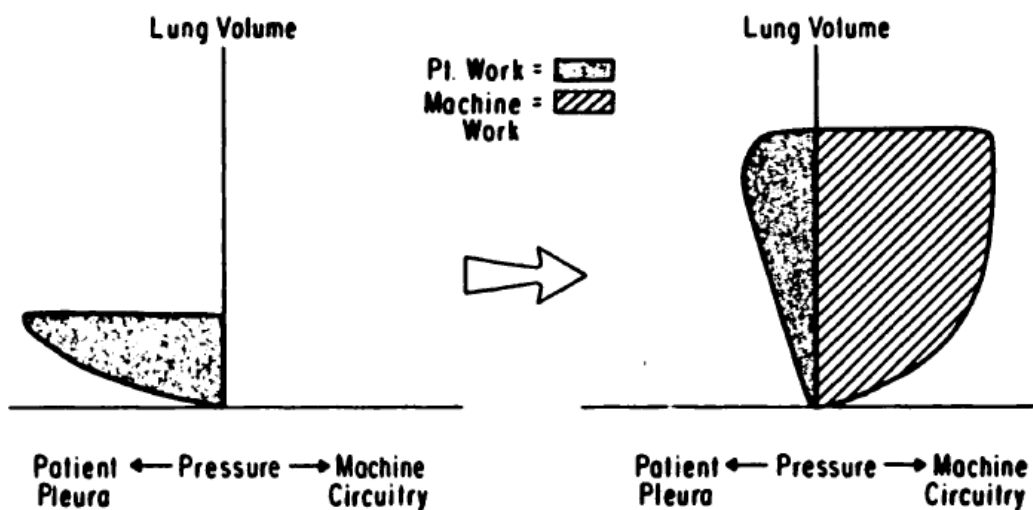
Figure 7 Schematic diagram depicting how patient effort alters pressure volume loop.

Schematic diagram depicting how pressure assisting a patient's spontaneous breath can alter the pressure volume change characteristics of that work. The horizontal axes

represent pressure (patient generated on the pleural space to the left, machine generated on the ventilator circuitry to the right) and the vertical axes represent lung volume change for a single breath. The left panel depicts an unassisted breath. The shaded area under this curve represents patient workload. The right panel depicts a pressure-supported breath in a lung. Note, for a similar level of patient total work, the pressure volume change work ratio for that breath are markedly reduced by pressure assisting the breath.

The aim of weaning on mechanical ventilation is to gradually shift the pressure volume curve to the left and let infant assume greater work of breathing.

4.6 What is the knowledge gap?

- There is no clear consensus of defining weaning on mechanical ventilation
- Pressure Support Ventilation seems to favour weaning on mechanical ventilation- however variable levels of support has not been investigated in a controlled study.
- Whether reducing the weaning duration on mechanical ventilation improves rates of chronic lung disease is still unknown.

5 Extubation readiness

Whilst most clinicians would agree with need for mechanical ventilation, there is no consensus on when to commence weaning to facilitate early extubation. The dangers of prolonged intubation would include bacterial colonisation, soft tissue injury such as subglottic stenosis and ventilator induced lung injury leading to poor long-term outcomes such as bronchopulmonary dysplasia and death. Up to 30% infants fail extubation and require further intubation and are re-commenced on mechanical ventilation. Re intubation is not innocuous with reported complications that include raised intracranial pressures, hypoxia and cardiovascular instability (Kelleher et al., 2009). It is therefore necessary to identify the infants who might fail extubation. However there is limited evidence that could guide clinicians in this decision-making.

5.1 Causes of extubation failure

Extubation failure is essentially an imbalance between respiratory load and respiratory capacity. This is explained in Table 2.

5.2 Predicting successful extubation

Multiple attempts have been made in the past to identify the babies for successful extubation. There are a few post extubation tests designed such as measure of functional residual capacity, post extubation x ray of the chest and measurement of the lung volumes (Dimitriou and Greenough, 2000). However these are of limited use as extubation has already happened. Researchers have also investigated use of occlusion tests to verify if this was useful and concluded low gestational age and older postnatal age (prolonged ventilation) were better predictors of extubation than measurement of respiratory muscle strength or respiratory load (Dimitriou et al., 2002).

5.2.1 Clinical studies

One of the earliest study to identify an objective test for extubation readiness is the minute ventilation test (Wilson et al., 1998). In this observational study 64 infants with a birth weight of <2500g, the authors reported 86% success in extubation (defined as extubation for at least 24 hours) if their spontaneous minute ventilation in the 10-

minute trial on ET CPAP was ≥50% of mechanically generated minute ventilation.

In another observational study involving 41 infants [median gestation 27 weeks (range 25-29 weeks)], infants spent 2 hours on ETCPAP following specific weaning protocol (Vento et al., 2004). The researchers hypothesised from their previous study a spontaneous minute ventilation of at least 125ml/kg as minimum necessary to sustain spontaneous breathing upon extubation. They reported successful extubation (defined as 72 hours) in 73.2% infants and associated higher respiratory rate mean 53 (28-67) vs. 43 (37-56) in successful extubation. The findings of this study although helpful, do not satisfy in explaining the high respiratory rate and low oxygen consumption in the successful group. This is contrary to generally held belief that high respiratory rate is associated with higher work of breathing and therefore associated higher oxygen consumption. It may be that the rather long duration on ET CPAP could have tired a proportion of babies and thus been disadvantaged. The authors of the study also acknowledge this issue.

Szymankiewicz (Szymankiewicz et al., 2005) investigated differences in pulmonary mechanics in ventilator dependent preterm infants (mean gestation 29.1 week±2 weeks) who were extubated following specific extubation criteria. 39% required reintubation within 72 hours. Pulmonary mechanics were studied in 51 infants before extubation.

They found significant differences between successful and unsuccessful infants in their pulmonary function. They concluded tidal volume of >6mls/kg, minute ventilation of >309ml/kg/min, work of breathing of <0.172J /lt and airway resistance of ≤ 176 cm H_2O /L/sec predicted successful extubation.

The predictive capability of successful extubation by minute ventilation test was further compared with clinical judgement in a randomised controlled trial (Gillespie et al., 2003). Infants randomised to minute ventilation test underwent 10 minute ET CPAP trial as described above in study by Wilson. They described, a significantly shorter duration of ventilation to extubation in the MVT group compared to infants extubated by clinical judgement (mean 8 hours versus 36 hours). They concluded the positive predictive value of the MVT for extubation to be 76% (95% CI, 55-89%).

More recently in an observational study (Kamlin et al., 2006) the investigators determined the accuracy of the three tests used to predict successful extubation in preterm infants (birth weight <1250g) considered ready for extubation. Tidal volumes, minute ventilation, heart rate, and oxygen saturations were recorded before and after the ET CPAP. The three tests were expired minute ventilation during ET CPAP, ratio of minute ventilation during ET CPAP to mechanical ventilation and the spontaneous breathing test (SBT). Extubation failure was defined as need for re intubation within 72 hours. The authors

concluded that only SBT was the most accurate with a sensitivity of 97% and specificity of 73%. The positive predictive value was 93% and the negative predictive value was 89%.

The same authors later compared the SBT to clinical decision making in a randomised controlled trial. They recruited 180 infants of birth weight less than 1250g. They reported there was no difference in the time to first extubation or in the duration of total respiratory support. However the study reflected infants' extubated through SBT discontinued mechanical ventilation at higher mean airway pressure than through clinical judgement but there was no difference in the need for re intubation.

In another prospective study (Currie et al., 2011), twenty ventilated infants median gestation 31 weeks (range 24-39 weeks) ventilated by either assist control mode of ventilation or pressure support ventilation underwent measurements of transdiaphragmatic pressure using dual pressure transducer tipped catheter. This yielded the diaphragm tension time index (TTdi). They also calculated the respiratory muscle tension time index (TTmus) from a non-invasive airway pressure measurement. The researchers concluded that the infants failing extubation had a significantly higher TTdi and TTmus. A TTdi >0.15 and TTmus >0.18 was 100% sensitive and specific in predicting extubation failure. Although this seems to be promising in its application, the clinical application in routine practice is limited by the availability of the

technology at the bedside and 'perceived' invasive technique of placing the dual pressure transducer catheter.

5.3 Present study

In the present study, we chose to apply minute ventilation test as an objective measure for readiness to extubation (Gillespie et al., 2003). A modified approach of the same test was used in the another randomised controlled trial (Gupta et al., 2009b) where the research team used five minutes instead of 10 minutes to measure spontaneous minute ventilation via ET CPAP. They had 104 infants, mean gestation 27.9 weeks (SD 1.8), and birth weight 1077g (SD 256). The study investigated two methods of CPAP support post extubation. They reported 77% infants maintained successful extubation at 72 hours in both the groups.

As the clinical team at both the centres was well aware of the minute ventilation test we chose the modified minute ventilation test as objective measure of extubation readiness for our study.

6 Adjunctive therapies for weaning

Although strict weaning protocol benefits patients towards faster weaning and extubation (MacIntyre, 2001), adjunctive therapies also help to facilitate extubation. The evidence and the strategies utilising adjunctive therapies to facilitate extubation are discussed in this chapter.

6.1 Caffeine Citrate

Methylxanthine alkaloids such as aminophylline, theophylline and caffeine citrate have been used to treat apnoea of prematurity. The predominant site of activity involves the central nervous system and the cardiovascular system. This is largely increasing excitatory pathway by translocation of intracellular calcium, and inhibit adenosine receptors. The pharmacological mechanism that alters the neonatal apnoea include: improved sensitivity of medullary respiratory centre to CO_2, increased afferent nerve stimulation to brain stem, increased catecholamine response, stimulation of central inspiratory drive, improved skeletal muscle contraction. In a large multicentre trial (Schmidt B, 2006), infants weighing between 500 and 1250 grams (median gestation 28 weeks) were randomised in the first ten days of life to receive caffeine citrate or placebo. 2006 infants participated. The study concluded decrease in the incidence of bronchopulmonary.

Further analysis (Davis et al., 2010) suggested early administration was associated with faster weaning on mechanical ventilation. Hence in the current study, caffeine citrate 20 mg/kg loading dose at the earliest opportunity was given and further maintenance dose was continued until 34 weeks gestation. This approach is also supported by the Cochrane meta analysis(Henderson-Smart, 2010) The review included seven studies and concluded caffeine citrate reduced failure of extubation within one week (RR 0.48, 95% CI 0.32 to 0.71).

6.2 Use of diuretics

Use of diuretics in infants with bronchopulmonary dysplasia is widely practiced. However there is a lack of good quality current evidence to support this(Stewart A, 2011). The perceived advantage comes from a study in preterm infants who received furosemide or chlorthiazide within the first five days (Green TP, 1983). Although the study investigated early water management with severity of respiratory distress syndrome the study results have been extrapolated for later management. In the current practice, use of diuretics is at the discretion of the attending physician.

6.3 Use of CPAP

CPAP has been utilised as an adjunct to maintain extubation. In a meta analysis comparing CPAP with head box oxygen supplementation, the authors concluded CPAP is superior to prevent re intubation rates (Davis, 2003). Multiple physiologic reasons support its use in particular

this is related to increase in functional residual capacity, decreased work of breathing and respiratory stimulus in preventing apnoea of prematurity.

In a randomised controlled trial, comparing Infant Flow Driver with Bubble CPAP, researchers established Bubble CPAP was superior in infants ventilated for ≤ 14 days to maintain successful extubation (Gupta et al., 2009b). In view of familiarity with the technique, identical patient base to that reported in the above trial and ease of application we chose to support extubated infants with Bubble CPAP.

6.4 Heated Humdified High Flow Nasal Cannula oxygen (HHHFNC)

There have been several clinical studies comparing HHHFNC to nasal CPAP in non inferiority study designs and has been shown to have similar efficacy and safety to nasal CPAP when applied as a post extubation strategy (Yoder et al., 2013), (Collins et al.), (Manley et al., 2013). Meta analysis (six studies, 934 infants) in Cochrane review in 2016 (Wilkinson et al., 2016) showed HHFNC when used as respiratory support after receiving mechanical ventilation – there was no difference in the rates of re-intubation. Long-term outcomes such as chronic lung disease and death were also not different when compared to CPAP. There is also a decrease in soft tissue injury with use of HHFNC (Collins et al.).

6.5 Postnatal Corticosteroids

Corticosteroid use could be divided into two categories.

Use of prophylactic dexamethasone for extubation in view of laryngeal oedema has been reported with some success (Khemani et al., 2009). Although this Cochrane review has 11 trials, only two were neonatal. The study by Couser, (Couser et al., 1992) included the 'high risk' infants who had multiple intubation and traumatic intubation or received mechanical ventilation for at least 14 days (n=50). First dose of Dexamethasone was given at least four hours before extubation and then further two doses were administered. The results of this study suggested a decrease in the incidence of stridor and rate of re intubation in the Dexamethasone treated group. In view of inconclusive strong evidence for treatment or otherwise the decision was left at the discretion of the attending physician.

Use of corticosteroids for facilitating extubation after prolonged intubation-Use of low dose Dexamethasone therapy in select infants who received mechanical ventilation for more than two weeks and who had failed extubation on at least two occasions is well recognised (Doyle et al., 2006). Although the Cochrane review (Halliday et al., 2009) suggests benefits in the immediate short term outcomes (incidence of BPD and IVH), they advice, caution in the post natal steroid use in view

of lack of evidence in the long term neuro sensory outcomes. However, in a meta- regression of 20 studies (1721 randomised infants), postnatal use of systemic corticosteroids and the risks of cerebral palsy and mortality was further reviewed as per the risk for chronic lung disease (Doyle et al., 2005). They concluded there was a significant negative relationship between the treatment effect on death or cerebral palsy and the risk for chronic lung disease in control groups. With the risks for chronic lung disease below 35%, corticosteroid treatment significantly increased the chance of death or cerebral palsy, whereas with risks for chronic lung disease exceeding 65%, it reduced this chance. The decision to commence steroid treatment was based after discussion with the parents. The dose and duration of the treatment used in this study is followed as per the DART trial protocol (Doyle et al., 2006).

6.6 Use of Cyclo oxygenase inhibitors for PDA treatment

Use of cyclo oxygenase inhibitor has been in practice since 1975 when Ment et al reported it reduced IVH apart from closing PDA. Since then indomethacin and ibuprofen have been used in a number of clinical trails to reduce the co-morbidity of PDA associated with RDS and preterm babies. For few years only IV Ibuprofen is commercially available in UK.

The use of NSAID for closure of PDA has mainly two-fold approach in UK-

a. Use of Ibuprofen as early prophylaxis –defined as attempt to close the PDA within 72 hours

b. Late symptomatic closure.

Early prophylactic closure was based on routine echocardiographic assessment. This was based on echo finding of large PDA (i.e. PDA diameter of ≥ 1.5mm, and a Pulsatile or growing flow pattern in PDA).

Late symptomatic treatment was based on clinical findings and difficult ventilation management attributed to presence of significant PDA in absence of other obvious cause. In view of lack of clear evidence on the treatment approach, the decision to treat is left to the discretion of the attending physician.

6.7 Vitamin A for preventing chronic lung disease

In a meta analyses of Vitamin A for prevention of bronchopulmonary dysplasia (Darlow and Graham, 2011) compared nine studies (1291 infants). They report intramuscular vitamin A seems to be beneficial in reducing death or oxygen requirement at one month of age (RR 0.93, 95% CI 0.88 to 0.99; RD -0.05, 95% CI -0.10 to -0.01; NNTB 20, 95% CI 10 to 100; 1165 infants) and oxygen requirement at 36 weeks postmenstrual age (RR 0.87, 95% CI 0.77 to 0.98; RD -0.08, 95% CI -0.14 to -0.01; NNTB 13, 95% CI 7 to 100; 824 infants). However the uptake for this evidence has been poor perhaps from the need for multiple intramuscular doses.

6.8 Use of inhaled Nitric Oxide therapy

There is no clear evidence in the use of inhaled Nitric Oxide (iNO) therapy in preterm infant. The lack of evidence is from wide variation in the gestation of the infants, dosage regimes, timing of the treatment intervention and duration of treatment.

Based on various trial entry criteria, one of the classifications as a treatment strategy (Subhedar and Dewhurst, 2007) is :

- Early prophylactic- when treatment is instituted < 72 hours,
- Early rescue treatment -when treatment is given in the first week of life and
- Late treatment -when treatment is commenced more than 72 hours of life

Early prophylactic treatment confers marginal benefits for the combined outcome of death and chronic lung disease. However, this effect was only seen in a sub group (infants weighing at least 1000 grams) of the study population (Kinsella et al., 2006). Similar effect was seen in study involving preterm infants with mean gestation 27 weeks and mean birth weight of 1000 grams stratified in five groups (Schreiber et al., 2003).

All other strategies have shown no benefits in the group receiving nitric oxide therapy. Therefore, current treatment approach in both the units use inhaled Nitric oxide therapy on a case-by-case basis.

7 Methods

7.1 Introduction

Mechanical ventilation is an art in as much it is a science. Current treatment strategy to ventilate newborn babies has evolved over the years. There are a number of modalities and modes of ventilation but the underlying principle is to choose the mode as per the underlying lung disease.

Once the infant is stabilised the process of weaning commences and the work of breathing is gradually transferred from the ventilator to the infant. There is limited evidence on the best mode of weaning and the strategies to wean preterm babies on ventilator. It is often experience based rather than evidence based.

Synchronised Intermittent Mandatory Ventilation (SIMV) is the most popular form of assisted mechanical ventilation(Van Kaam et al., 2010) in Europe and UK (Mallya et al., 2010). A general perception is infants weaned on SIMV mode of ventilation could be disadvantaged from fatigue prior to extubation. Pressure support ventilation could help by providing the 'inspiratory boost' to overcome resistance of the ventilator system. This could be advantageous for gradual shift of work of breathing to infant.

In a randomised controlled trial comparing SIMV alone to SIMV+PS (up to 50% of the Peak inspiratory pressure), addition of PSV facilitated shorter duration of ventilation (Reyes et al., 2006).

Though there is no consensus on the best approach to wean the infant off mechanical ventilation, clinicians agree that prolonged mechanical ventilation should be avoided to prevent Ventilator Induced Lung Injury (VILI).

The following questions remain largely unanswered.

a. How to define weaning on mechanical ventilation?
b. When to commence weaning?
c. Mode of respiratory support during weaning
d. Predicting successful extubation

 SIMV is time cycled pressure or volume controlled ventilation with fixed inspiratory and expiratory time which could cause patient ventilator asynchrony and thereby VILI needing prolonged ventilation. PSV is a flow cycled pressure limited mode of ventilation. PSV has the advantage of letting the infant take control of the frequency and the duration of breathing with the benefit of better patient ventilator synchrony and less VILI perhaps needing shorter duration of ventilation. In addition, variable flow feature to satisfy patient demand provides comfort. In pure PSV mode there is no back up rate. Hence to tackle apnoea of

prematurity, in neonatal medicine, PSV is always provided along with SIMV.

7.2 Objectives

To study if weaning on Pressure support ventilation (PSV) as compared to Synchronised intermittent mandatory ventilation (SIMV) affects duration of weaning from mechanical ventilation in preterm infants born between 23+0 and 31+6 weeks gestation.

7.2.1 Primary outcome

The primary outcome of interest for this study was duration of weaning on mechanical ventilation. The duration of weaning was defined as the time interval from commencing the randomised mode to passing the minute ventilation test.

7.2.2 Secondary outcomes

The secondary outcomes for this study include:

a. Total duration of mechanical ventilation

b. Incidence of extubation failure

c. Duration of non invasive respiratory support post-extubation

d. Total duration of respiratory support until discharge or death

e. Discharged on home oxygen

f. Bronchopulmonary dysplasia at 36 weeks post menstrual age

g. Air leak post randomisation needing treatment

h. Pulmonary Haemorrhage

i. Definitive or complicated Necrotising enterocolitis (NEC) – stage II or III

j. Weight gain until discharge or death

k. Retinopathy of prematurity (ROP) Stage 2 or more

l. Patent Ductus Arteriosus (PDA)

    a. PDA Requiring medical treatment

    b. PDA requiring surgical closure

m. Severe IVH (Grade 3/4)- Intra-ventricular haemorrhage with ventricular enlargement or parenchymal extension

n. Cystic Periventricular leukomalacia (PVL)

o. Number of Sepsis episodes

p. Death before discharge

7.3 Definition of secondary outcomes

7.3.1 Total duration of mechanical ventilation

Time when mechanical ventilation via endotracheal tube was first commenced to the time when the infant was successfully extubated.

7.3.2 Incidence of extubation failure

This was defined as need for re intubation and mechanical ventilation through endotracheal tube within 72 hours of extubation.

Re-intubation criteria: pH<7.25 with pCO_2 >8 kPa and or FiO_2 more than 50%.

If such a situation occurred, the infant would be weaned as per study protocol in the previously assigned mode.

Data on extubation failure was prospectively collected.

7.3.3 Duration of non invasive respiratory support post extubation

Non-invasive respiratory support was defined as providing respiratory support through an interface that does not cross the vocal cords. This could be a nasal interface using any pressure generation device. Common nasal interface during the study period included nasal mask or prongs, or nasal cannulae to deliver positive airway pressure. The unit policy was to use 'bubble CPAP' post extubation initially but on a case-by-case basis clinical decision for using variable flow CPAP was also considered e.g. in presence of moderate to severe nasal injury. As a step down approach, High Flow Nasal Cannula oxygen was also provided in some babies. The use of bi-level CPAP was left at the discretion of the clinician but this was not routinely practiced. Thus duration of non-invasive respiratory support was calculated as the total duration of all these methods of delivering respiratory support during the infant's stay in the neonatal unit after extubation.

7.3.4 Total duration of respiratory support

This was calculated by accounting respiratory support type recorded contemporaneously by the nurses on an hourly basis in their observation charts. This includes total duration of mechanical ventilation and non-invasive respiratory support until discharge or death.

7.3.5 Discharge on home oxygen

If the infant was discharged on home oxygen therapy to maintain oxygen saturation above 94%, a pre-discharge overnight saturation study was performed to confirm the proportion of time spent below the threshold to justify home oxygen supplementation.

7.3.6 Bronchopulmonary dysplasia

Data was collected to define severity of BPD. Babies who required oxygen supplementation or any respiratory support for more than 28 days were assessed at 36 weeks post-menstrual age. Severity of BPD was classified as mild, moderate and severe (Sahni R, 2005, Ehrenkranz et al., 2005). It was aimed to perform Jones test (Walsh et al., 2003) to define percentage of oxygen requirement in babies requiring <30% oxygen but no respiratory support. Supplemental oxygen was provided just enough to maintain saturations as per unit policy and recorded for classification.

7.3.7 Air leak post randomisation

Only large collections of extra-pulmonary air reported after initiating the allocated mode of study, confirmed by chest x-ray and needing intervention such as needle thoracocentesis and or chest drain insertion as part of clinical management were recorded for analysis.

7.3.8 Pulmonary Haemorrhage

Pulmonary haemorrhage was defined as either frank blood or 'pink stained' endotracheal tube secretions with clinical signs of deterioration such as increase in ventilator requirements, escalation of respiratory support including increase in oxygen or change in biochemical profile, and or clinical condition sufficient to instigate blood products for treatment was considered as significant pulmonary haemorrhage and recorded for data collection.

7.3.9 Necrotising enterocolitis

Necrotising enterocolitis (NEC) was defined using Bell's staging criteria. Only definitive or complicated NEC (stage 2 or worse) was considered significant. We considered NEC definitive, if the infant was kept nil orally and commenced on at least 5 days antibiotics regime to cover anaerobic microorganisms.

7.3.10   Weight gain

The difference between infant's discharge weight and birth weight was divided by the length of stay in the hospital to work out average weight gain per day.

7.3.11   Retinopathy of prematurity

Babies were routinely screened as per the unit protocol (beginning 6 weeks postnatal age). Only stage 3 and above was considered as significant and included in data analysis (Association of Perinatal, 1996).

7.3.12   Patent Ductus Arteriosus

Babies were managed for PDA either conservatively, medically or those who required surgical closure of PDA. Data was collected for babies who received medical treatment for PDA or surgical closure. Medical treatment was offered either as targeted early treatment in first 72 hours using echocardiography or late symptomatic treatment at clinician discretion. The drug used for medical closure was ibuprofen.

7.3.13   Intraventricular Haemorrhage

As per unit policy cranial ultrasonography was performed either by Consultant Radiologist and or trained ultra sonographer in the first week of life and again at six weeks postnatal age. However if there were clinical concerns additional scans were performed. Standard views

were obtained to establish normality or for classifying the extent of the bleed as proposed by Papile (Papile et al., 1978).

7.3.14   Hydrocephalus needing shunt

Following any intracranial bleed the neonate was monitored at weekly intervals and their head circumference plotted on the age specific growth charts. If there were any clinical concerns with regards to increase in head circumference or ultrasound findings on head scan, a neurosurgical consultation was requested. If hydrocephalus was diagnosed, further management was continued as per the advice of neurosurgical team. Data on babies requiring shunt insertion for management of hydrocephalus was recorded for comparison.

7.3.15   Cystic Periventricular leukomalacia

PVL was defined as cystic changes in the periventricular white matter region. This was defined as either present or not present (Khwaja and Volpe, 2008).

7.3.16   Sepsis

Definitive sepsis episodes were defined as either a positive growth of a virulent micro organism in either blood, CSF or urine specimen which was obtained due to clinical concerns in the infant necessitating antibiotic treatment. In addition, if the infant received at least five days treatment of antibiotics without any positive growth then this was also considered as sepsis episode

7.4 Study site

This was a multicentre randomised controlled trial. The two participating centres recruiting infants were University Hospital of North Tees (SITE 1), Stockton-on-Tees and James Cook University Hospital (SITE 2), Middlesbrough. Both the units are level three neonatal units as per British Association of Perinatal Medicine Criteria. SITE 1 has 5 intensive care cots and SITE 2 has 10 intensive care cots. There were a total of 203 admissions of infants less than 32 weeks gestation in the two years preceding the study period in the two centres. The units are part of the Northern Neonatal Network and represent neonatal care for the south of the region. There is a well-established 24-hour neonatal transport service for ex-utero transfer of babies from other hospitals in the region requiring intensive care treatment.

7.5 Inclusion criteria

Infants born between 23+0 weeks and 31+6 weeks' gestation ventilated for respiratory distress from surfactant deficiency were eligible for participating in this study. RDS was diagnosed as respiratory insufficiency manifested by either rising oxygen requirement or inadequate CO_2 clearance along with clinical signs of respiratory distress. The diagnosis of surfactant deficiency was confirmed by age at presentation, chest X-ray findings and clinical presentation of the infant adjudged by the clinician on call.

The other mandatory criteria before considering randomisation were:

1. Need for mechanical ventilation for at least 6 hours – this criterion excluded infants who could have been managed by non-invasive respiratory support and therefore not reflecting the true cohort of infants with surfactant deficiency needing mechanical ventilation. This criteria helped to eliminate selection bias

2. Signed parental consent

7.6 Exclusion criteria

Infants were excluded from participating in the study if they had

- Antenatally diagnosed severe congenital anomalies affecting survival and in particular known airway anomalies
- Known neuromuscular abnormalities
- No parental consent.

7.7 Ethics

The national research ethics committee via the Integrated Research Application System (IRAS) and the Hospital Research and Development Department reviewed the study protocol and provided approval. The trial was registered at the International Standard Randomised Controlled trial registry and a unique identifier issued

(ISRCTN74272142). University hospital of North Tees was the sponsor for this study. The study protocol was also reviewed by an external expert who was well researched in the field of neonatal ventilation to assess the robustness of the study.

7.8 Consent

Parent information leaflet (see appendix 1) was given antenatally to expectant mothers admitted to the delivery suite whenever possible or at the earliest opportunity postnatally. A baseline eligibility form was used to screen all the admissions that helped in identifying the eligible babies for participation in the trial. Parental consent was obtained after they were given every opportunity to ask questions and seek clarification. At all stages it was highlighted that they could withdraw this consent without affecting their infants' care.

The baseline eligibility form also helped to record the reason for non-enrolment at both the sites. In addition we also had access to Neonatal Audit Programme for both the sites that recorded all admissions to the respective units to ensure eligible infants were not missed.

7.9 Randomisation

The cohort of eligible infants was stratified into three groups based on their gestation at birth. This was done to allow both study groups balanced for gestation.

Gestation at birth	Acronym
23^{+0} to 25^{+6}	Very Very Prem group (VVPrem)
26^{+0} to 28^{+6}	Very Prem group (V Prem)
29^{+0} to 31^{+6}	Prem

A Consultant in Tropical medicine with an interest in clinical research based at SITE 2 helped to generate the concealed randomisation sequence. He was not involved with the trial in any other way. Block randomisation with a variable block size of two to six blocks using random number tables was used. The sequence was emailed to the ward matron. She was also not involved with the study at any stage. The sequence was sealed in an opaque sealed envelope which were serially numbered and marked and placed in three separate boxes clearly showing the stratified group as listed above. The infant was randomised only if he/she met all of the inclusion criteria and exclusion criteria.

At the time of randomisation, a log was maintained with the patient details with the assigned mode with date and time recorded. The opaque envelope was kept with the eligibility form for later verification.

As this was an open labelled trial, allocated mode was highlighted at the bed side and on their ventilator to remind health care professionals to follow weaning as per the assigned mode to prevent cross over and contamination from trial protocol violation.

7.10 Ventilation strategies

Intubated infants received porcine exogenous surfactant at a recommended first dose of 200 mg/kg (Sweet DG, 2010) Infant received further 100 mg/kg dose of surfactant treatment if despite the first dose they needed more than 30% oxygen and mean airway pressure on ventilator of >8 cm H_2O at 12 hours of life. Volume controlled ventilation modality was the preferred method to commence mechanical ventilation in both the units. All babies needing mechanical ventilation were commenced on volume controlled Assist Control mode (A/C mode). In the occasional circumstance, when A/C mode failed to provide adequate support then High Frequency Oscillatory Ventilation (HFOV) was commenced. Use of HFOV did not exclude the eligible infants from participation and further weaning in the assigned mode. Avea ventilator (Care Fusion corporation, San Diego, USA; previously Viasys Healthcare) was used in both the units.

Both nursing and medical staff received regular training and updates and was comfortable in troubleshooting routine problems with use of ventilator.

The ventilator trigger systems use variable orifice differential pressure flow transducer or pneumotachograph near the proximal end of the endotracheal tube to detect small variation of flow in the ventilator circuit. Routinely the flow trigger is usually set at 0.2 L/minute. Whilst in the assist control (A/C) mode, the initial back up rate was set between 40 and 60 breaths per minute. Oxygen supplementation was titrated to maintain saturations as per unit policies. This was changed after the BOOST II trial interim report (Stenson et al., 2011). After the recommendations, at SITE 1 policy was changed from targeting 88-92% (lower alarm limit at 85% and upper limit at 95%) to targeting oxygen saturations between 91-94% (lower alarm limit at 90% and upper at 95%). Whilst at SITE 2, target oxygen saturation was changed to 91-94% with alarm limits of 85-95%. A check X-ray was performed routinely in all infants post intubation to verify tube position and to assess the severity of surfactant deficiency (Slama et al., 1999).

Infants were monitored hourly with ventilator observations documented in the intensive care charts as usual practice. Ventilator adjustments in the initial stages aimed at maintaining tidal volumes between 4 and 6mls/kg/breath. PEEP was initially commenced at 5 cms H_2O but this was adjusted and increased to 6 cms H_2O or higher if the Pressure

Volume loops reflected need of higher PEEP for lung opening. Blood gas analysis to manage ventilation was decided by the clinician on a case-by-case basis.

The trial protocol was rigorously implemented for ventilation management after entry into the trial and therefore all acute care aspects of the infant were managed as per standard unit policies.

A loading dose of caffeine citrate (20mg/kg) was administered to the infant followed by 5mg/kg maintenance dose (Schmidt B, 2006). It was a standard practice in both the units and caffeine administration was commenced early during the course of ventilation.

There was variable use of low dose Morphine infusion for pain relief and for comfort whilst receiving mechanical ventilation (Anand et al., 2004). Although some physicians chose to use it during the acute phase of the illness, it was stopped before the infant was commencing the randomised mode. In the occasional situation when a more mature infant with BPD was unsettled and 'fighting' the ventilator, other measures such as Chloral Hydrate was provided for sedation to achieve better patient ventilator synchrony.

7.11 Trial entry criteria

Randomised infants were commenced in the assigned mode if the infant maintained all of the following parameters for at least two consecutive hours. This was recorded on trial enrolment form (Appendix 3):

- Mean airway pressure less than 10 cm H_2O

- FiO_2 less than 40%

- Good respiratory drive demonstrated by spontaneous breaths more than or equal to 50% of the total respiratory rate.

As an aide memoir, nursing staff caring for the infant was also required to maintain a 'tick box' chart (see Appendix 3) indicating the infant meeting the trial entry criteria. This served as prompt and as a trigger to the clinician on-call suggesting the infant is ready to commence the randomised mode.

This was a slight deviation from the normal practice in both the units. Infants were traditionally weaned significantly on the volumes or pressures whilst in the A/C mode before switching to the partial support modes such as SIMV with PSV. In the present study, infants were commenced on the weaning modes when they met the aforesaid weaning criteria.

Hence, weaning in the assigned mode commenced earlier than routine practice perhaps. Weaning in the control arm (SIMV +PSmin group) was primarily reducing high back up rate to a rate of 10 (section 7.13) and weaning in the intervention arm (PSmax +10 breaths of SIMV) was primarily reducing pressure support level to PSmin before performing the minute ventilation test (section 7.14).

7.12 Overview of Ventilation management

Eligible preterm infant (23+0 to 31+6) with RDS requiring mechanical ventilation, stratified into three groups (23-25+6, 26-28+6, and 29-31+6) at randomisation

Control Arm -conventional (SIMV group)

Intervention arm (PSV group)

Commence SIMV at 40/min delivering Vti 4-6mls/kg and PS_{min} to deliver 2-3mls/kg for other spontaneous breaths

Commence PS_{max} to deliver 4-6mls/kg with low SIMV rate of 10/min to deliver 2-3mls/kg

Wean by decreasing SIMV rate maintaining constant PS_{min} until SIMV reaches 10 breaths/min.

Wean PS_{max} until PSV reaches PS_{min} delivering 2-3mls/kg with constant SIMV at 10breaths/min

Minute ventilation test If MVs: MVm >50% then extubate

Extubate when above criteria achieved. Commence CPAP at 6cms if necessary and continue weaning as per unit protocol.

RDS- Respiratory Distress Syndrome of Newborn
SIMV- Synchronous Intermittent mandatory ventilation
PSV- Pressure support ventilation
PS_{min}- Minimum pressure support (2-3mls/kg)
PS_{max}-Maximum pressure support (4-6mls/kg)
TV -Total Ventilation =Minute ventilation (MV)
MVM- Mechanical MV
MVS- Spontaneous MV

Consider Re intubation if:
- $pH < 7.2$ & $pCO_2 > 8.0$
- major apnoea requiring IPPV
- $FiO_2 > 0.6$

7.13 Weaning on Synchronised Intermittent Mandatory Ventilation

At all stages review the infant clinically at least every 12 hourly for weaning

Infants with RDS and ventilated by Volume or Pressure A/C mode and achieved entry point criteria and randomised to SIMV group

Loading dose caffeine citrate = 20mg/kg

Monitor leak
Aim <25% to maintain PEEP

(SIMV group)
Commence SIMV at 40/min and volumes/pressures aiming Vti 4-6mls/kg/breath
Provide constant PS_{min} for spontaneous breaths aiming to deliver 2-3mls/kg **(this should not change)**.

Wean SIMV as tolerated, with constant PS_{min}
Attempt to maintain minute ventilation (MV) 240-360mls/kg/min
Continue daily maintenance caffeine 5mg/kg/day, increase to 10mg if necessary.

If TV is not satisfactory and/ or blood gas not satisfactory go back one step

If recurrent apnoeas or major apnoea needing IPPV or
pH <7.25, pCO_2>8.5, or FiO_2>0.6 to maintain saturation as per unit protocol

If well

Continue weaning SIMV until delivering 2-3mls/kg Vti at 10 breaths /min with constant PS_{min}

Perform Minute ventilation test- if MVs: MVm is > 50% with no bradycardia, apnoea or desaturation needing >10% FiO_2 then extubate.

Extubate when above criteria met with acceptable gas exchange
Commence CPAP at 6 cm of H_2O and wean as per departmental protocol.

7.14 Weaning on Pressure Support Ventilation

Infants with RDS and ventilated by Volume or Pressure A/C mode and achieved entry point criteria and randomised to PSV group

Ensure loading dose of caffeine citrate = 20mg/kg is given

Monitor ET leak, aim <25% to maintain PEEP. Review at least 12hourly for weaning

Intervention arm (PSV group)
Pressure Support (PS$_{max}$) to support spontaneous breaths at 4-6mls/kg
Provide SIMV at backup rate of 10 breath/minute delivering 2-3 mls/kg Vti
(this should not change)

- Wean PS by 1 -2 cm and maintain constant SIMV at 10 breaths/min
- Continue daily maintenance caffeine 5mg/kg/day, increase to 10mg as indicated
- Attempt to maintain minute ventilation (MV) 240-360mls/kg/min

Monitor clinically at least 12 hourly along with the hourly observations Blood gas every 8 hourly or as clinically indicated.

If blood gas is not satisfactory go back one step.

- If recurrent apnoeas or major apnoea needing IPPV or
- Poor blood gas: ph<7.25, pCO$_2$>8.5 and or FiO$_2$ >0.6 to maintain saturations as per unit protocol

If well

Continue weaning PS until PS$_{min}$ aiming to deliver 2-3mls/kg to support the spontaneous breaths with constant SIMV at 10 breaths/min

Perform Minute ventilation test- if MVs: MVm is > 50% with no bradycardia, apnoea or desaturation needing >10% FiO$_2$ then extubate.

Commence CPAP at 6 cm of H$_2$O and wean this support by 1 cm every 12 hours to a minimum of 4 cm.

At all stages review the infant clinically at least every 12 hourly for weaning

7.15 Minute ventilation Test

Minute ventilation test (MVT) was used as an objective assessment for readiness to extubation. MVT test was originally used in SITE 2 in different clinical studies (Singh et al., 2006, Gillespie et al., 2003, Gupta et al., 2009b).

The Minute ventilation test consisted recording heart rate, respiratory rate, oxygen saturation, oxygen requirement, minute ventilation and tidal volumes for five consecutive minutes whilst on minimal mechanical ventilation (MVM) followed by five further consecutive minutes whilst spontaneously breathing (MVS) on endotracheal CPAP (no pressure support and no mandatory back). The average minute ventilation during the two epochs was used for calculating the ratio.

7.15.1   MVT success criteria

If MVS /MVM was more than 50% the infant was deemed ready for extubation or 'PASS'.

7.15.2   MVT failure

The infant was considered to be failing the MVT test if it developed:

- o Severe bradycardia following hypoxia needing IPPV **and or**
- o If the oxygen requirement was more than 15% above the baseline to maintain oxygen saturation

The test was repeated again in eight hours if there was no further changes in the clinical condition.

7.16 Post extubation management

After passing the MVT, all possible steps were taken to minimise the delay in extubation and further management on non-invasive respiratory support. 'Bubble CPAP' was the default method of non-invasive respiratory support due to putative advantage of shorter duration of CPAP support. Such an approach has been shown to be helpful in infants ventilated for less than 14 days (Gupta et al., 2009b). If bubble CPAP was not available then variable flow CPAP device was commenced. In either case CPAP was commenced at 6 cms H_2O and reduced every six to twelve hours to a minimum of 4 cms H_2O before discontinuing. If CPAP needed recommencing then it was recommenced at 6 cms H_2O pressure.

Bi-level CPAP was not a routine mode of respiratory support and this was left to the discretion of the senior clinician on a case-by-case basis to limit re-intubation when clinically considered to be beneficial. When Synchronised Bi-level CPAP was commenced, a back up rate of 30 breaths per minute was provided. Bi-level CPAP commenced with an inspiratory peak pressure of 9 cms H_2O and positive end expiratory

pressure of 6 cms H_2O. This was assessed every 6 hours and weaned by one cm H_2O pressure whenever possible before discontinuation of CPAP.

Humidified High flow nasal cannula oxygen was used as step down approach in infants who developed respiratory distress after weaning off CPAP therapy. The flow was never prescribed more than 8 L/min.

As per unit policy whenever possible while receiving non-invasive support, nasal interface was alternated between nasal prongs and nasal mask to minimise nasal injury.

7.17 Re intubation criteria

The trial protocol suggested to consider re-intubation if there were any or all of the following features:

- Respiratory compromise was evident along with increasing oxygen requirement (FiO_2 >60%)
- Uncompensated respiratory acidosis developed (pH<7.20, and pCO_2 >8 kPa
- Major apnoea needing intermittent mandatory ventilation or a major cardio vascular compromise requiring resuscitation.

If the infant was re-intubated within 72 hours of extubation then weaning on mechanical ventilation was commenced in the previously assigned mode. If re intubation occurred any time later than 72 hours post-extubation, then weaning on mechanical ventilation was left at the discretion of the attending clinician.

7.18 Serious Adverse Events reporting

Considering the gestation of the infants included in this study, the following were considered as expected serious adverse events that did not merit reporting for further investigation:

- Necrotising enterocolitis
- Chronic lung disease
- Air leak syndrome
- Pulmonary haemorrhage

- Intracranial haemorrhage

- Retinopathy of prematurity

- Death- Local policy of child death review was followed.

These outcomes were investigated as secondary outcomes of interest.

Any other adverse events was planned for further follow up by the research team until complete resolution of the issue was identified. During such a time it was at the discretion of the clinical team to decide whether to continue the infant in the study and follow the trial protocol.

7.19 Co-intervention and contamination

There were two other studies conducted at the same time as this study with concomitant recruitment of the eligible infants into these research trials.

1. Multicentre randomised controlled trial investigating Iodine Supplementation in preterm infants born less than 31 weeks gestation (I2S2 Trial Clinical trial number NCT 00638092). This was a double blind placebo controlled trial investigating the effect of Iodine supplementation on long term neurodevelopmental outcome at two years corrected age. However this was not a competing study. Participating in this study did not exclude infants from participating in other studies.

2. A multicentre randomised controlled trial investigating CPAP or SiPAP (CoSi trial Controlled trial registry number 15997073) in

preterm infants born between 28^{+0} and 31^{+6} weeks gestation as primary mode of respiratory support. The trial included only those infants who did not receive any positive pressure ventilation via endotracheal tube immediately after birth. Hence infants who progressed to receive an endotracheal tube were eligible to recruit in POST trial. Non-invasive respiratory support prior to intubation is not considered to have any effect on duration of ventilation including weaning on mechanical ventilation. As there was an emphasis on both studies, non-invasive respiratory support at birth perhaps helped to recruit infants who truly required endotracheal intubation for respiratory distress.

7.20 Duration of the study

After obtaining ethics and research approvals the study at SITE 1 commenced in January 2011 with first infant recruited on 26/01/2011. The study started recruitment at SITE 2 in August 2011 with first patient recruited on 20/09/2011.

However, due to slower than expected recruitment at one of the two centres it was decided by the data monitoring committee to stop the study with 93 infants instead of 110 infants as planned initially and to analyse the results for primary outcome analysis to write this dissertation in order to fulfil the student requirement to obtain the Doctorate in Medicine pending submission.

7.21 Data collection

Data collection was recorded on standard case report forms (see Appendix 5). The data was collected prospectively and completed at the time of discharge or death of the infant. Patient confidentiality was maintained at all stages and only necessary information relevant to the study was extracted from the case notes. The data collection and storage followed the guidance as per Caldecott guardian. This was later transcribed onto excel spread sheet for further analysis using SPSS® statistical software. At all stages data protection guidelines was followed. At the time of final analysis, accuracy of the transcription was confirmed by manually validating the data.

8 Statistical analysis

8.1 Sample size and Power estimation

Sample size calculation was based on the results from a previous randomised controlled trial comparing volume controlled ventilation to time cycled pressure limited ventilation (Singh et al., 2006). The weaning protocol followed in that trial is currently the standard practice in both the units and served as the control arm in this trial. They reported duration of weaning (achieving mean airway pressure ≤ 8cm H_2O for 12 consecutive hours) using SIMV in volume-controlled mode with minimal pressure support as 80 hours. To show a difference of 25% between the two arms at 80% power and two sided alpha of 0.05 we would need a total of 162 infants and at similar alpha level with 80% power to show a 40% difference we would need a total of 66 infants (SAS 9.4 TS Level 1M0). Based on this we chose to demonstrate a 33% difference (80 vs. 53 hours) a therefore a total of 90 babies were required (45 in both groups) with a two sided alpha of 0.05 and 80% power.

8.2 Statistical tests

All data were analysed on an intention to treat basis with all randomised infants included. To determine the statistical test for the analysis the data was checked for normality using Kolmogorov-Smirnov test. Parametric or non-parametric statistical methods were used

accordingly if the data was normally distributed or not. Unpaired Students t test or Wilcoxon rank- sum test or Mann Whitney U test was used comparing the control and the study arms. Chi square test was used to compare the categorical outcome measures.

Spearman's correlation coefficient of variables on primary outcome was. run to predict the variables thought to have significant impact on Primary Outcome.

Time based analyses of duration to achieve the primary outcome measure and duration of ventilation was done using Kaplan-Meier curves. A log rank test was run to determine if there were differences in the survival distribution between the two groups.

All statistical analyses were performed using SPSS for windows version 22 (SPSS Inc., Chicago, Illinois).

9 Results

9.1 Enrolment

After obtaining approvals from the National Ethics Committee and the Hospital Research and Development department the study commenced recruiting at SITE 1 in January 2011 and in August 2011 at SITE 2 site. A total of 247 babies were identified eligible for enrolment of which 93 were enrolled (Figure 8: Flow diagram showing recruitment and randomisation of babies).
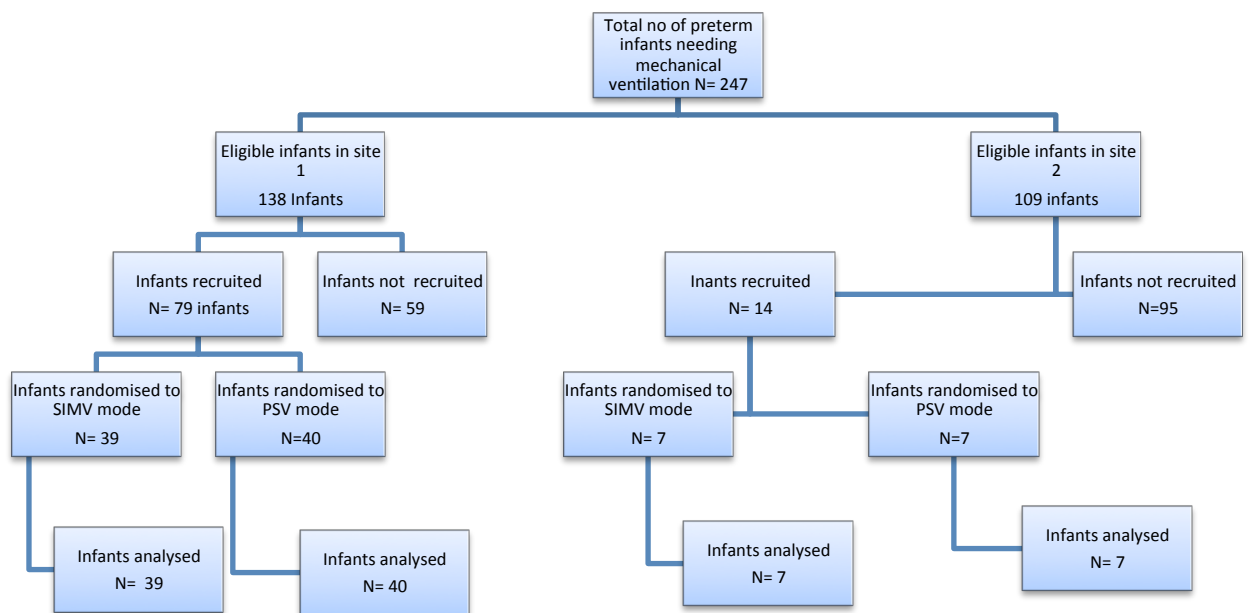
Figure 8: Flow diagram showing recruitment and randomisation of babies

The historic data for 2 years previous to commencing the study suggested an average of 10 infants in the eligible gestation group were

admitted per month i.e. 4 babies per month at University Hospital of North Tees (SITE 1), and, 6 babies per month at James Cook University Hospital (SITE 2).

Taking into consideration approximately 75% recruitment, the study was anticipated to complete in 16 months time.

However, REC approval for study extension was requested on two occasions due to slower than anticipated recruitment in one of the two centres. The study was stopped in SITE 1 in Sept 2013 with last recruitment in May 2013. Recruitment was stopped in SITE 2 earlier than SITE 1 due to poor recruitment rate in March 2013, 18 months from commencing the study, with last recruitment in October 2012.

9.1.1 Recruitment activity at SITE 1

57% of eligible infants available for recruitment were consented and randomised see Figure 9.
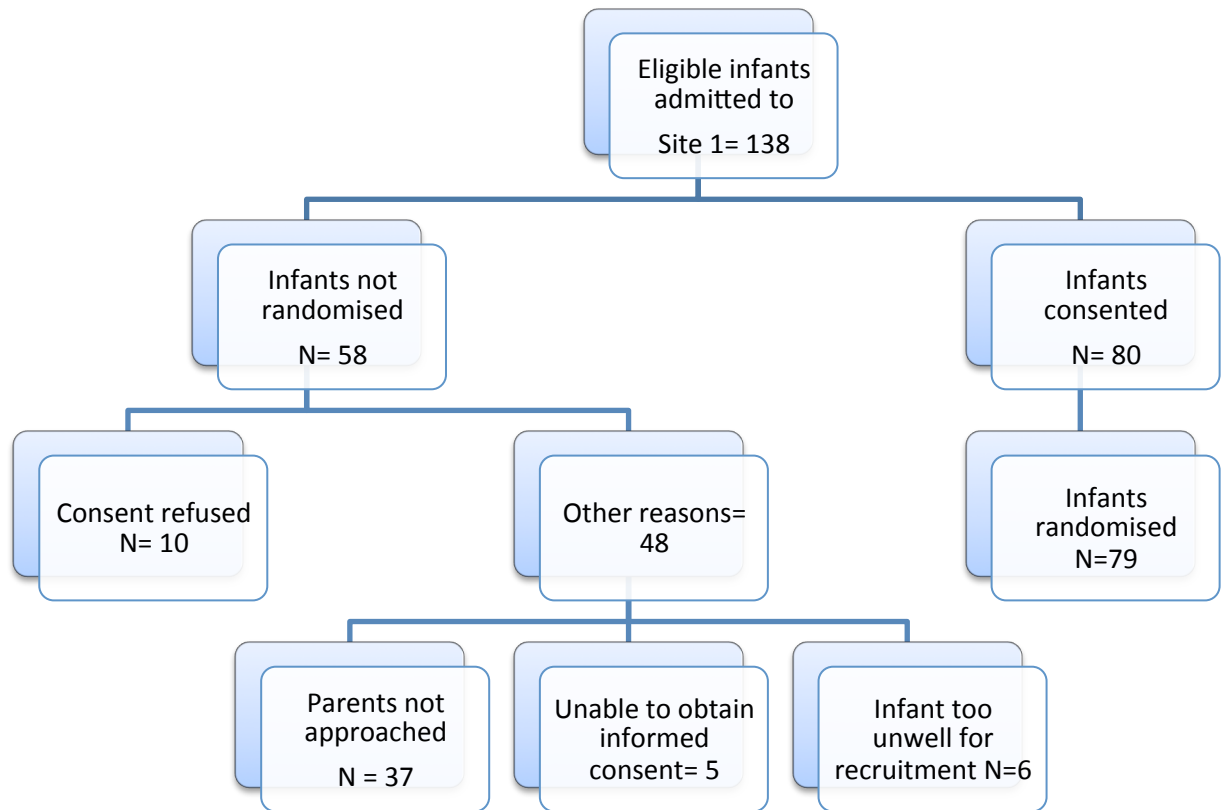
Figure 9: Flow diagram showing reason for non-recruitment of eligible infants at SITE 1

9.1.2 Recruitment activity at SITE 2

13% of the eligible infants were consented and randomised see Figure 10.
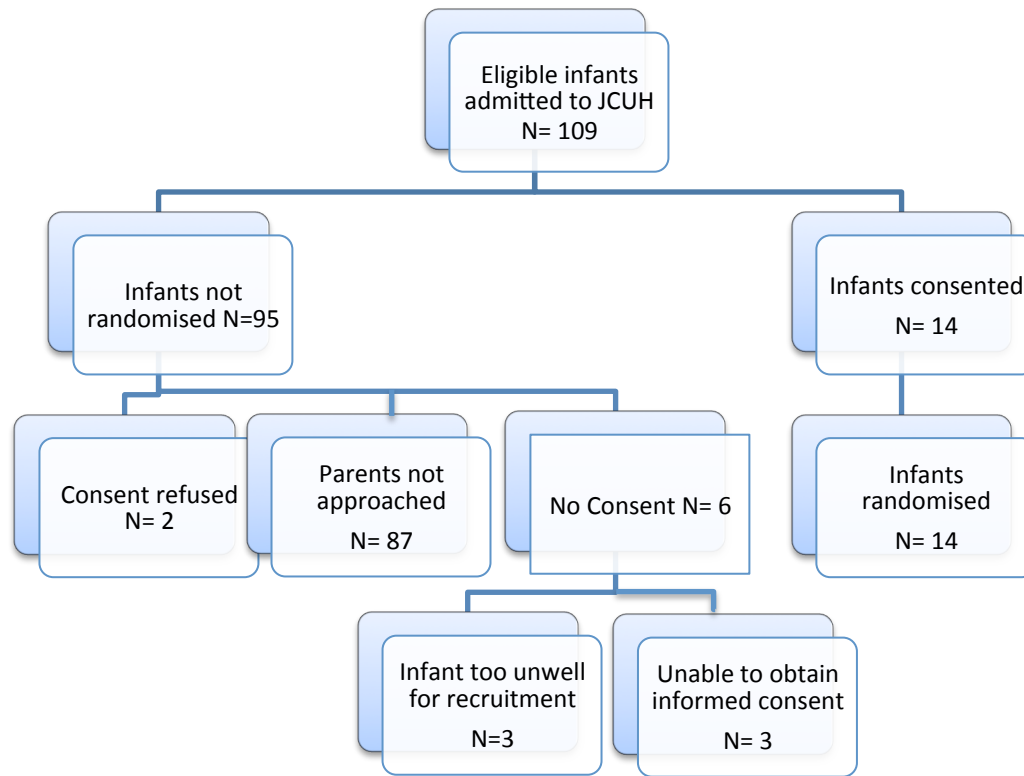
Figure 10: Flow diagram showing reasons for non-recruitment of eligible infants at SITE 2

9.2 Maternal characteristics

Characteristic	SIMV group N= 46	PSV group N= 47	p value
Antenatal steroids	43 (93.5%)	45 (95.7%)	0.490
Incomplete course	1(2.3%)	15(33.3%)	0.000
At least 1 completed course	42 (97.7%)	30 (66.7%)	0.000
No steroids	3 (6.5%)	2 (4.3%)	0.490
Prolonged rupture of membranes	12 (26.1%)	11 (23.4%)	0.476
Prelabour rupture of membranes	0	0	N/A
Chorioamnionitis*	12 (35.3%)	10 (34.5%)	0.579
Ante partum haemorrhage	7 (15.2%)	3 (6.4%)	0.149
Pregnancy induced hypertension^	4 (8.7%)	5 (10.6%)	0.514
Maternal diabetes	0	0	N/A
Mode of delivery Vaginal delivery Caesarean section	24 (52.2%)	24 (51.1%)	
1. In Labour	8 (17.4%)	10 (21.3%)	
2. Not in labour	14 (30.4%)	13 (27.7%)	0.473

Table 4: Baseline maternal characteristics

*Chorioamnionitis – defined as fever with raised inflammatory markers and/or histopathologic features

^Pregnancy induced hypertension-needing treatment

9.3 Baseline characteristics of the study population

Baseline characteristics of the babies randomised into the two groups is highlighted in Table 5

Characteristic	SIMV group N= 46	PSV group N=47	p value
Gestational age in weeks Median (IQR)	27.2 (3.83)	27.5 (3.90)	0.612
Birth weight (grams) Median (IQR)	950 (373)	980 (560)	0.439
Male infants	25 (54.3%)	28 (59.6%)	0.382
Multiple birth Twins	23 (50%)	17 (36.2%)	0.128
In born Postnatal transfer	35 (76.1%) 11 (23.9%)	36 (76.1%) 11 (23.4%)	0.574
Intubated at birth	33 (73.3%)	31 (67.4%)	0.348
Mechanical ventilation from birth	33 (71.7%)	31 (66.0%)	0.353
Modality of ventilation • Pressure limited	9 (20.5%)	4 (8.5%)	0.092

• Volume controlled	35 (79.5%)	43 (91.5%)	
CRIB 2* score Median (IQR)	9.0 (5)	8.0(5)	0.666

Table 5: Baseline characteristics of the infants

*Clinical risk index for babies II

9.4 Comparison of baseline characteristics between inborn and out born infants

Inborn infants constituted 76% of the total recruited. Table 6 shows characteristics of babies. First dose of surfactant administered was significantly different (177 mg/kg vs. 139 mg/kg). There was no other significant difference between the two groups.

Characteristics	Born in the participating centre N= 71	Postnatal transfers N=22	p value
Gestational age (weeks) Median (IQR)	27.40	28.06	0.278
Birth weight (grams)	910 (551)	1130 (344)	0.121
CRIB –II score	9 (5)	6.50 (5)	0.316
Birth order • Singleton • Higher	42	11	0.470

order	29	11	
Intubated at birth	51	13	0.193
1st dose of Surfactant (milligrams/kg)	177	139	0.008
Antenatal steroids • No dose/partial course • Full course	10 58	6 14	0.183

Table 6: Baseline characteristics of babies born at the study centre and those admitted following postnatal transfer

9.5 Comparison of the two study groups- stratification based on the gestational age at birth

The infants were recruited in three groups, based on the gestation at birth. Table 7 shows the numbers of babies recruited on each of the gestational groups.

Gestation at birth	SIMV group N (%)	PSV group N (%)	p value
$23^{+}0$ to 25^{+6}	12 (26.1%)	10 (21.7%)	1.00
26^{+0} to 28^{+6}	19 (41.3%)	21 (45.7%)	1.00
29^{+0} to 31^{+6}	15 (32.6%)	15 (32.6%)	1.00

Table 7: Proportion of babies in the randomised mode based on gestation at birth

9.6 Time duration to enrol babies into the study

The trial protocol recommended that parents of pre term infants needing mechanical ventilation be approached for consenting when the infant was stabilised. Since the trial was designed to investigate the weaning modes of ventilation it was deemed, not necessary to approach parents in the early phase to minimise parental anxiety. This also served to obtain an informed consent.

Consenting procedure was followed as per section 8.8. When consent was available antenatally or soon after birth, and the preterm infant was ventilated for more than six hours they were considered eligible for randomisation.

Figure 11 shows the bar chart of time to randomisation once eligible infants consented to participate in the trial. The median time for randomisation for both groups was less than 48 hours with IQR =1, (Mann-Whitney U test p 0.692).
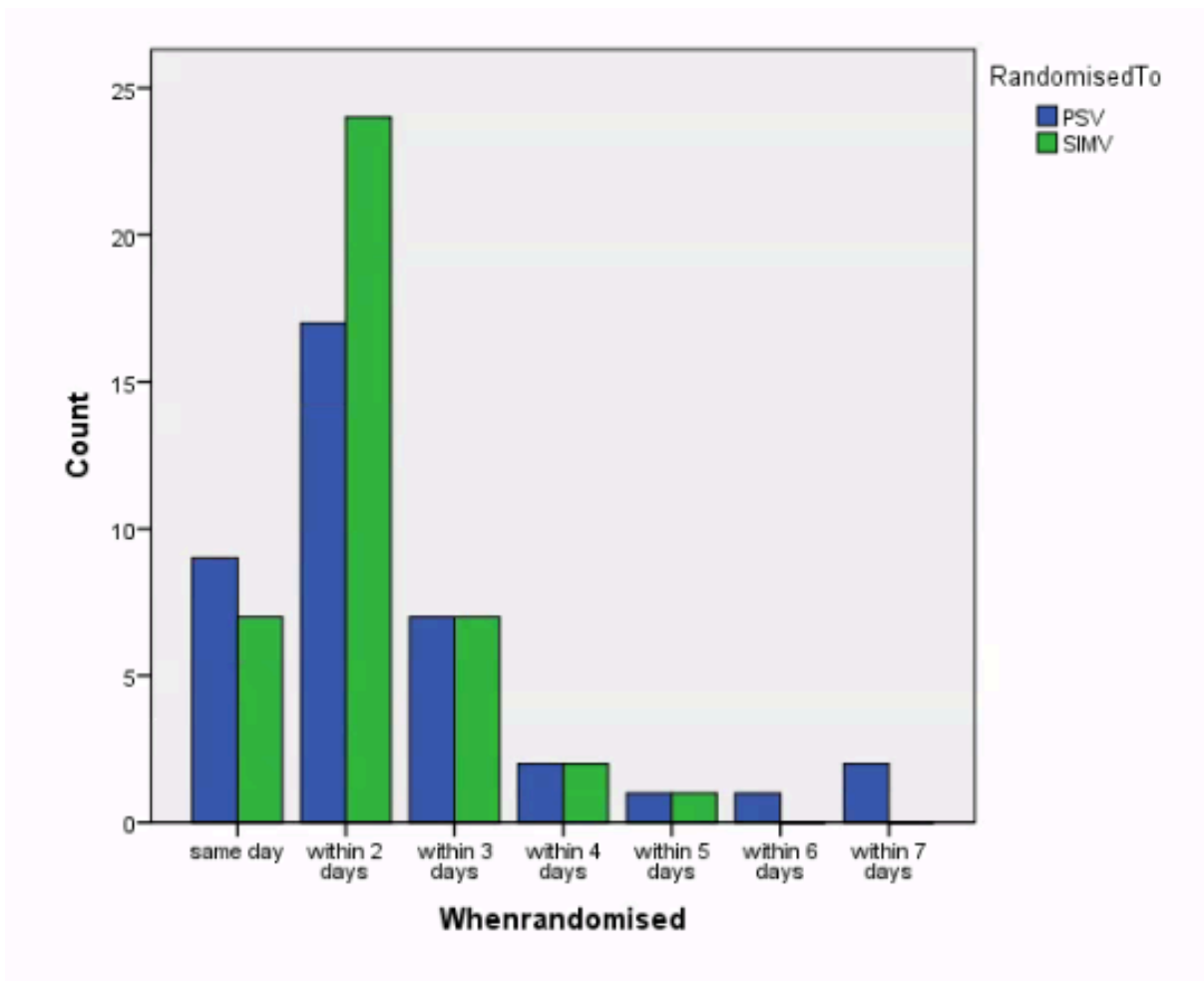
Figure 11: Box plot for time to randomisation after consent of eligible infants

9.7 Comparison of two study groups based on the length of primary mode of ventilation prior to commencing randomised mode.

Table 8 shows the proportion of time infants received the primary mode of ventilation prior to commencing randomised mode.

Duration of ventilation	SIMV N= 46 (%)	PSV N=47 (%)	p value
Up to 72 hours	35 (76%)	35 (74%)	1.00
Over 72 hours	8 (17%)	10 (21%)	1.00

Table 8 Proportion of time infants received primary mode of ventilation prior to randomisation

Note: There were 5 infants (3 from the SIMV group and 2 from the PSV group) randomised but did not commence the randomised mode due to clinical deterioration. Their data is not included in the above analysis.
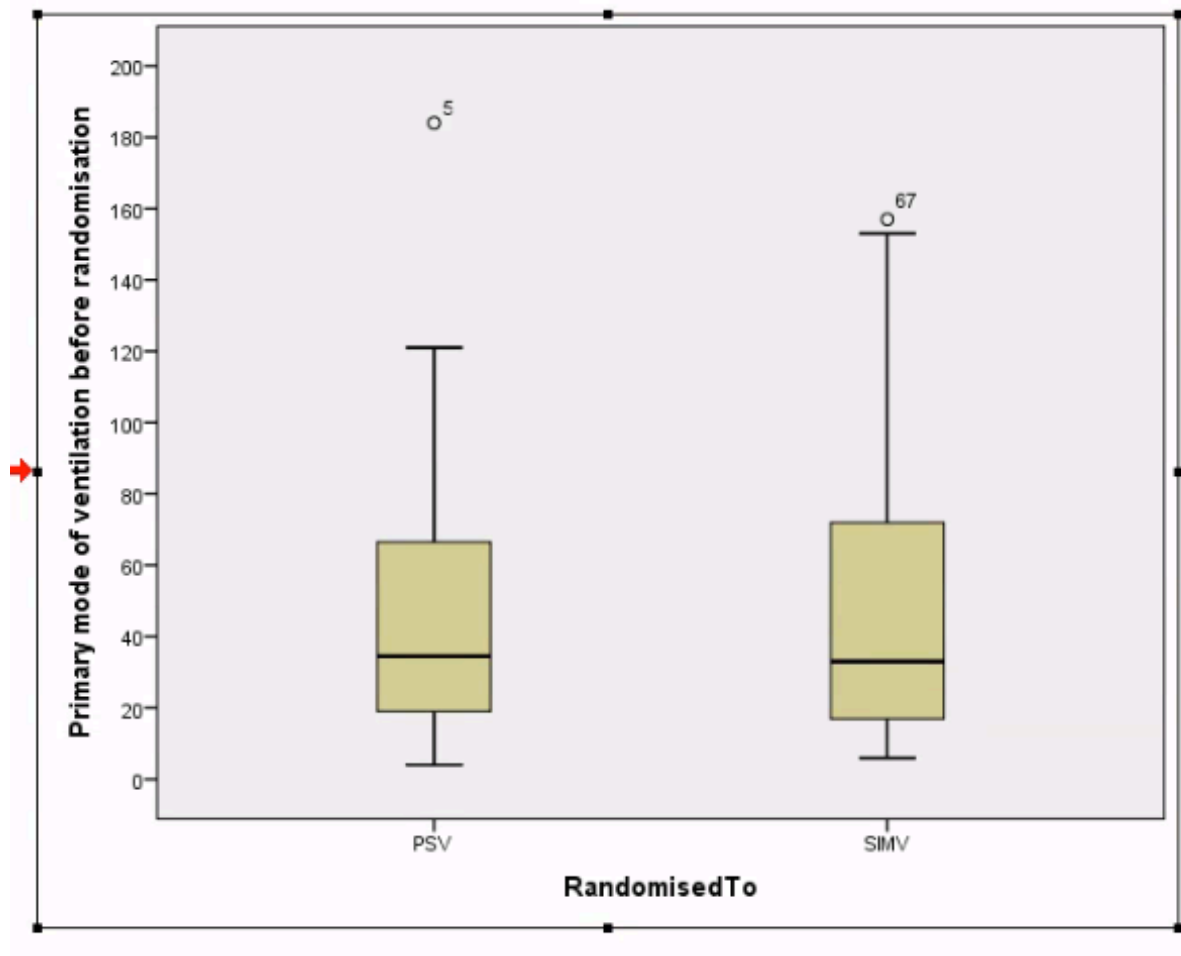
Figure 12 Box plot of the duration of primary mode of ventilation prior to commencing the randomised mode

9.8 Comparison of the severity of the lung disease prior to commencing the randomised mode

The following parameters in Table 9 were collected to reflect the severity of the lung disease from surfactant deficiency. The data was collected from the intensive care charts prospectively as documented by the nursing staff. The highest value for a particular parameter recorded for at least two consecutive hours in the ITU chart were deemed significant and used for comparison in this analysis.

Variable	SIMV mode	PSV mode	p value
Peak inspiratory pressure (cm/H_2O)	23	24	1.00
Mean Airway pressure (cm/H_2O)	9	9	1.00
FiO_2 (median)	35	30.5	0.994
Oxygenation index	10.2	8.2	0.994

Table 9: Highest ventilator settings prior to commencing the randomised mode

9.9 Comparison of disease severity based on need for multiple surfactant therapy

Table 10 shows proportion of infants needing multiple surfactant therapy. There was no significant difference between the two groups.

Surfactant therapy	SIMV N=46(%)	PSV N=47 (%)	p value
1 dose	45 (49.5%)	46 (50.5%)	1.00
2 doses	12 (26%)	13 (27.6%)	1.00
3 doses	1 (2%)	0	1.00

Table 10 Proportion of infants needing multiple surfactant therapy

9.10 Comparison of problems of primary ventilation prior to randomisation

Table 11 shows problems associated with primary mode of ventilation prior to commencing randomised mode. There was no significant difference between the two groups.

Problems of ventilation	SIMV	PSV	p value
Air leaks needing treatment	5 (11.9%)	4 (8.9%)	0.733
PIE	3 (7.1%)	3 (6.7%)	1.00
Pneumonia	0	3 (6.7%)	0.134
Pulmonary haemorrhage before randomisation	7 (17.9%)	2 (5.4%)	0.154

Table 11 Problems associated with ventilation

9.11 Time delay to commence randomised mode from when trial entry criteria achieved

A ten-hour delay in commencing the randomised mode was observed in both the groups (Table 12). Although Mann Whitney U test showed this delay was significant in both the groups with infants in SIMV arm commencing randomised mode two hours earlier than infants in PSV arm, this difference was not statistically significant (Mann Whitney U test p=0.47).

	Trial entry criteria achieved	Randomised mode commenced	p value
SIMV Median (IQR)	22.0 (27)	32.0 (34)	0.000
PSV Median (IQR)	23.50 (46)	34.5 (48)	0.000

Table 12 Time delay to commence the randomised mode after achieving the trial entry criteria

9.12 Respiratory parameters at commencing weaning of mechanical ventilation in the assigned mode

Table 13 shows the respiratory parameters at the time of commencing randomised mode. A Mann- Whitney U test confirmed there were no significant differences between the two groups.

Respiratory parameter	SIMV	PSV	p value
Mean airway pressure at weaning Median (IQR)	7 (1)	8.0 (1)	0.390
FiO_2 at weaning Median (IQR)	21% (4)	21% (2)	0.545
Inspired tidal volume Median (IQR)	5.6 (1.7)	5.6 (1.8)	0.875
Minute volume Median (IQR)	323 (125)	329 (147)	0.986
$PaCO_2$ (kPa)	5.21 (1.52)	5.14 (1.67)	0.391

Table 13 Respiratory parameters at the time of commencing randomised mode

9.13 Respiratory parameters prior to performing minute ventilation test whilst receiving minimal mechanical ventilation

The respiratory parameters were compared between the group prior to commencing the minute ventilation test see Table 14. The mechanical ventilation aimed to provide an inspired tidal volume of 2-3mls/kg/breath. There was no significant difference between the groups.

Respiratory Parameter	SIMV	PSV	p value
Minute ventilation (ml/kg/min) Median (IQR)	367.2 (150.2)	321.1 (118)	0.76
Respiratory Rate	61 (16.2)	62 (15)	0.88
Inspired Tidal volume	5.69 (2.49)	5.61 (2.17)	0.77
FiO_2	21%(6.5)	21% (7)	0.72

Table 14 Respiratory parameters prior to performing minute ventilation test

9.14 Comparison of respiratory parameters at the time of minute ventilation test whilst receiving ET CPAP

Respiratory parameters whilst receiving ET CPAP (Table 15) were compared at the time of performing minute ventilation test. There was no significant difference between the groups.

Respiratory parameters	SIMV	PSV	p value
Spontaneous Minute ventilation Median (IQR)	306 (190)	258.8 (106.8)	0.101
Spontaneous Respiratory Rate Median (IQR)	66.8 (14.6)	65.6 (14.05)	0.913
Spontaneous Inspired Tidal volume Median (IQR)	4.55 (2.57)	4.89 (2.34)	0.928
FiO_2 supplementation	21 (7)	21 (7)	0.874

for spontaneous breaths Median (IQR)			
RSBI MVM	11.2 (6.3)	11.2 (8.01)	0.933
RSBI MVS	15.0 (8.0)	13.8 (10.4)	0.915

Table 15 Respiratory parameters at the time of minute ventilation test

9.15 Minute ventilation not performed

Passing the Minute ventilation was an objective assessment for readiness to extubate. Table 16 details the reasons for not performing the MVT.

Case number	Alive	Reason for non performing MVT	Reintubated in 72 hours (Yes/No)
1	Yes	Transferred to another hospital before MVT	N/A
2	Yes	Consultant decision, failed low rate SIMV	No
3	Yes	No clear reason	No
5	Yes	Failed multiple extubation and therefore withdrawn to follow protocol	No
6	No	Died before getting randomised mode	N/A
7	Yes	Consultant decision, did not	No

		tolerate weaning	
18	No	Died before getting randomised mode	N/A
21	Yes	Did not commence randomised mode, transfer for tertiary care	
26	Yes	Self extubated	No
38	No	Died before MVT	N/A
50	Yes	Transfer for tertiary care	N/A
52	No	Died before MVT	N/A
55	Yes	Transferred for tertiary care	No
92	Yes	Transferred for tertiary care	No
93	Yes	No clear reason	No

Table 16 Reasons for not performing Minute ventilation test.

In only two infants there was no clear reason for not performing the minute ventilation test. This was a major trial protocol violation. This

issue was discussed in the directorate meetings and appropriate

measures such as further training and staff awareness was increased.

9.16 Proportion of infants failing Minute Ventilation Test

A total of 23 episodes (in 8 infants) needed repeat minute ventilation test. 12 episodes (52%) in SIMV group and 11 (47%) episodes occurred in the PSV group.

Table 17 shows the proportion of infants failing their first MVT and subsequent tests prior to the final MVT test.

Randomised Mode	Failing first MVT	Failing second MVT	Failing third MVT
SIMV (N)	5	1	1
PSV (N)	3	3	2

Table 17 Proportion of infants failing the minute ventilation test prior to final minute ventilation test

9.17 Comparison of re-intubation rate in infants when MVT performed versus when not performed

	Reintubation in < 72 hours	No reintubation in <72 hours	Total
MVT not performed	0 (0%)	6 (100%)	6 (7.1%)
MVT performed	10 (12.8%)	68 (87.2%)	78 (92.9%)
Total	10 (11.9%)	74 (88.1%)	84 (100%)

Table 18: Comparison of infants needing reintubation when MVT not performed

A chi- square test was conducted for reintubation episodes when MVT was not performed. Fisher's exact test (2 sided) was used in view of cell frequencies less than 5. There was no statistically significant association between reintubation and MVT (p=1.00).

9.18 Minute ventilation journey prior to extubation

Randomised mode	MVT1 MVS:MVM	No. of MVT Tests	Episodes of reintubation in <72 hours	Final MVT
PSV	86%	2	1	10 DAYS
SIMV	97%	1	1	TRANSFERRED OUT FOR NEC
SIMV	104%	2		24 HOURS
SIMV	78%	2	1	5 DAYS
SIMV	FAILED IN LESS THAN 5 MINUTES	2		48 HOURS
SIMV	52%	3	1	TRACHY
PSV	63.5%	5	1	48 HOURS
PSV	80%	3		72 HOURS
SIMV	81%	2		8 HOURS
SIMV	95%	2	1	27 DAYS
PSV	92%	1	1	TRANSFERRED OUT

PSV	73%	3	2	40 DAYS
SIMV	90%	4	2	5 DAYS
PSV	FAILED IN LESS THAN 5 MINUTES	4		48 HOURS
PSV	90.6%	1	1	12 HOURS

Table 19: Table showing the details of the minute ventilation test in infants after the first minute ventilation test.

9.19 Need for re-intubation within 72 hours of extubation

There were a total of 10 episodes of re ventilation in less than 72 hours of extubation with 5 each in PSV arm and SIMV arm respectively (Table 20). Chi squared analysis for success of passing minute ventilation test and reintubation rates between the two groups showed no difference (p= 1.00).

Reintubation in <72 hours N (%)	SIMV	PSV	Total
No	41 (89.1)	42 (89.4)	83 (89.2)
Yes	5(10.9)	5 (10.6)	10 (10.8)
Total	41 (100)	42(100)	93 (100)

Table 20 Need for re-intubation within 72 hours of extubation

9.20 Primary Outcome measure

Kaplan Meier survival analysis was used to compare the time taken from commencing the randomised mode to passing the minute ventilation test. If there was self-extubation or tube dislodgement and the infant did not require re-intubation in 72 hours then this was also considered as achieving the primary outcome. A similar percentage of censored cases were present in the SIMV and the PSV group. The median time to extubation in the SIMV arm was 42 (95% CI, 28.23 to 55.76) hours. The median time to achieving the primary outcome in the PSV arm was 31 (95% CI, 12.59 to 49.40) hours. A log rank test was run to determine if there were differences in the survival distribution between the two groups. The survival distribution between the interventions was statistically not significant, Chi-square 0.768, p 0.381.

Figure 13: Kaplan Meier survival curves showing time taken to passing the minute ventilation test.

The vertical axis shows cumulative survival and horizontal axis time in

hours

9.21 Spearman's Correlation coefficient of variables on primary outcome

Variable	Spearman's Rho	P value
Partial Antenatal steroids	0.213	0.052
Gestational age at birth	-0.638	0.000
Birth weight	-0.637	0.000
Inborn	0.228	0.034
Intubated at birth	0.329	0.002
CRIB 2 score	0.607	0.000
Ventilated from birth	0.369	0.000
Mode of ventilation	-0.256	0.018
Maximum Oxygenation index prior to commencing randomised mode	0.210	0.013
First dose of surfactant (mg/kg)	0.211	0.052

Air leak needing treatment	0.221	0.048
PIE changes	0.426	0.000
Ventilator associated Pneumonia	0.225	0.044
Use of inotropes	0.438	0.000
Length of primary mode of ventilation prior to commencing randomised mode	0.351	0.001
Use of diuretics to wean ventilation	0.447	0.000
Use of post natal steroids	0.530	0.000

Table 21 Univariate analysis of variables affecting primary outcome

9.22 Multiple regression analysis of Primary outcome measures

A multiple regression (Table 22) was run to predict the primary outcome from the variables listed thought to have significant impact. The variables statistically significantly predicted the duration of the primary outcome $F_{(13, 33)} = 12.86$, $p < 0.000$, adjusted $R^2 = 0.77$. Of all of the variables, only gestation at birth, need for intubation at birth, length of primary mode of ventilation prior to randomisation and need for post-natal steroids contributed significantly to the prediction model.

Below is the summary of the multiple regression analysis.

Variable	Unstandardised regression coefficient	Standard error of the coefficient	Standardised coefficient	P value
Partial Antenatal steroids	99.61	51.80	0.186	0.063
Gestational age at birth	-46.75	21.25	-0.466	0.035
Inborn	32.87	43.26	0.061	0.453
Intubated at birth	-126.13	37.29	-0.322	0.002
CRIB 2 score	4.41	11.41	0.079	0.701

Maximum Oxygenation index prior to commencing randomised mode	1.270	1.978	0.056	0.525
First dose of surfactant (mg/kg)	-.018	0.270	-0.006	0.947
Air leak needing treatment	42.60	71.45	0.055	0.555
Use of inotropes	1.04	0.729	0.122	0.162
Length of primary mode of ventilation prior to commencing randomised mode	-2.201	0.765	-0.293	0.007
Use of diuretics to wean ventilation	87.82	137.96	0.093	0.529
Use of post natal steroids	467.56	84.09	0.600	0.000*

Table 22 Multiple regression analysis of variables affecting primary outcome

9.23 Effect of gestational age on primary outcome

The study was primarily performed to identify the effect of gestational age on the primary outcome (passing the minute ventilation test) Table 23. The initial sample size calculation required a total of 110 infants for subgroup analysis. However, due to slower than anticipated recruitment rate, and upon advice of the data monitoring committee along with statistician's input the study was stopped with 93 infants randomised. A Mann-Whitney U test confirmed there was no difference between the groups.

Primary outcome (Passing minute ventilation test) Median (standard error)	Randomisation arm		p value
	SIMV	PSV	
23^{+0} to 25^{+6}	252 (264.8)	550 (570.9)	0.25
26^{+0} to 28^{+6}	49 (14.4)	45 (35)	0.98
29^{+0} to 31^{+6}	25 (3.1)	17 (1.9)	0.28

Table 23: Gestation distribution between the two randomised modes.

9.24 Impact of gestation at birth on primary outcome

Kaplan Meier survival analysis was used to compare the time taken from commencing the randomised mode to passing the minute ventilation test. If there was self-extubation or tube dislodgement and the infant did not require re-intubation in 72 hours then this was also considered as achieving the primary outcome. A similar percentage of censored cases were present in the SIMV and the PSV group.

In the group stratified to the 23+0 to 25+6 birth gestation (Figure 14), the median time to extubation in the SIMV arm was 252 (95% CI, 0 to 771) hours. The median time to achieving the primary outcome in the PSV arm was 550 (95% CI, 0 to 1669) hours. A log rank test was run to determine if there were differences in the survival distribution between the two groups. The survival distribution between the interventions was statistically not significant, Chi square 1.274, p =0.25
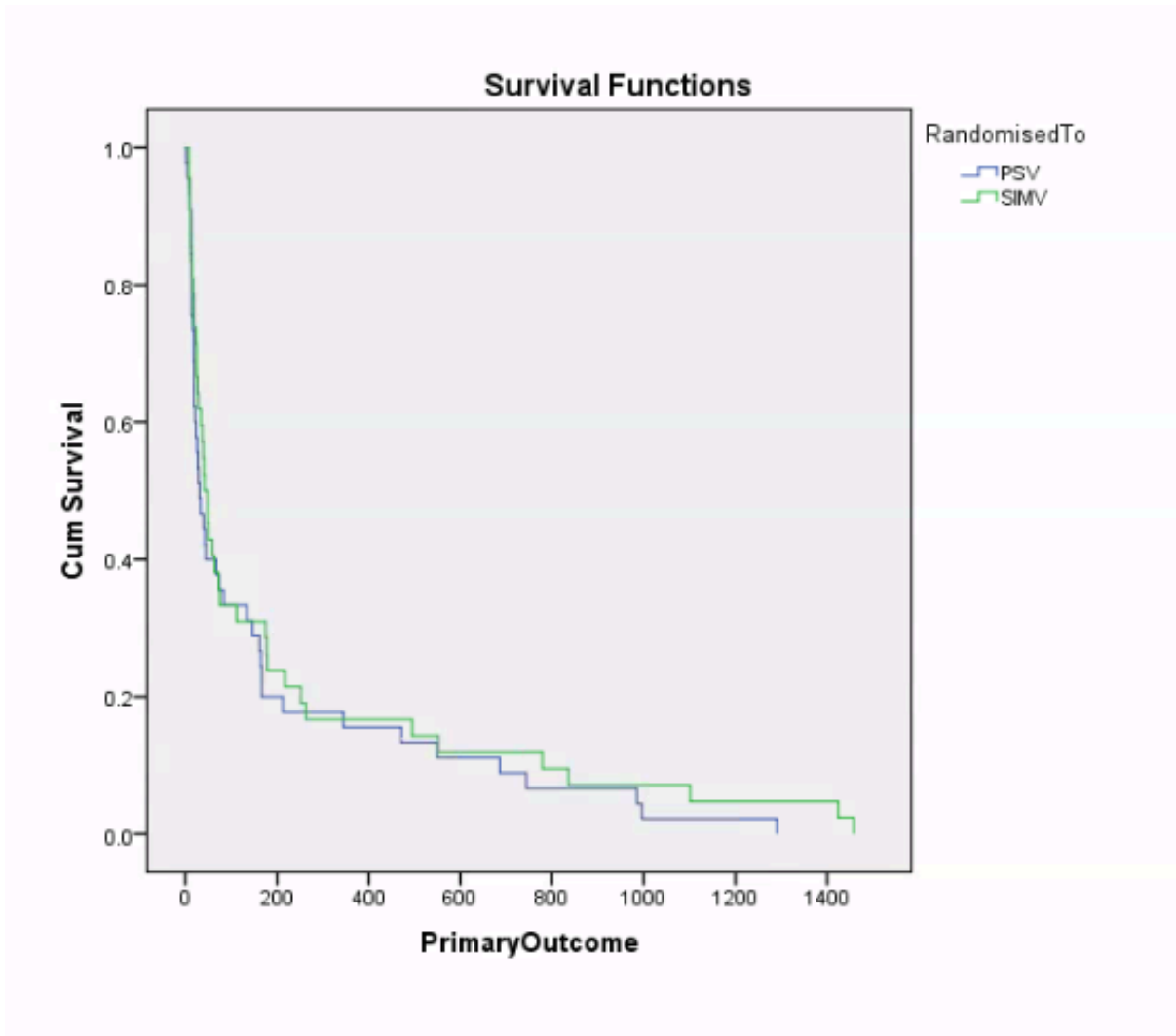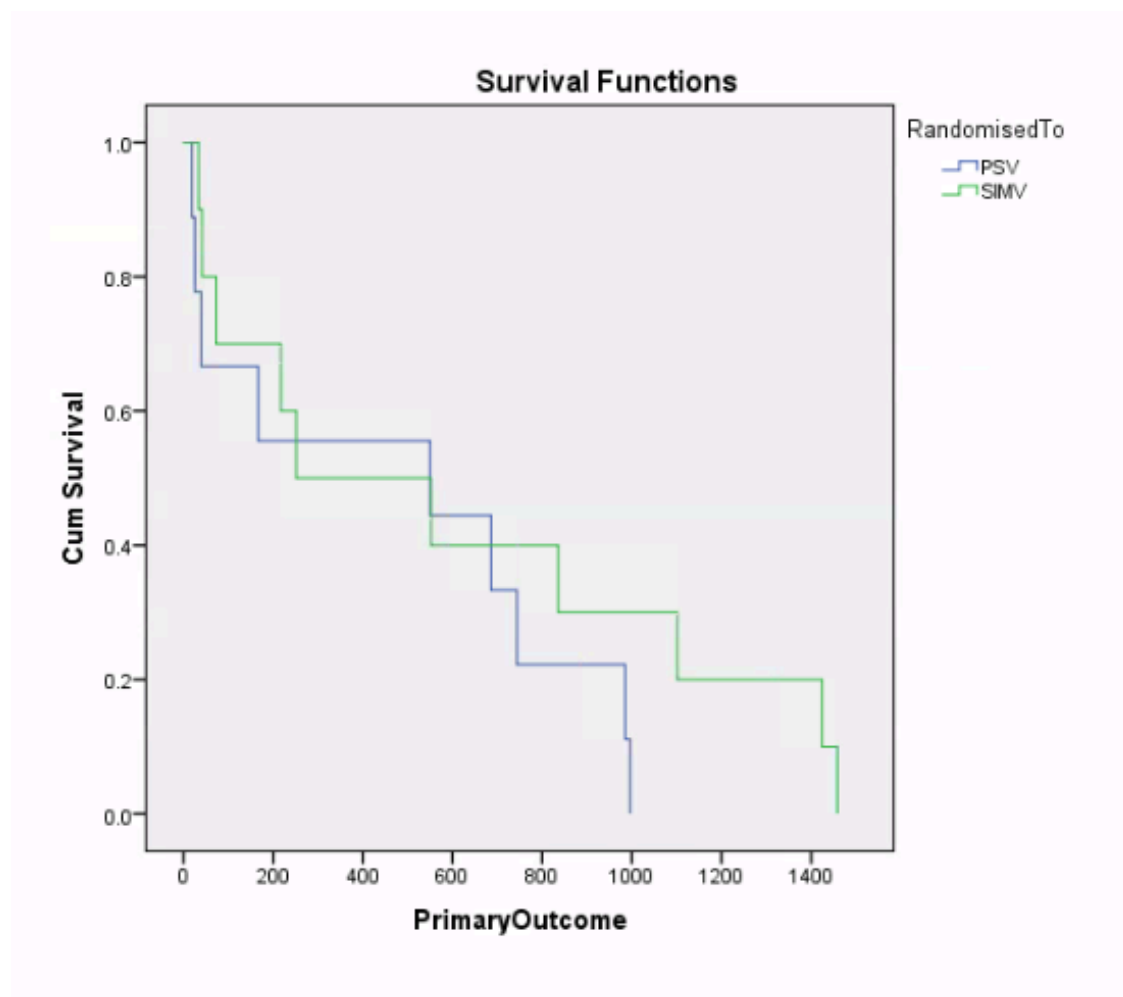

Figure 14 Kaplan Meier survival curves showing time taken to achieve the primary outcome in the infants stratified in 23+0 to 25+6 gestation group.
The vertical axis shows cumulative survival and the horizontal axis time in hours

In the group stratified to the 26+0 to 28+6 weeks (Figure 15), the
median time to achieve the primary outcome in the SIMV arm was 49
(95% CI, 20.76 to 77.23) hours. The median time to achieve the
primary outcome in the PSV arm was 45 (95% CI, 0 to 113.78) hours.
A log rank test confirmed the observed difference was not statistically
significant, Chi-square 0.00, p =0.98.

Figure 15 Kaplan Meier survival curves showing time taken to achieve the primary
outcome in the infants stratified in 26+0 to 28+6 gestation group.
The vertical axis shows cumulative survival and the horizontal axis time
in hours

In the group stratified in the 29+0 to 31+6 weeks (Figure 16), the median time to achieve the primary outcome in the SIMV arm was 25 (95% CI, 18.10 to 31.19) hours. The median time to achieve the primary outcome in the PSV arm was 17 (95% CI, 13.21 to 20.78) hours. A log rank test confirmed the observed difference was not statistically significant, Chi-square 1.05, p =0.30.

Figure 16 Kaplan Meier survival curves showing time taken to achieve the primary outcome in the infants stratified in 29+0 to 31+6 gestation group.

The vertical axis shows cumulative survival and the horizontal axis time in hours

9.25 Impact of birth weight on the primary outcome measure

The infants were divided into three groups, see Table 24: Effect of birth weight on primary outcome. Mann-Whitney U test showed no difference between the groups.

Primary outcome (Passing minute ventilation test)	Randomisation arm		p value
	SIMV Median (IQR)	PSV Median (IQR)	
500-1000 grams Median wt. (IQR) 802 (210) vs. 777.5 (223)	144 (500) hrs	166 (542) hrs	1.00
1001-1500 grams Median weight 1240 (150) vs. 1150 (285)	20 (25)	22 (20)	0.525
Above 1501 grams	32.50 (41)	14 (3)	0.154

Table 24: Effect of birth weight on primary outcome

9.26 Impact of birth weight on Primary Outcome

Post hoc analysis, was also carried out for the different weight groups to verify its impact on the primary outcome Figure 17, Figure 18 & Figure 19. In infants with birth weight <1000 grams, the median time to achieve the primary outcome in the SIMV arm was 112 (95% CI, 0 to 238.02) hours. The median time to achieve the primary outcome in the PSV arm was 165(95% CI, 69 to 260.38) hours. A log rank test confirmed the observed difference was not statistically significant, Chi square 0.174, p =0.67

Figure 17 Kaplan Meier survival curves showing time taken to achieve the primary outcome in the infants with birth weight <1000 grams.
The vertical axis shows cumulative survival and the horizontal axis time in hours

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In infants with birth weight 1001 to 1500 grams, the median time to achieve the primary outcome in the SIMV arm was 20 (95% CI, 13.69 to 26.30) hours. The median time to achieve the primary outcome in the PSV arm was 22 (95% CI, 13.47 to 30.52) hours. A log rank test confirmed the observed difference was not statistically significant, Chi square 0.100, p =0.75

Figure 18 Kaplan Meier survival curves showing time taken to achieve the primary outcome in the infants with birth weight between 1001-1500 grams.
The vertical axis shows cumulative survival and the horizontal axis time in hours

In infants with birth weight >1500 grams, the median time to achieve the primary outcome in the SIMV arm was 24 (95% CI, 0.00 to 53.4) hours. The median time to achieve the primary outcome in the PSV arm was 14 (95% CI, 13.40 to 14.60) hours. A log rank test confirmed the observed difference was statistically significant, Chi square 4.36; p =0.03

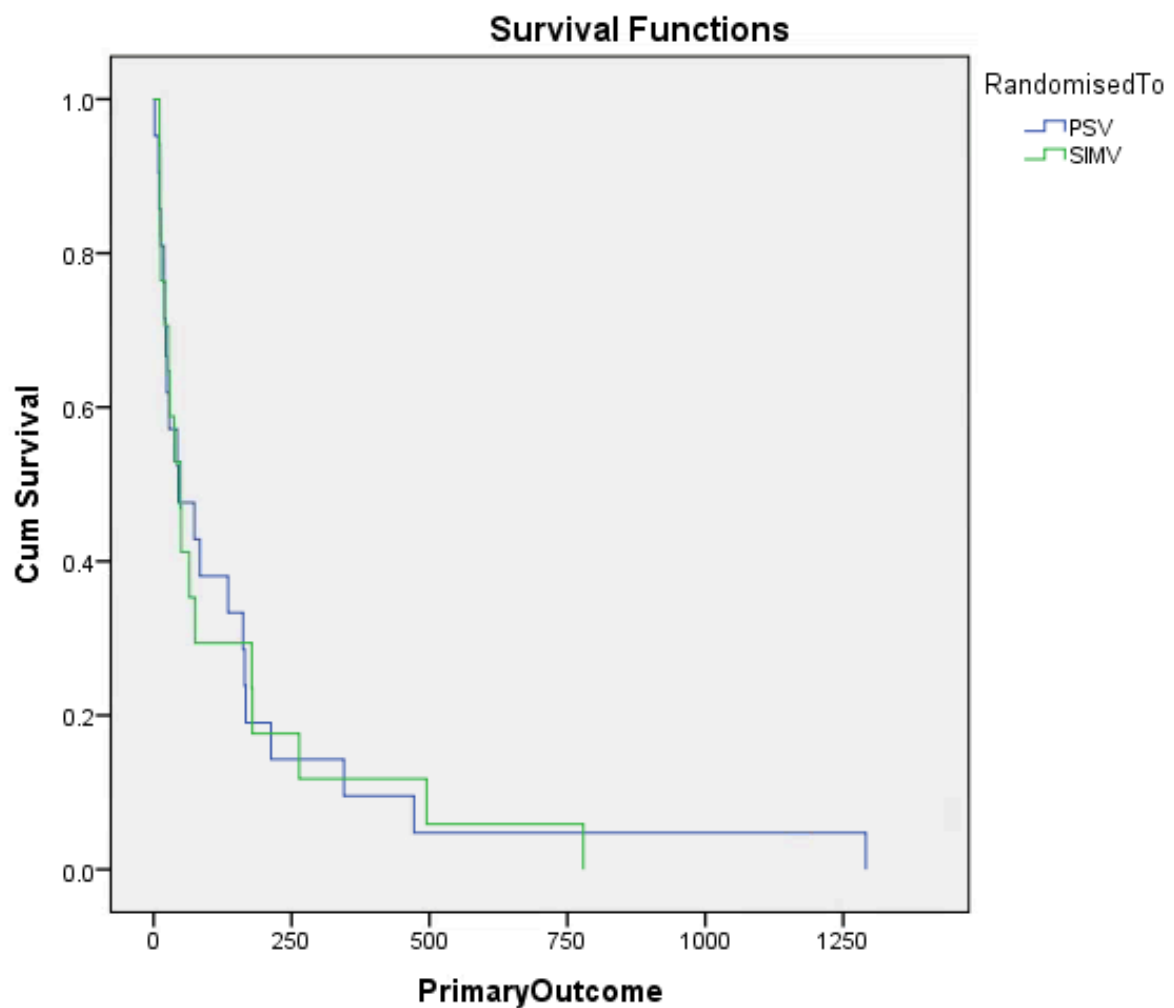Figure 19 Kaplan Meier survival curves showing time taken to achieve the primary outcome in the infants with birth weight >1500 grams.

The vertical axis shows cumulative survival and the horizontal axis time in hours

9.27 Duration of initial mode of mechanical ventilation on primary outcome measure

The effect of duration of initial ventilation was studied by post hoc analysis. Babies were stratified into two groups based on the duration of preceding ventilation; ≤ 1 week and those requiring > 1 weeks (Table 25). A Mann- Whitney U test was performed to assess the significance.

Primary outcome (Passing minute ventilation test) Median (Hour)(IQR)	Randomisation arm		p value
	SIMV N=34	PSV N=35	
≤1 week ventilation	38 (67)	26 (133)	0.49

Primary outcome (Passing minute ventilation test) Median (Hour)(IQR)	Randomisation arm		p value
	SIMV N=8	PSV N=10	
≥1 week ventilation	408 (1244)	125.5 (564)	0.51

Table 25: Effect of duration of initial ventilation on primary outcome

9.28 Total duration of respiratory support

Figure 20 shows Kaplan Meier survival analysis for the median time for total duration of respiratory support in the SIMV arm was 312 (95% CI, 185.15 to 438.84) hours. The median time for total duration of respiratory support in the PSV arm was 512 (95% CI, 184.09 to 839.90) hours. A log rank test confirmed the observed difference was not statistically significant, Chi square 0.140, p=0.709
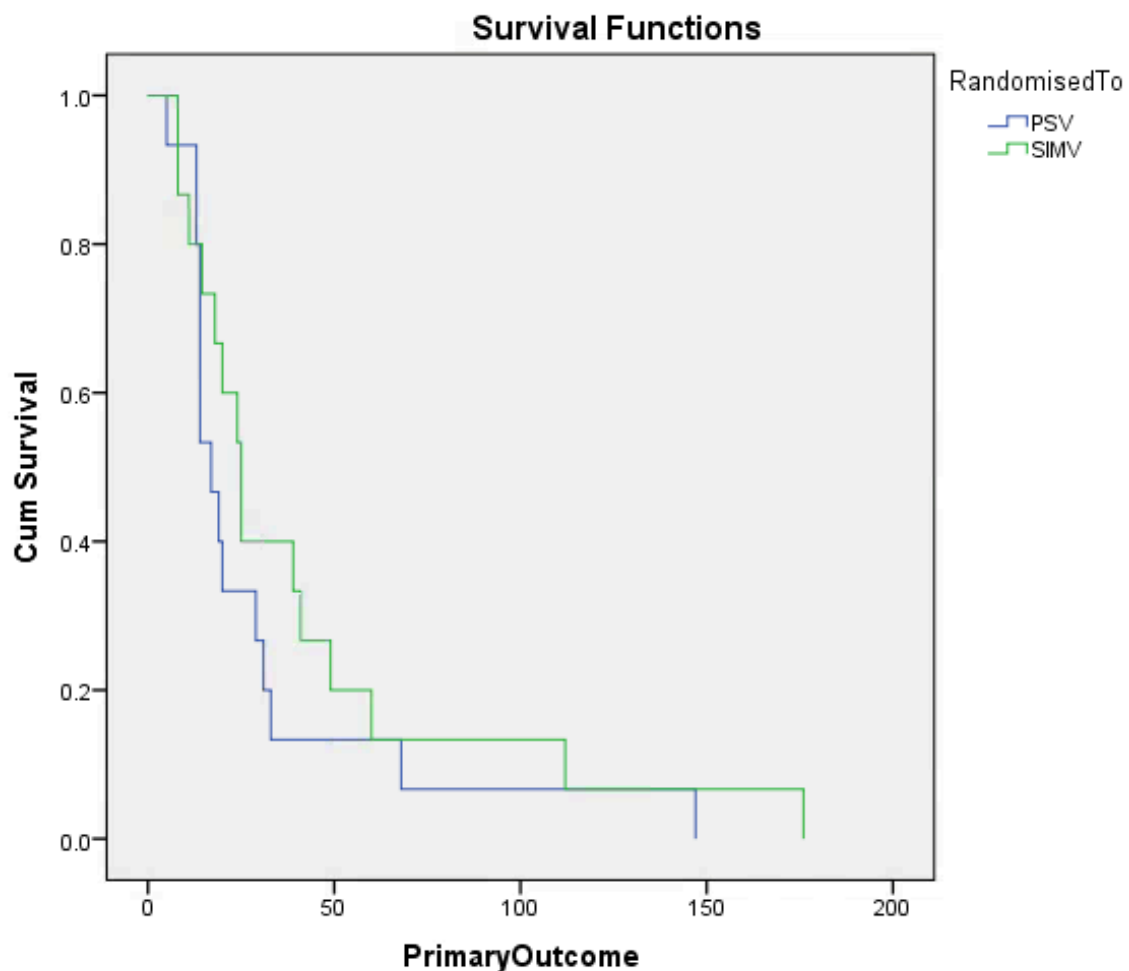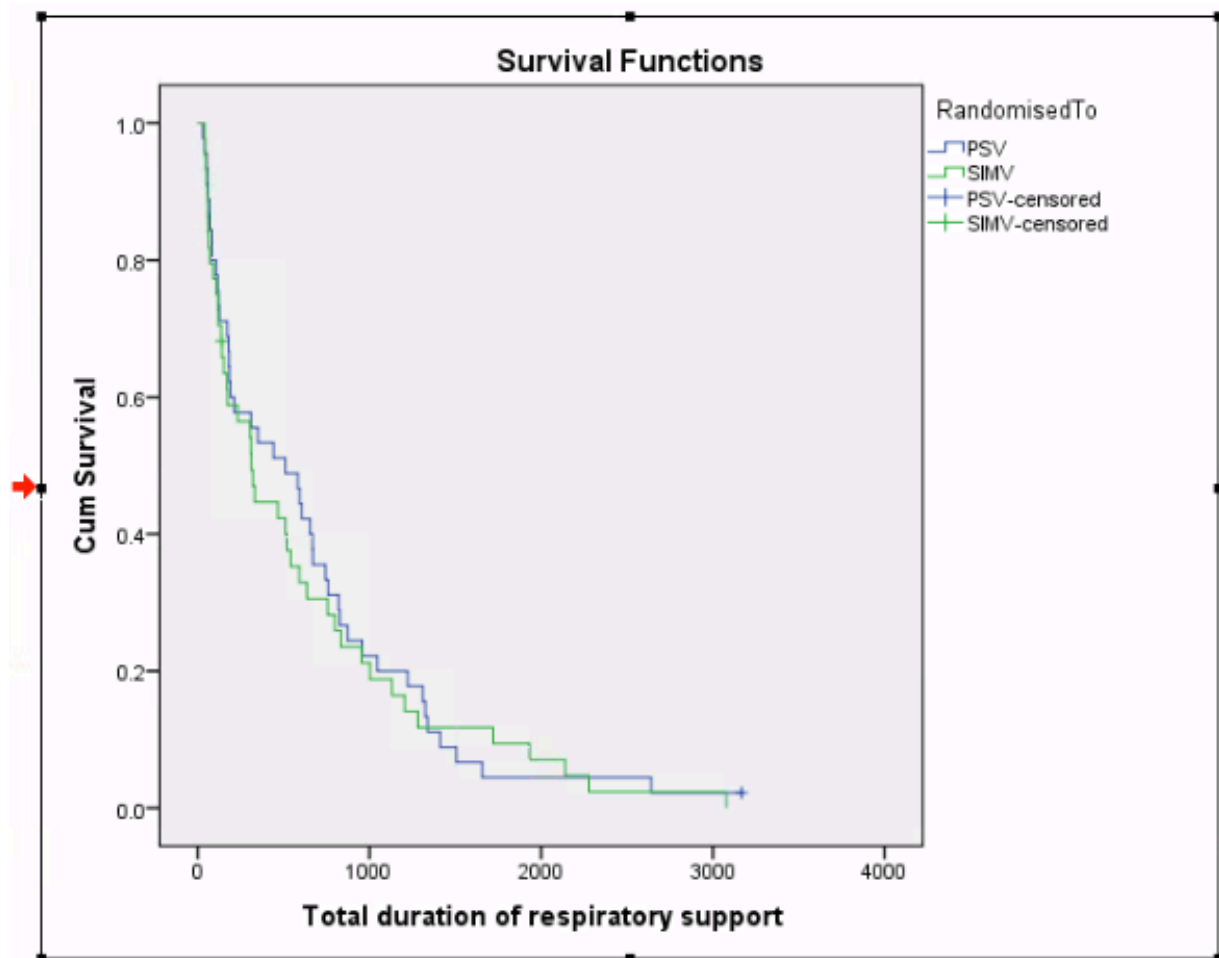

Figure 20 Kaplan Meier survival curves showing time for total duration of respiratory support between the two groups.

The vertical axis shows cumulative survival and the horizontal axis time in hours

9.29 Duration of respiratory support according to the gestational age at birth

In infants with birth gestation 23+0 to 25+6 weeks, the median time for duration of respiratory support in the SIMV arm was 1283 (95% CI, 1057.4 to 1508.5) hours. The median time in the PSV arm was 829 (95% CI, 627.3 to 1030.6) hours. A log rank test confirmed the observed difference was not statistically significant, Chi square 2.39, p =0.1
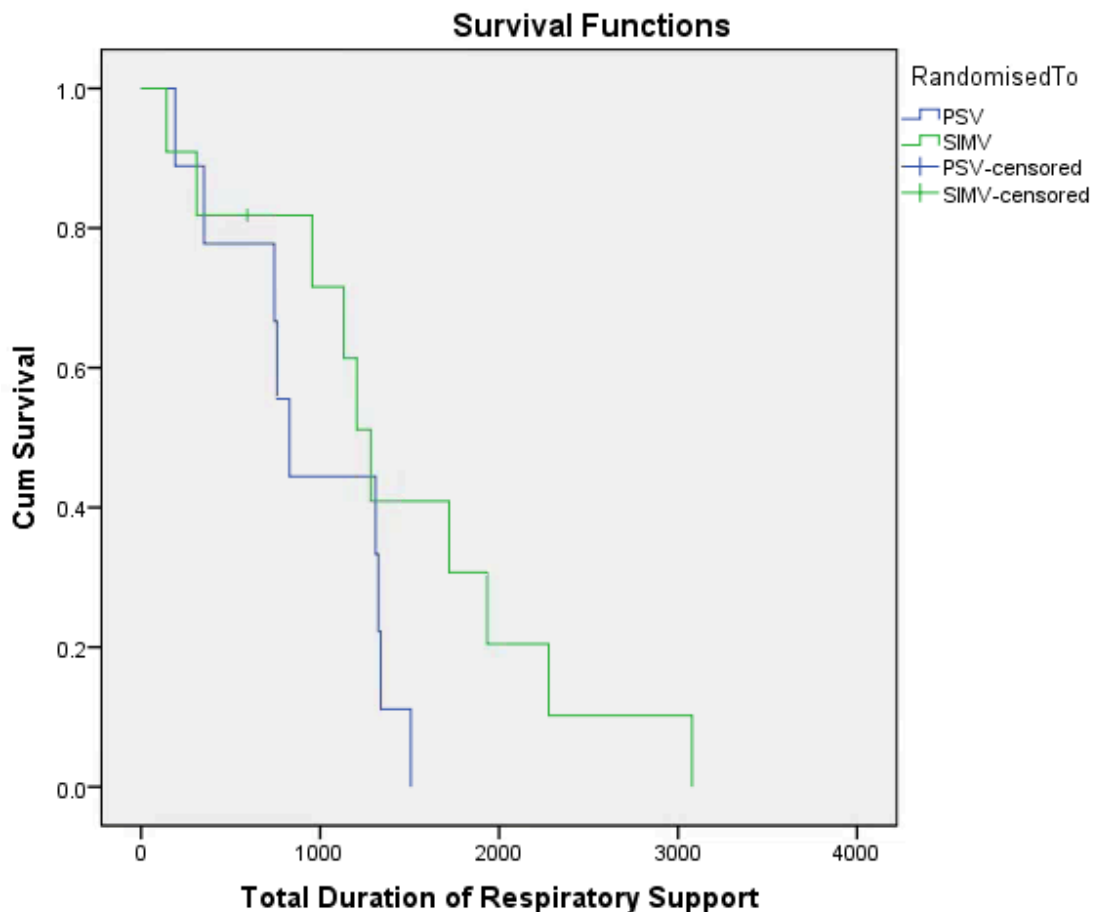
Figure 21 Kaplan Meier survival curves showing time for total duration of respiratory support in infants stratified to 23+0 to 25+6 weeks.
The vertical axis shows cumulative survival and the horizontal axis time in hours

In infants with birth gestation 26+0 to 28+6 weeks, the median time for respiratory support in the SIMV arm was 467 (95% CI, 213.1 to 720.8) hours. The median time in the PSV arm was 670 (95% CI, 556.35 to 783.6) hours. A log rank test confirmed the observed difference was not statistically significant, Chi square 1.12, p =0.289
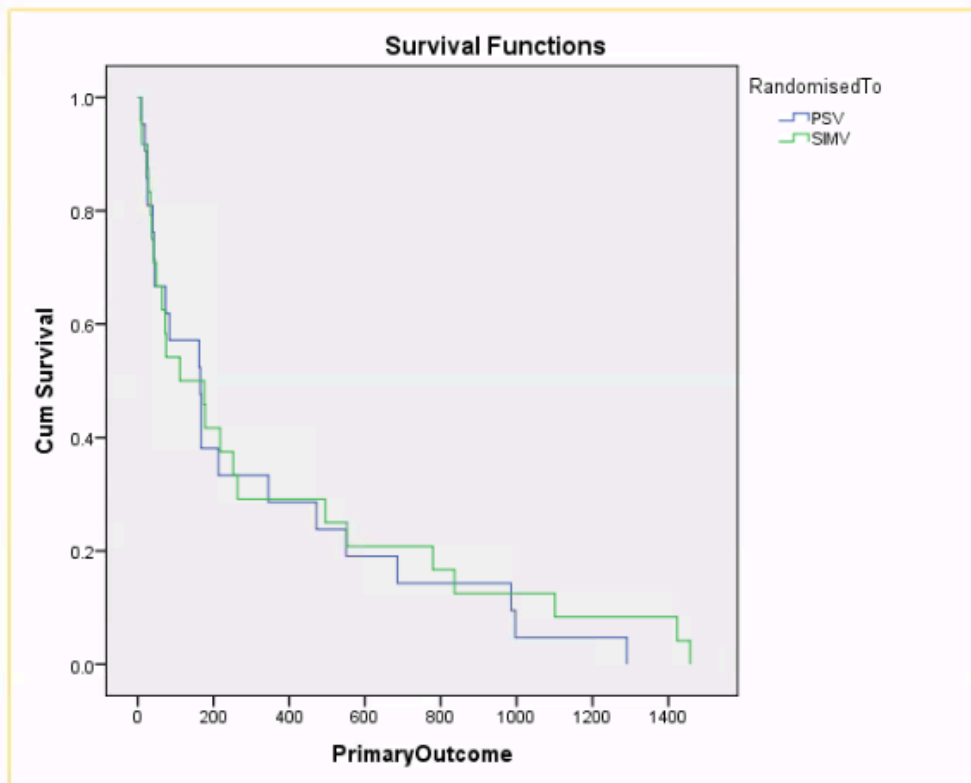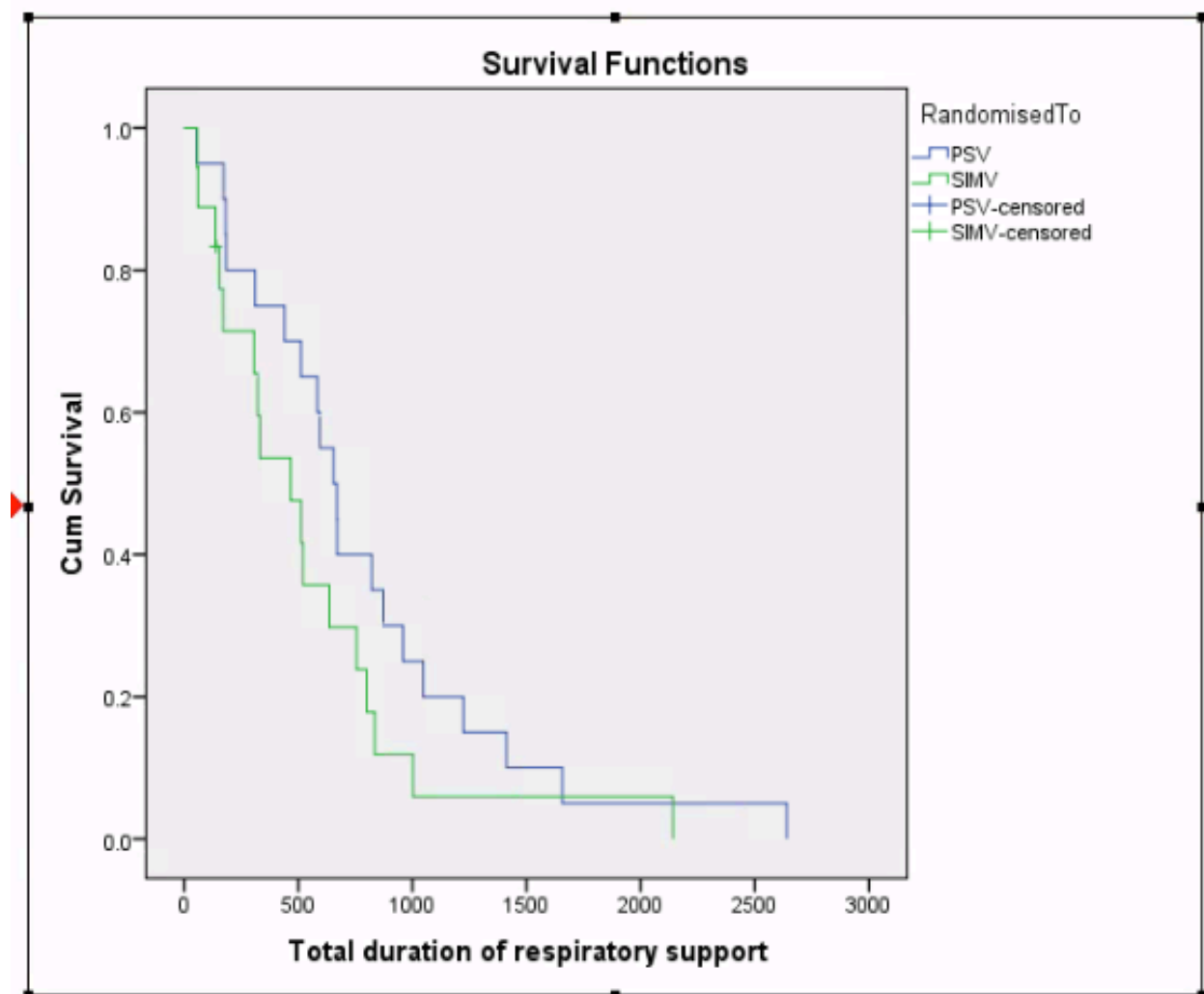

Figure 22 Kaplan Meier survival curves showing time for total duration of respiratory support in infants stratified to 26+0 to 28+6 birth gestation.

The vertical axis shows cumulative survival and the horizontal axis time in hours.

In infants with birth gestation 29+0 to 31+6 weeks, the median time for respiratory support in the SIMV arm was 91 (95% CI, 35.45 to 146.54) hours. The median time in the PSV arm was 83 (95% CI, 40.08 to 125.92) hours. A log rank test confirmed the observed difference was not statistically significant, Chi square 0.001, p =0.973
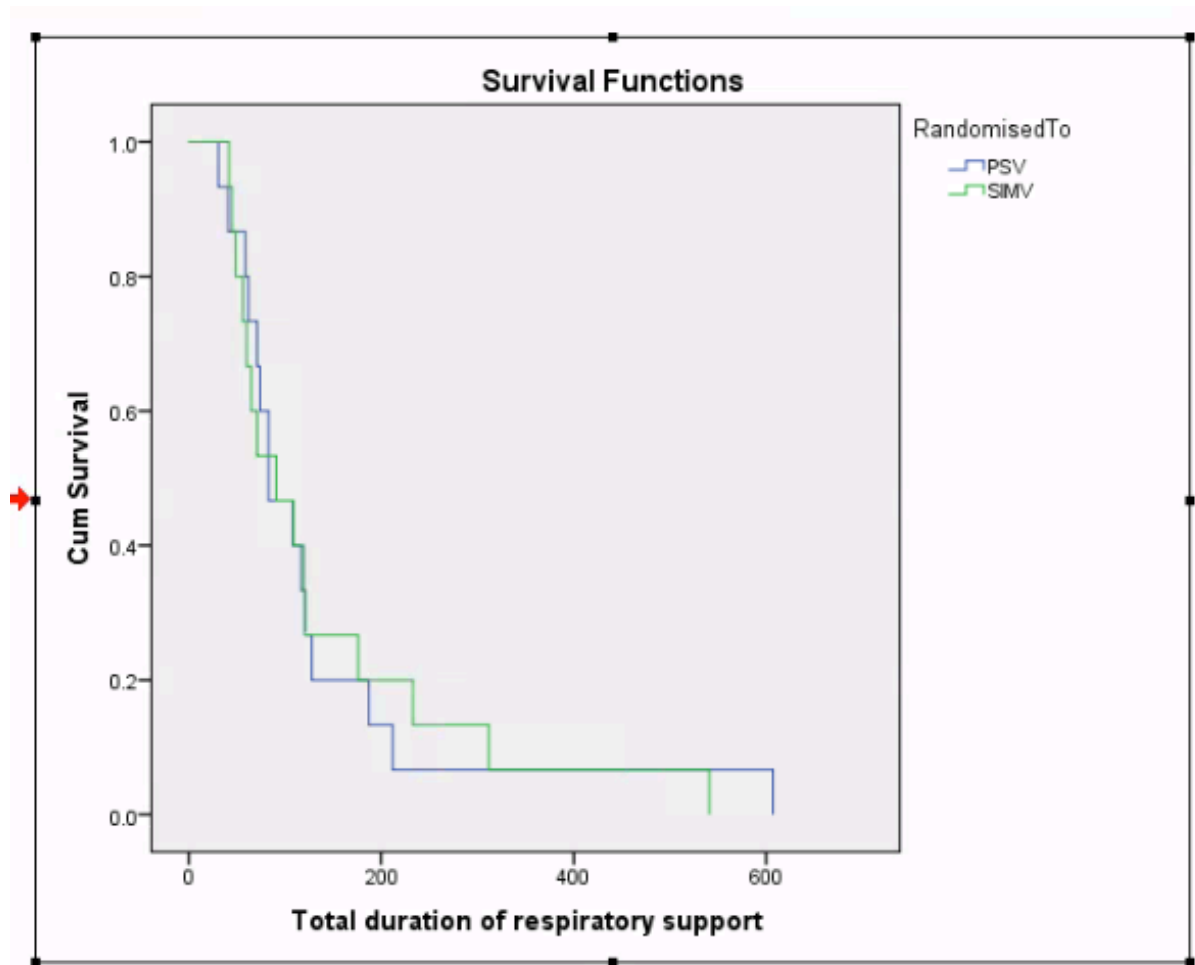
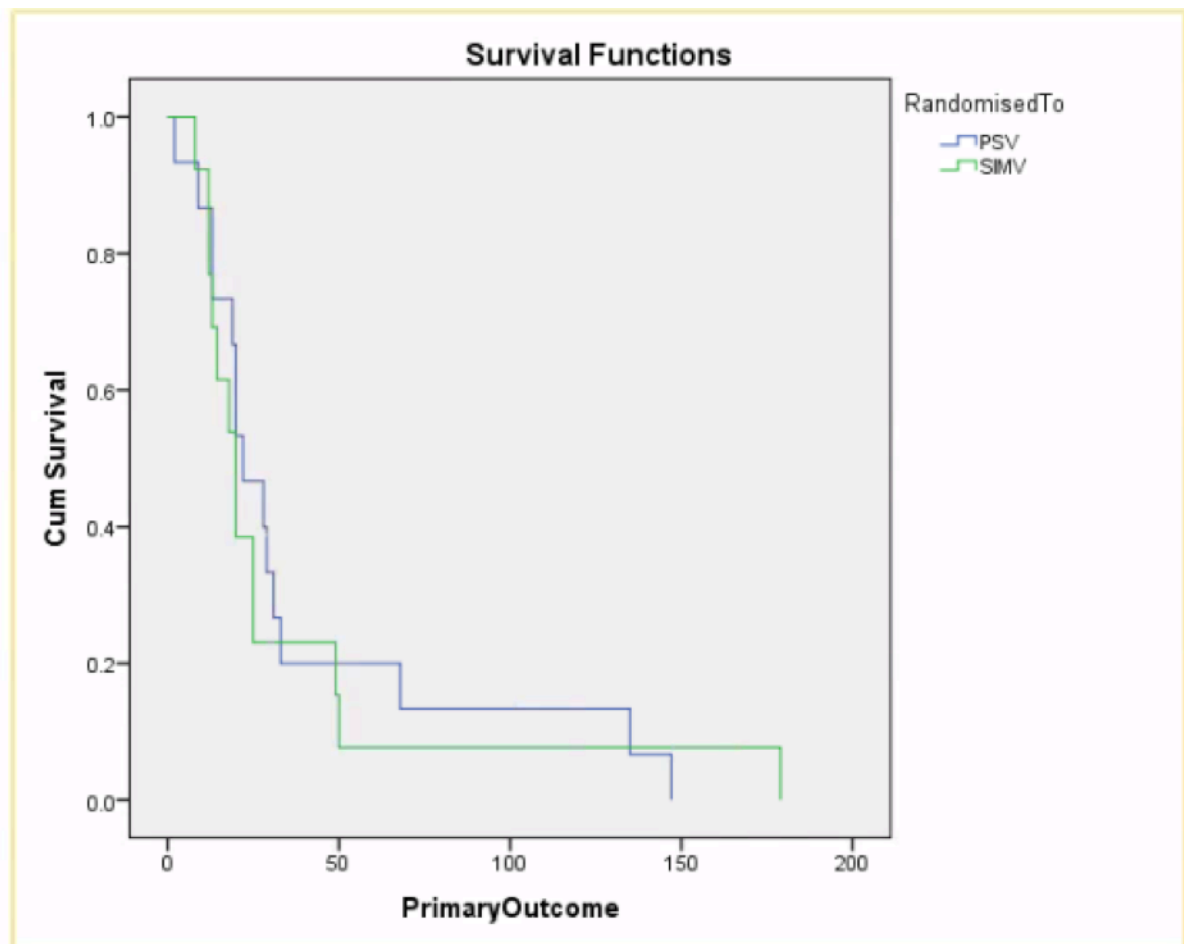

Figure 23 Kaplan Meier survival curves showing time for total duration of respiratory support in infants stratified to 29+0 to 31+6 birth gestation.
The vertical axis shows cumulative survival and the horizontal axis time in hours

9.30 Adjuvant therapy to assist extubation

Chi squared test for the effect of diuretic therapy and need for postnatal steroid use did not differ from each other significantly.

Treatment	SIMV group N=44	PSV group N=43	p value
Diuretics	5 (11.4%)	2 (4.7%)	0.434
Post natal corticosteroid use	7 (16.3%)	6 (13.7%)	0.503

Table 26 Adjuvant therapy to aid extubation

9.31 Difference in the weight gain between the two groups

Variable Median (IQR)	SIMV N= 29	PSV N= 34	p value
Enteral Feed commenced on	3 (2)	3(2)	0.51
Full enteral feeding established on	9 (4)	11 (9)	0.30
Birth weight reached on	16 (8)	14 (5)	0.10
Weight gain per day	18.4 (7.59)	18.1 (8.21)	0.56

Table 27: Weight gain per day between the two groups

Mann Whitney U test confirmed the observed difference between the two groups was not statistically significant.

9.32 Duration of hospital stay

KM analysis of the duration of the hospital stay between the randomised groups showed the median duration in the SIMV arm was 69 (95% CI, 52.7 to 81.2) days. The median time for discharge home in the PSV arm was 70 (95% CI, 61.9 to 78) days. A log rank test confirmed the observed difference was not statistically significant, Chi square 0.039, p =0.52
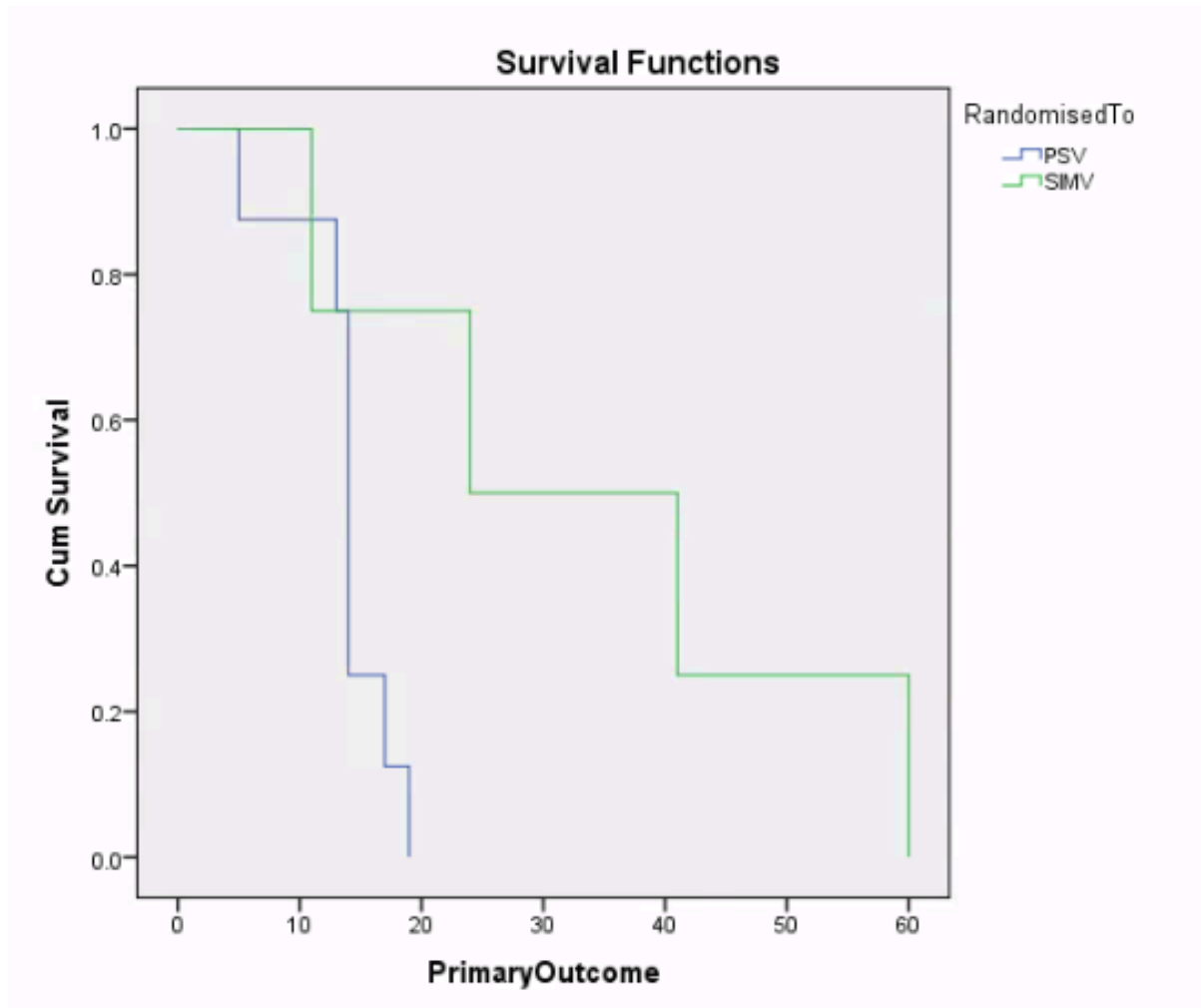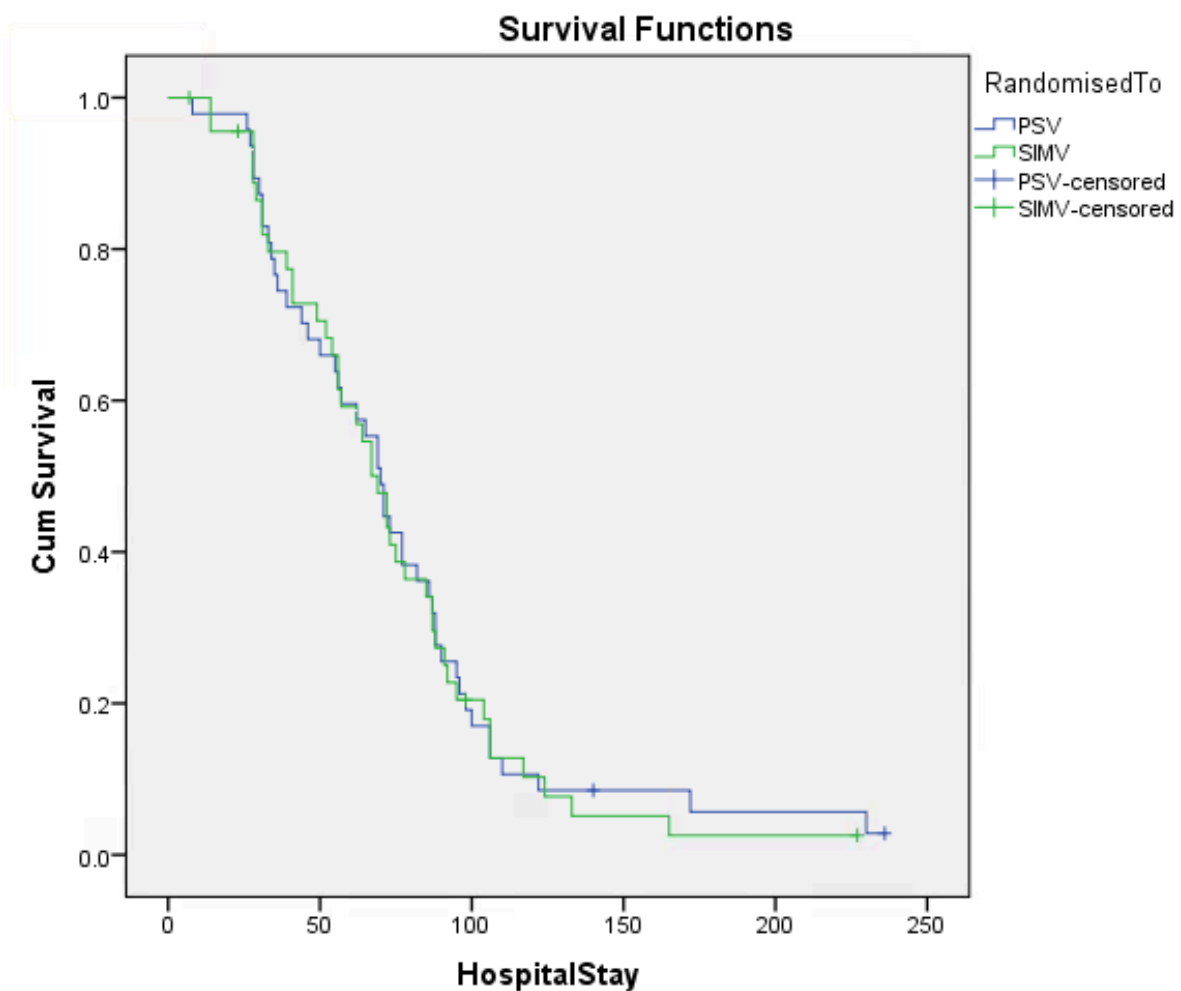

Figure 24 Kaplan Meier survival curves showing duration of hospital stay between the two randomised groups.

The vertical axis shows cumulative survival and the horizontal axis time in days

9.33 Survival to discharge

There were a total of 7 deaths. 5 in the SIMV group and 2 deaths in the PSV group. Note however, 2 infants died before commencing the randomised mode. Chi square analysis of this outcome was not significant (p=0.20). Odds of death (PSV: SIMV) for death= 2.7 (95% CI -0.50 to 14.5). This changed to odds ratio of 1.6 (95% CI 0.26 to 10.3).

Variable N (%)	SIMV	PSV	Total
Alive	41 (93.2%)	45 (95.7%)	86 (94.5%)
Dead	5 (10.8%)	2 (4.3%)	7 (7.5%)
Total	46 (100%)	47 (100%)	93 (100%)

Table 28: Chi square analysis for death as variable between the two groups

9.34 Time of death of infants in the study

Case no	Randomised ARM	Gender	Birth Gestation	Age at death	Cause of death
9	SIMV	FEMALE	28.4	30.5	NEC
19	PSV	MALE	24.1	32	NEC
38	PSV	MALE	24.3	8	NEC
52	SIMV	MALE	24.2	26	NEC
66	SIMV	MALE	28.4	32.4	SEPSIS

Table 29 Time of death of infants in the study

9.35 Incidence of Bronchopulmonary Dysplasia

Chi squared analysis did not show any statistical significance in the incidence of BPD between the two groups.

BPD	SIMV group N=42	PSV group N=43	p value
BPD at 28 days	29 (69%)	30 (69%)	0.309
BPD at 36 weeks PMA	22 (52%)	24 (55%)	0.815
Home oxygen	18 (42%)	21 (48%)	1.00

Table 30: Comparison of BPD incidence in the two-study group

9.36 Other complications of prematurity

Outcome	SIMV (N)	PSV (N)	ODDS ratio (95% CI)	p value
Any IVH	13	15	0.840 (0.344-2.048)	0.438
Grade 3 IVH or more	7	9	0.737 (0.248-2.18)	0.784
Hydrocephalus needing shunting	0	3	0.933 (0.86-1.00)	0.242
PVL	1	1	1.04 (0.063-17.29)	1.00
Air leak needing chest drain in the randomised mode	1	1	1.00 (0.06-16.48)	1.00
Pulmonary Haemorrhage after commencing randomised mode	4	3	1.41 (0.29-6.75)	0.712

PDA treated in <72 hours	2	5	0.37 (0.06-2.02)	0.434
PDA treated after 72 hours	6	7	0.85 (0.26-2.78)	1.00
PDA needing surgical ligation	3	3	0.976 (0.18-5.11)	1.00
NEC (Bell stage 2 or more)	17	16	1.14 (0.48-2.69)	0.828
NEC needing surgery	3	4	0.75 (0.15-3.56)	1.00
Sepsis	32	30	1.46 (0.51-4.14)	0.601
ROP stage 2 or more	12	18	0.56 (0.22-1.42)	0.255
ROP needing surgery	6	5	1.27 (0.35-4.55)	0.756

Table 31: Incidence of other common complications of prematurity in the two groups

9.37 Comparison of ventilation control in the two randomised mode

Hypocarbia was defined as $PaCO_2$ value less than 4KPa (Ambalavanan and Carlo, 2001). An unpaired student t test was performed to assess the variability in the two groups. The CO_2 values recorded in the observation chart in the assigned mode were averaged during the period and the average value of each infant was compared against the other using unpaired t test as the values were normally distributed (KS test for normality, p=0.380 for PSV and 0.490 for SIMV).

	SIMV	PSV	p value
Mean CO_2 Mean, 95%CI	5.61 (5.27-5.95)	5.72 (5.41-6.03)	0.622
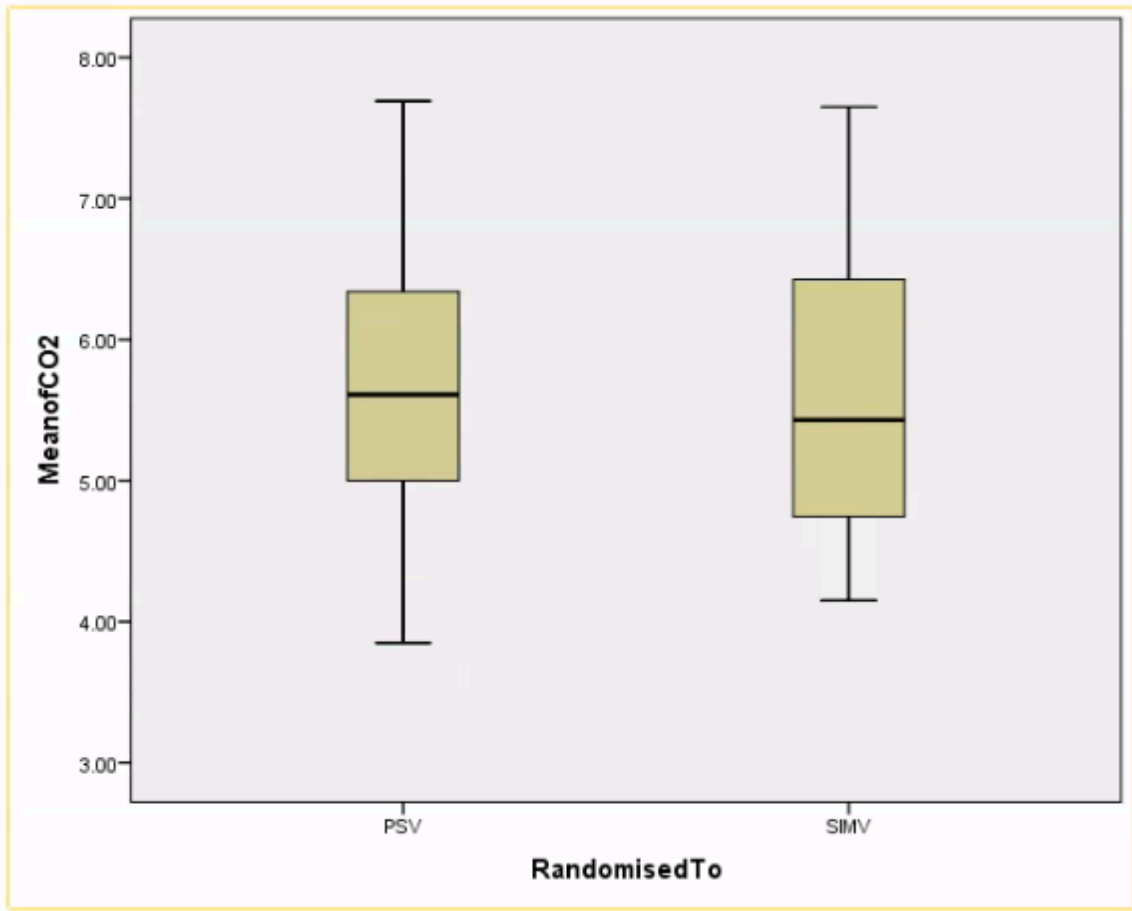
Figure 25 Box plot of CO_2 recorded whilst in the randomised mode

10 Discussion

Improved antenatal care, fetal surveillance, use of antenatal steroid therapy coupled with use of surfactant therapy has had a positive impact on the intact survival of the preterm infants. Use of volume controlled ventilation (Wheeler et al., 2010), and improved understanding of the patient ventilator interaction has helped to minimise the incidence of ventilator induced lung injury and other morbidities including chronic lung disease and death.

Microprocessor based technology has facilitated development of newer ventilation modes each with perceived advantages. Pressure support ventilation is relatively newer mode of ventilation that allows improved patient ventilator interaction. PSV is reported to be better tolerated and more comfortable when compared to volume controlled continuous mandatory ventilation in intubated awake adults (Betensley et al., 2008).

There is wide practice variation when it comes to 'weaning' on mechanical ventilation. In current practice, there is an urgent need to define what is 'weaning' on mechanical ventilation. The general perception is, supporting only fixed number of breaths instead of all the breaths i.e. changing from A/C mode to SIMV is viewed as 'weaning' on mechanical ventilation. It is perceived, in doing so, there is a transfer of

work of breathing from ventilator to the infant. On the same corollary, therefore reducing any ventilation on a given mode should be considered as weaning on mechanical ventilation.

Weaning on mechanical ventilation and subsequent extubation in majority of the UK neonatal units is directed by clinician's subjective decision and their assessment. This assessment is usually based on combination of clinical examination along with the clinician's 'hunch', biochemical monitoring in form of blood gases and in some cases radiographic guidance to monitor 'optimum' lung volumes. These are inadequate as none of the above assessments include objective criteria to include preterm infants' contribution to the work of breathing in achieving the desired tidal volume.

10.1 Rationale for the present study

The feasibility and safety of Pressure support ventilation (PSV) has been tested in previous physiological studies and in randomised controlled trial (Reyes et al., 2006), (Patel et al., 2012), (Farhadi Roya, 2016). In most of the studies, the level of PSV applied is generally less than 50% of the difference between peak inspiratory (PIP) and peak end expiratory pressure (PEEP), or arbitrarily set between 10 and 12 cms of H_2O. This is generally in conjunction with SIMV as the parent mode.

Choosing an arbitrary 'fixed' level of PSV might not suffice all infants because of varied severity of disease process. Therefore existing clinical studies precludes the generalisability of applying a 'fixed level' of PSV for weaning infants on mechanical ventilation. This estimation is further compounded by lack of easy cot side assessment of work of breathing.

Generally weaning is initiated by the change in ventilation strategy from A/C mode to SIMV once the mean airway Pressure (MAP) is below 10 cm H_2O and supplemental oxygen less than 40%.

In the United Kingdom, majority of the tertiary neonatal units use SIMV alone (73% in 2007 and 64% in 2010) for respiratory support during acute stages and for weaning on mechanical ventilation. However, there is a practice change with an increasing recognition that SIMV alone with fixed number of back up rate is not sufficient to support spontaneous

respiration for weaning on mechanical ventilation. Currently up to 19% units use varying levels of PSV support (Mallya et al., 2010), compared to no units in 2007 (Sharma and Greenough, 2007).

Hence a randomised study to define weaning objectively and utilising variable PSV support for weaning infants is required to assess if this approach facilitates earlier and successful extubation.

10.2 Aim of this study

The aim of the study was to compare the duration of weaning on mechanical ventilation using variable PSV level with the standard approach of weaning on SIMV.

10.3 Regulatory approvals

National Research Ethics Committee (Newcastle and North Tyneside Research Ethics Committee) approval (approved 10/01/2011) and Hospital Research and Development Review Board approval was sought before commencing the study. The study was also registered with International Standard Randomised Controlled Trials Number (Ref no. 74272142) at the start of the study. Parents' comments were sought prior to finalising the parent information leaflet (see Appendix 1) and it was encouraging to see their enthusiasm with this study.

10.4 Study objectives

This study targeted expired tidal volume using variable PSV support delivered to the infant instead of a set pressure as elucidated in the previous studies.

This was an open label randomised controlled study, designed to compare duration of weaning of mechanical ventilation in preterm infants with RDS using study mode of variable PSV with standard weaning mode of SIMV.

Infants born between 23+0 weeks but less than 31 completed weeks (31+6 weeks) were included in the study. Based on gestation at birth, infants were stratified in three groups:

a. 23^{+0} to 25^{+6} weeks

b. 26^{+0} to 28^{+6} weeks

c. 29^{+0} to 31^{+6} weeks

Gestation was chosen over birth weight for stratification because of its correlation in predicting the neonatal mortality and morbidity (Wariyar et al., 1989), (Verloove-Vanhorick et al.).

The primary objective of duration of weaning was objectively defined as time from commencing the randomised mode to passing the minute ventilation test (MVT).

10.5 Methodology

This is a two unit randomised controlled study comparing weaning on PSV with weaning on SIMV. The two participating study centres primarily use volume-controlled ventilation at birth and both the medical and the nursing staffs are well versed with the study modes. The limitations of testing PSV as a study mode in an open label RCT such as ours was mitigated by the existing practice of using advanced ventilation modes on both the units. This is an important variable when testing any ventilation modality to minimise bias in an unmasked study and for staff acceptance. Familiarity with the ventilation mode helped to site set up and conduct the study with relative ease.

Eligible infants were stratified into three gestation groups as mentioned above. The stratification for recruitment was important to achieve a balance between the two study modes of ventilation and to minimise the associated risks of prematurity in any one group. We included infants born less than 24 weeks (but over 23 weeks gestation) because of paradigm shift in their management in the last few years with increased survival rates (Costeloe et al., 2012).

Infants were deemed ready to commence the randomised mode when they achieved

a. Mean Airway Pressure (MAP) of <10 cm H_2O for at least 6 hours, and,

b. Oxygen supplementation of less than 0.4 along with

c. Good respiratory drive- defined as at least 50% of the back up rate.

The combination of ventilator settings and infants' clinical condition are intricately linked. The entry criteria facilitated transfer of work of breathing from the ventilator to the infant. The objective criteria of when to commence randomised mode ensured the traditional subjective 'clinician hunch' approach eliminated bias in the study.

Once weaning in the assigned mode was commenced the study protocol directed further weaning on mechanical ventilation. If the clinical condition warranted, the study mode was stopped until resolution of the clinical issue and weaning was recommenced in the assigned mode. The senior clinician on duty always assessed such a situation. The study protocol had clear pathways when such changes could be made. Once the infant was randomised and allocated to a study mode no cross over was allowed.

Before commencing randomised mode, all sedatives and morphine infusion was stopped to prevent apnoea. All infants received caffeine citrate loading dose of 20 mg/kg followed by the maintenance dose of 5 mg/kg once a day. This was increased to 10 mg/kg depending upon clinical requirement (Schmidt B, 2006). Use of Caffeine is a standard practice to facilitate extubation and to prevent apnoea of prematurity (Davis et al., 2010).

Prior to commencing the study, multiple training for all of the staff was used to explain the study protocol in the two participating centres. In addition new starters were also explained the study protocol at their department teaching programme. Despite these measures, there was slower than expected recruitment in one of the two centres. Hesitation of deploying low back up rate in the PSV study mode compared to the conventional arm was perhaps the reason for that.

For both groups of infants the study protocol aimed to maintain a tidal volume of 4-6mls/kg/breath. In volume controlled SIMV ventilation mode this was achieved by dialling the desired volume of gas. The initial back up rate on commencing weaning was 40 breaths/minute. In the PSV mode, the peak pressure achieved in Assist Control (A/C) mode for achieving the desired tidal volume was targeted. This ensured appropriate tidal volume was targeted at the start of the study. In true PSV mode there is no back up rate. Thus to prevent labelling as 'failure' of weaning from fleeting apnoeas in the PSV mode - ten low volume (2-

3mls/kg) SIMV breaths were added to the PSV arm. It is unlikely that the low rate and low volume SIMV breaths in the PSV arm would have significantly contributed to the minute ventilation. Thus weaning was purely based on variable PSV level. Expired tidal volume was targeted for ventilator changes to compensate for volume leak in the circuit.

SIMV with some pressure support (delivering 2-3mls/kg/breath) is the standard weaning method in both the units. From a previous study (Dimitriou et al., 1995) low rate SIMV (less than 20 breaths/minute) has been shown to be disadvantageous to the infants from fatigue leading to extubation failure. In that study, they report rate below 20 was associated with increased duration of weaning. In order to avoid imbalance and to compare study groups, Pressure Support aiming 2-3 ml/kg/breath was provided to support spontaneous breathing in the SIMV arm. This was deliberate and ensured the infants were not disadvantaged with fatigue from low rate SIMV prior to extubation.

Passing the minute ventilation test was necessary to demonstrate readiness of extubation and be able to cope with the work of breathing upon extubation. The objective test has shown to reduce the duration of mechanical ventilation than clinicians' perception of readiness to extubate (Gillespie et al., 2003). There are other extubation assessment tools (Kamlin et al., 2006), (Kamlin et al., 2008) arguably with greater sensitivity and positive predictive value. The study by Kamlin et al., suggests that infants can be safely extubated at higher

mean airway pressure than clinician perception with no differences in the rates of re-intubation and other clinical outcomes thereby reducing the duration of mechanical ventilation. Minute ventilation test has been previously used in ventilation studies conducted in the participating units previously and this was well integrated and accepted by the clinical and research staff. We therefore chose minute ventilation test as an objective measure for extubation readiness.

The progression of recruitment was projected on the historical clinical activity based on the admission rates in the two units. A short-term clinical outcome such as duration of weaning as primary outcome was considered more achievable and meaningful given the time constraints for study completion. Sample size calculation was based on the clinically considered significant reduction (33% reduction) on primary outcome and the logistics of completing the study in timely manner. As the weaning protocol in our study closely matched the weaning protocol used in the volume ventilation study (Singh et al., 2006) the sample size calculations used the published data. A statistician's input was sought to confirm that at least 85 infants were sufficient to provide 80% power with two-sided alpha of 0.05 to detect any statistical differences between the two groups.

10.6 Results

The delays in obtaining centre specific approval to commence study in one of the two sites led to commencing the study at different times with a seven-month difference between the two participating centres. Slower than anticipated recruitment activity in one of the two centres further lead to prolongation of study (see Figure 26 and Figure 27 for recruitment activity).
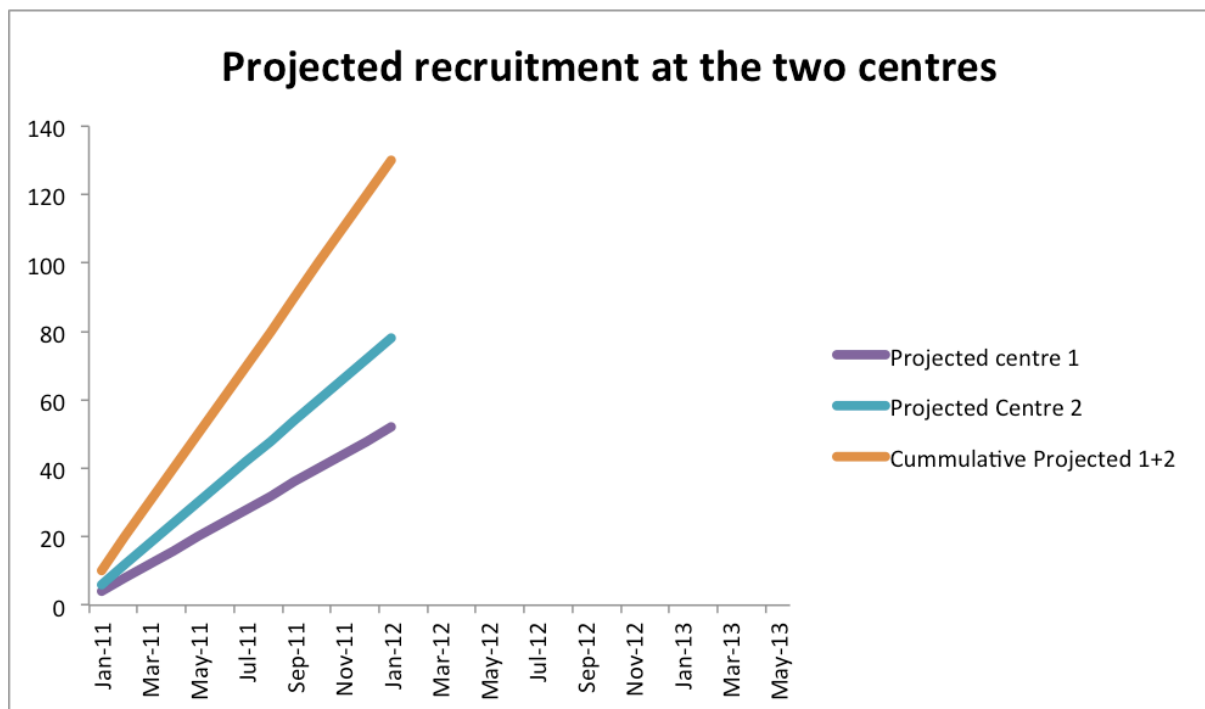
Figure 26: Projected recruitment at the two centre
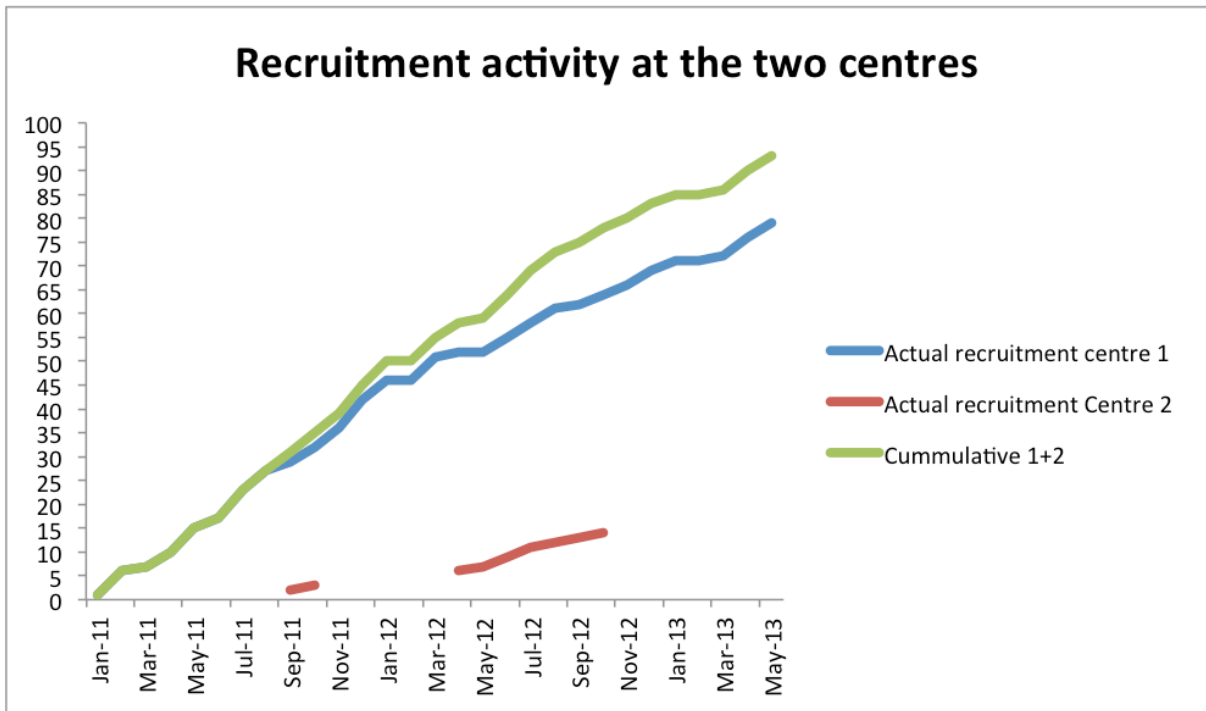
Figure 27: Actual recruitment activity at the two centres

Consent for participation was to be considered during the resolving phase of the RDS. This was deliberate as it was assumed explaining weaning on mechanical ventilation would be easier at that stage. However it soon became apparent that infants made fast progress and some infants were commenced on standard weaning mode prior to gaining consent. To boost infant recruitment, following trial steering committee meeting it was suggested that parents be approached for consent as soon as possible after admission to the neonatal unit.

Another issue for poor uptake was a lack of consensus amongst the clinical team on previously agreed weaning protocol. It was perhaps earlier than usual commencement of the SIMV mode in the control arm, which was a deviation from the usual practice at this site.

A request to capture patient data from the eligible but not recruited infants to compare primary outcome measure with the recruited infants was turned down by the national ethics committee with a suggestion that a new application for the same be put forth for consideration. Due to time constraints this was not pursued.

The two study groups matched for all the maternal and the infant baseline characteristics. Although the uptake of steroids was high in both the groups, there were a higher proportion of infants who received incomplete course of steroids in the PSV group, and higher proportion of infants who received more than one completed course of steroid in the SIMV group. As this could significantly affect the severity of Respiratory Distress and other associated outcomes this variable was used in the multiple regression analyses for the primary outcome and this was found to be not significant (p=0.063).

Although the standard practice is to administer 200 mg/kg of exogenous surfactant [Poractant Alpha (Curosurf®) is the standard exogenous surfactant therapy], infants born in the participating centres received significantly higher surfactant therapy (177 mg/kg vs. 139 mg/kg; p=0.008). However, there was no difference in the duration of primary mode of ventilation before randomisation between the two groups (Mann Whitney U Test p=0.62). There were no other demographic differences between the two study groups.

The median time to enrol in both the groups was similar at less than 48 hours (IQR=1, Mann Whitney U test p=0.69). This ensured that the two groups were similar at the time of randomisation. There was no other significant difference between the groups. The randomised mode was commenced within 72 hours in 77% in both the groups.

Lung disease severity between the groups was compared using maximum peak inspiratory pressure, maximum mean airway pressure, oxygen supplementation and Oxygenation Index prior to commencing the randomised mode and there was no difference between the groups. In addition, CRIB2 score between the two groups was not statistically different (Mann Whitney U test p=0.66). This was further supported by the fact that both groups received equal number of multiple surfactant therapy.

Some of the commonly occurring problems of ventilation that further compound the course of respiratory distress syndrome such as air leaks, ventilator associated pneumonia and pulmonary haemorrhage were also compared. There were no significant differences between the two groups.

Although an hourly check list of variables to assess readiness to commence randomised mode was available to prevent delay in commencing the randomised mode, there was a significant delay in both the groups (10-hour delay in SIMV group vs. 11-hour delay in the

PSV group). The delay reflects the pragmatic issues such as shift changes, lack of staff and staff bias in an open label RCT study.

There was no difference in the respiratory parameters - respiratory rate, minute ventilation, inspired tidal volume or oxygen supplementation between the two groups prior to minute ventilation test. This is not surprising and supports the trial design of adding low PSV (aiming 2-3mls/kg/breath) to support spontaneous breaths in the low rate SIMV mode to prevent fatigue prior to extubation. Contrary to the popular belief of inability to use 'true PSV' with no back up rate due to apnoea of prematurity, our study suggests very immature infants can be safely weaned in this mode without significant issues. This is an important finding. CO_2 clearance was also equal in the two arms. This is possible from effective transfer of work of breathing from the ventilator to the infant and most likely from respiratory muscle preconditioning by use of pressure support. There were a lower proportion of infants failing the MVT in the SIMV group compared to the PSV group (4 vs. 10 respectively). However, there was no difference in the rate of re-intubation within first 72 hours. Whether this is due to ventilator induced diaphragm dysfunction (Jaber et al., 2011) from prolonged ventilation needs further investigation.

The median time to extubation in the SIMV group was 42 hours. Infants randomised to the PSV group achieved the primary outcome sooner with median time to extubation at 31 hours. (95%CI 12.59-49.4hours),

but this was not significant. The survival distribution between the interventions was statistically not significant, Chi-square 0.768, p=0.381. Specifically, this difference favouring PSV group was seen in > 26 weeks gestation infants, however the differences were not statistically significant. A plausible explanation for this could be the availability of 'demand flow' in the PSV mode to satisfy air hunger and more stable respiratory drive from Hering-Breuer reflex. The other reason could be synchrony at inspiration and expiration, with least disruption to the spontaneous breathing cycle. Preconditioning of the respiratory muscles and preventing atrophy from prolonged ventilatory support could also be another important contributing factor for this observed effect (Knisely et al., 1988) (Jaber et al., 2011). However the insignificant difference favouring the PSV could be due to small sample size and larger studies could are needed to investigate this further.

The total duration of respiratory support showed a median time of 312 hours in the SIMV group as compared to 512 hours in the PSV group. This difference was not statistically significant. The total duration of respiratory support included all forms of respiratory support provided. A possible explanation for this difference is the use of High flow device as a non-invasive respiratory mode instead of CPAP device. The use of humidified high flow nasal cannulae (HHFNC) support came into practice after the study was commenced. Infants were supported with CPAP at initial extubation as per trial protocol. In a proportion of infants needing some form of respiratory support after weaning on CPAP

humidified high airflow was used as a subsequent 'step down' therapy. The uncontrolled use of HHFNC could be the reason for the observed difference. Prolonged duration of respiratory support has been seen in randomised controlled studies comparing HHFNC with CPAP (Abdel-Hady et al., 2011) Another factor for the observed difference could be the role of partial course of antenatal steroid (higher in the PSV group), although statistically there was no difference between the two groups, based on our knowledge from historic studies this cannot be ignored.

There was no significant difference in the use of adjuvant therapy (i.e. use of diuretics and post natal steroids) to assist extubation. Although the study was not designed to investigate other secondary outcomes, death and chronic lung disease are important outcome measure of interest. There were a total of 5 deaths after randomisation: 3 in the SIMV group and 2 in the PSV group. This difference was not statistically significant.

There was no difference in: days to reach the birth weight, days to establish full enteral feeding or average weight gain per day prior to discharge between the two groups. The results were identical (Table 27). This is an important finding and adds more information to our understanding of interaction of mode of ventilation and energy expenditure. In a randomised controlled study comparing PSV with flow cycled A/C mode (Patel et al., 2012) the authors conclude there was no difference in the energy expenditure and work of breathing. But there

was no information on weight gain between the two groups. Thus it appears flow cycling extends its benefits to both the groups by providing greater synchronicity to prevent 'fighting the ventilator' scenario and asynchronous breathing leading to higher energy expenditure. When PSV was compared with SIMV (Gupta et al., 2009a), authors observed, addition of PSV stabilised breathing and increased minute ventilation. This was proportional to the level of PSV. The observation suggested improved respiratory efficiency. However, our data suggests the end point of such benefits is not translated in definite clinical outcomes such as effective weight gain per day. The observed effect highlights the obvious – there are many other factors not considered in this study rather than mode of ventilation that contributes to infant growth.

There was no difference in incidence of bronchopulmonary dysplasia between SIMV and PSV at 28 days (69% in both groups) and at 36 weeks (52% vs. 55%). There was no significant difference in the infants going home with oxygen supplementation between the two groups. Although the two weaning modes differ from one another in their breath delivery, we targeted tidal volume for adjusting ventilator setting to prevent ventilator induced lung injury. This could be the reason for equal incidence of chronic lung disease and home oxygen supplementation in both the groups.

There was no difference in any of the secondary outcomes of interest between the two groups. Infants weaned in the PSV arm had a longer duration of stay. Median duration of hospital stay [SIMV-69 (95% CI, 52.7 to 81.2) days, vs. median duration of weaning in PSV arm 70 (95% CI, 61.9 to 78) days] p=0.52. Our results are different from the previous randomised controlled study comparing PSV to SIMV weaning (Reyes et al., 2006). The likely reason could be inclusion of more immature infants (inclusion criteria of 23^{+6} gestation) and use of HHFNC leading to need for longer duration of respiratory support.

Since this study commenced, data on newer mode of ventilation – Neurally Adjusted Ventilatory Assist (NAVA) has been published suggesting greater synchronicity and decreased work of breathing (Beck et al., 2009). This benefit was observed despite presence of large ET leak (Stein and Howard). The ability to deliver assisted breaths and to maintain synchronicity by monitoring diaphragmatic activity in presence of large leak holds advantage over conventional ventilation and particularly useful as a non invasive respiratory modality. The improved patient ventilator interaction was studied in another observational study (Piastra et al., 2014) suggesting lower heart rate, lower arterial blood pressure and improved comfort score in a group of infants with ARDS needing HFOV and weaned on NAVA as compared to weaning on PSV. Weaning on NAVA was considered to be superior to PSV. However a major limitation is that infants were compared in two different epochs retrospectively. As the data was published in an

abstract form complete details on methodology is unavailable. A limitation of NAVA to current date is non-availability of transducers for infants below 26 weeks gestation. Any use in infants below this gestation is purely experimental and lacks robust scientific evidence.

From adult experience, an important aspect of PSV mode of ventilation is patient comfort from greater synchrony at both inspiration and expiration. In that respect, the reported findings of greater comfort score in NAVA is not surprising.

Assessing pain scores/comfort scores could be challenging and practice variation makes it difficult to generalise the findings. Although there are validated tools in practice (mostly from paediatric intensive care practice), personal communication with the nurses at the cot side in both the units suggests subjective variation in recording comfort scores. Thus, although pain scores on 11 infants recruited in SITE 2 was collected for comparison, there were several issues surrounding training and subjective bias. Therefore, in an open labelled study such as ours, reporting pain/comfort scores was inappropriate. This could be considered in future studies.

Our study like most other open labelled studies would be affected by health care professionals' bias especially in commencing the assigned weaning mode. In both the groups there was at least ten-hour lag to commence the randomised mode. Whilst this could affect the primary outcome of the study, it did not favour any of the two arms. Other

important bias was the clinician perception and report of 'inability' to wean on any particular assigned mode as seen in three infants reported to fail weaning as per the study protocol. Two infants were assigned to PSV weaning protocol and one in SIMV arm. This has not been discussed in the previous randomised studies (Farhadi Roya, 2016), (Reyes et al., 2006). Farhadi et al used 15 SIMV breaths and Reyes et al used variable rate SIMV to maintain adequate gas exchange. Hence weaning was not on pure PSV.

PSV is designed to provide variable flow (demand flow) to meet patient demand. It is thought this could particularly favour infants with chronic lung disease. In our study, PSV took longer time to wean in the very immature infant group. This is also the group of infants with higher incidence of chronic lung disease. It is puzzling to see the results different from the current opinion. A likely explanation for this finding is that risk factors such as prematurity, antenatal events such as sepsis, maternal factors such as chorioamnionitis, mechanical ventilation, oxygen supplementation and other post natal stress could have contributed to chronic lung disease rather than the mode of respiratory support. It may also be our strategy of using PSV with only ten SIMV breaths was inadequate and iatrogenic in contributing to the longer duration of mechanical ventilation.

Although it was envisaged that whole body plethysmography would be used to study the work of breathing at variable PSV levels, cost

implications and time constraints to conduct this study meant it was not possible during the study period.

Comparing average total duration of mechanical ventilation in our study [PSV arm - 281.8 (95% CI 155.17- 408.61) hours and 306.4 (95% CI 152.3- 460.4) hours in the volume SIMV arm] with volume controlled ventilation study in 2006 (Singh et al., 2006) [Volume controlled ventilation arm 255 (95% CI 160-249) hours and 327 (95% CI 214-441) hours in the pressure controlled arm] suggests volume controlled ventilation with added pressure support is the way forward to reduce mechanical ventilation days. We recruited infants from 23 weeks' gestation compared to above 24 weeks in their study and infants in our study also had the worst OI prior to randomisation (11.56 for the PSV arm, 11.81 for the volume controlled arm compared to 6.6 for the volume controlled arm and 5.5 for the PSV group). These differences could be the reason for the slightly longer duration of mechanical ventilation in our study. The findings are however comparable and therefore suggest the results are generalisable to neonates of all gestation with surfactant deficient lung disease. The above finding is also the strength of the study in utilising the staff knowledge and their previous research experience in ventilation study. This made site set up and training the staff with the new study protocol relatively easy.

A few eligible infants were lost to randomisation early in the study period. Following advice from the trial steering committee it was

decided to gain consent and randomise the infants once 'early stability' was achieved. Hence future studies could be designed to stratify the infants based on gestation and on the duration of initial ventilation period to identify benefits in infants with chronic lung disease.

Our study limited data capture prior to discharge from our hospital or to home. This was intentional with limited resources and in the available limited time. A major limitation was poor uptake of the study in one of the two centres. This was most likely from deploying SIMV earlier than traditional approach and use of PSV with only ten SIMV back up breaths. This suggests a degree of anxiety for the clinical team deviating from the traditional set up of reducing the ventilator support significantly on the A/C mode prior to deploying (SIMV with some PSV) just prior to extubation.

11 Summary, Conclusions and Future Directions

There is good evidence favouring antenatal intervention of corticosteroid administration to labouring preterm mothers. This has led to increased incidence of preterm infants survivability (Costeloe et al., 2012). Postnatally, surfactant administration and targeting tidal volumes has further significantly reduced incidence of chronic lung disease and death (Wheeler et al., 2010) this is most likely by reducing ventilator induced lung injury. However an area of uncertainty is defining weaning on mechanical ventilation. Reducing mechanical ventilation days could lead to reduction in incidence of chronic lung disease.

A randomised controlled study was undertaken to wean infants early during the course of their respiratory distress from surfactant deficiency. Infants were stratified into three groups based in their gestation at birth. In the intervention arm, variable PSV commencing from PSVmax targeting 4-6mls/kg was weaned to PSmin targeting 2-3ml/kg. In addition, ten SIMV breaths targeting low tidal volumes (2-3ml/kg/breath) was added to the PSV breaths to compare it with the standard arm. In the standard arm, weaning on mechanical ventilation was as per standard practice with weaning on backup rate and dialled

volumes. 50% PSV (50% of the peak inspiratory pressure at the start of weaning, targeting 2-3ml/kg) was added to support spontaneous breaths over the SIMV back up rate. All other care was provided as per standard unit practice.

Duration of weaning was defined as the time taken from commencing the randomised mode to passing the minute ventilation test.

We conclude, there was no significant difference in the duration of weaning in the two weaning modes and there were no significant differences in the secondary outcomes of interest. However, an overall trend of faster weaning in the PSV mode was observed. The observed trend is likely from greater autonomy provided to the premature infant i.e. determining its own respiratory rate by managing when to breathe and how long to breath. The added feature of demand flow in PSV mode also could have satisfied their demand to generate a sigh breath, that could have helped to stabilise their breathing.

Our randomised controlled study adds more insight into variable level of PSV for weaning on mechanical ventilation with only a few (ten) SIMV breaths in the background. The results are comparable with the traditional SIMV weaning without any apparent disadvantages.

Weaning infants on mechanical ventilation involves interplay of many processes and in particular also optimising cardiac status. It is difficult to conceive that by optimising respiratory care alone would reduce

duration of weaning. Inability to wean and extubation failure has been related to cardiac compromise (Boles et al., 2007). This deserves a special mention here, as PDA is a common confounding clinical problem in our infants. This often contributes to difficult ventilation. Whilst all of the weaning studies including ours, PDA management was as per routine standard practice. Haemodynamic assessment and strategies to optimise it was not routinely assessed for extubation readiness. In future studies, it would be useful to include haemodynamic and cardiac monitoring in weaning and extubation assessment.

In addition, acquiring physiologic variables of work of breathing and ascertaining the actual transfer of work of breathing at variable PSV levels could provide us the insight into the 'critical' PSV level for preventing failure or prolonged duration of mechanical ventilation in the PSV mode.

Adult studies suggest patients experience greater comfort compared to other intermittent mandatory ventilation. Newer generation ventilators are able to provide pure PSV with back up built in when unreliable respiratory drive is detected. However this mode has not been tested to ascertain patient comfort.

Whether greater infant autonomy and greater comfort of breathing from better synchrony could lead to a reduction in chronic lung disease should also be investigated in future larger studies.

Appendix 1 Parent Information Leaflet

North Tees and Hartlepool NHS
NHS Foundation Trust

Information Leaflets for Parents

Pressure support Ventilation or Synchronised Intermittent Mandatory Ventilation for weaning premature babies on Mechanical Ventilation. A multi centre randomised controlled trial. [POST trial]

Information for Parents

Currently we are undertaking a study to compare two different methods of providing breathing support to babies during weaning (reducing support) on the ventilator. We are writing to invite you to let your baby take part in this research study. Before you decide it is important for you to understand why this research is being done and what it will involve for your baby. Please take the time to read the following information and feel free to discuss it with your family and friends. This leaflet is not meant to frighten or cause alarm, but to give you enough information to help you to decide whether your baby should take part in this study or not. If there is anything that is not clear to you, or you need more information, please feel free to ask us. This decision does not have to be rushed.

What is the purpose of the study?

Premature infants born more than 8 weeks before the due date often suffer from breathing difficulties due to reduced amount of a chemical called "surfactant". This is called as "acute respiratory distress syndrome (RDS)". Most commonly they require breathing support through a tube placed in the wind pipe (endotracheal tube) and assisted by the breathing machine (ventilator). The severity of RDS varies between babies and will gradually get better with time and support. As the lungs mature the level of breathing support is gradually reduced. This process is called "weaning" off the ventilator. The length of time of weaning differs between babies and depends on their degree of prematurity and severity of underlying lung problem.

Currently different special care baby units have different ways to wean babies on ventilator. Synchronised intermittent mandatory ventilation (SIMV) and Pressure support ventilation (PSV) are two recognised modes of ventilation for weaning on the ventilator. Both these modes are routinely used in premature babies. SIMV is widely used as the standard way for weaning and supports only fixed number of spontaneous breaths set on the ventilator, any additional breaths of baby remain unsupported. In the PSV mode, every breath of the baby is supported. Currently there is however lack of evidence in premature babies on any proven advantages of PSV over SIMV. This study is

designed to compare these two modes of ventilation (SIMV and PSV) for weaning premature babies on ventilator.

Why has my baby been chosen?

Your baby is chosen to take part in this study as he/she is born more than 8 weeks before the due date and has needed breathing support on a ventilator (breathing machine). As your baby improves, we would like to put your baby to one of the two modes (SIMV or PSV) and start weaning on the breathing machine. This will allow us to compare the two breathing modes in a scientific way. Before we enrol your baby into this trial, we would like you to read this information and decide if you would grant permission for your baby to participate in this study.

Does my baby have to take part?

You do not have to agree to your baby taking part in this study. Your decision whether or not to take part will NOT affect the care provided to your baby.

What will happen to my baby if I agree to take part in the trial?

If you agree, your baby will have an equal chance of being put into either of these two ventilation modes. It is not possible to know beforehand which one your baby will be allocated. The allocation will be done by computer generated allocation to have an equal number of

babies in the two study groups. This study design will allow comparing the two study modes scientifically.

No extra blood tests or injections are necessary over and above the routine care. The level of care your baby receives on the neonatal unit will be the same whether you decide to take part in the study or not.

What will happen to my baby if I do not agree to take part in the trial?

If you are not able to decide then your baby will receive what is currently practiced in the unit i.e. SIMV mode of ventilation, this is the unit's standard approach to reducing (weaning) breathing support. Your decision whether or not to take part will not affect the care provided to your baby.

What are the possible side effects or complications of the treatment?

There are no perceived additional side effects of participating in this study. The known complications and the risks associated with being premature would be the same in both the study groups, whether or not your baby participates in this study.

Both ways of the ventilation are safe. Both ventilation modes within the study conform to the manufacturers' recommendations and safety for use in newborn infants within the range of values that are routinely used in babies. We are only studying if one mode is better than the other in reducing the duration of weaning on mechanical ventilation.

Whichever group your baby is in, your baby will be monitored very closely by the hospital staff in the neonatal intensive care unit and conform to all the standard practices on the neonatal unit.

What are the possible advantages and disadvantages of taking part in this trial?

There are no direct advantages of participating in this study. The results of the study would however help in better understanding of these modes which might further assist in improving the care of these very preterm babies. There are no known or perceived disadvantages of participating in this trial.

What if new information becomes available?

The staff conducting this study will inform you of any new information that becomes available during the course of the study.

What if something goes wrong?

It is unlikely to have any major adverse effects of participating in this trial. You however remain covered by the trust indemnity scheme and participating in the trial does not affect your legal rights.

Will my taking part in this study be kept confidential?

Strict policies and procedures will be followed as per best practice guidance, issued by the Department of Health; November 2003 for confidentiality. If you choose so, your GP will also be informed that your

baby has taken part in this study. These details will be kept securely and will only be seen by the study team and people from the regulatory authorities. They may also look at your baby's notes to check that the study is being carried out correctly. Information about your baby will not be used for any purpose other than to answer the research question.

What will happen to the results of the research study?

At the end of the study, the anonymised results will be analysed and published in peer reviewed medical journal and will be presented in medical seminars and conferences. We could send you a summary of the final results of the study. A copy of the full journal article can be requested from the Chief Investigator. You and your baby will not be identified in any report or publication about the study.

Who is organising and funding this study?

The study is sponsored by University Hospital of North Tees. This study is a topic for a higher degree with the university pursued by the co-investigator.

Who has reviewed the study?

The study been assessed and approved by the NHS Research Ethics Committee, the Hospital Research and Development Committee,

independent parent of a baby and by a panel of external experts in the field of newborn ventilation.

Approval means the Committees are satisfied that your rights will be respected, that any risks have been reduced to a minimum and balanced against possible benefits, and that you have been given sufficient information on which to make an informed decision to take part or not.

What if I have concerns?

If you have any concerns or questions about this study or the way it has been carried out, you should contact the Principal Investigator [their name and contact details are on this page]. If you have any questions about this study you may also choose to get information from the hospital Research and Development department or you could alternatively contact INVOLVE (www.invo.org.uk/Resources.asp or contact 02380 651088) for more advice and support.

Thank you for reading this information leaflet. The doctor or nurse who gave you this leaflet will be pleased to discuss the study in more detail and provide further information if this would be helpful. Alternatively, the contact details of the study's Principal Investigator for the site is provided on this page.

Local contact for your Hospital is

NAME: Dr Prashant Mallya

DESIGNATION: Neonatal Research Registrar

CONTACT NO: 01642 624248 Bleep 6103

Appendix 2 Baseline eligibility form

Name: _____

Hospital No: _____

Date of Birth: _____

Baseline Eligibility Screening Assessment

Please use the screening questions below to assess eligibility for

participation in the POST UK trial

1	Gestational Age: _____/40 Scan EDD: _____/40 Agreed EDD: _____/40	GA between 23+0 and 31+6 are eligible	
		Yes	No
2	Ventilated for at least 6 hours	Yes	No
3	No severe congenital or neuromuscular disorder	Yes	No

	diagnosed antenatally or at the time of birth which could affect respiratory function		
4	Signed written parental consent for participation	Yes	No

Infant transferred from other units if have reached trial entry criteria at the time of randomisation will not be eligible

If answer is NO to any of the above then the baby is not eligible for participation.

Eligibility assessment outcome: Eligible   /   Non-eligible

If eligible for randomisation

Envelope Number	
Allocated to	

Please select the most appropriate answer if baby is eligible and not randomised:

1	Parents were not contacted /aware of the POST UK trial	Yes	No
2	Parents contacted but declined	Yes	No
3	Unable to obtain an informed consent	Yes	No
4	Infant self extubated in the 6 hours period and did not require further mechanical support	Yes	No
5	Infant too unwell for recruitment* * must be discussed with the senior clinician and documented in the clinical notes	Yes	No

Signature_____

Designation_____

Date_____

Appendix 3 Trial enrolment form

Name	
DOB	
Gestation at birth	

When intubated	Date and time
Trial entry criteria reached on	Date and time
Weaning mode commenced on	Date and time

Time																															
MAP <10cm																															
FiO$_2$ <40%																															
Spontaneous breaths																															

Time																															
MAP <10cm																															
FiO$_2$ <40%																															
Spontaneous breaths																															

TICK BOXES AS AND WHEN ACHIEVED

Appendix 4 Minute Ventilation Test

POST TRIAL
Minute ventilation Test

Name	
Hospital No	
Randomised to	

Whilst on mechanical ventilation

Time (in minutes)	Heart Rate	Respiratory Rate	FiO$_2$	Saturations	Tidal Volume	Minute ventilation (MVM-mls/kg/min)
End of 1st minute						
End of 2nd minute						
End of 3rd minute						
End of 4th minute						
End of 5th minute						
						Average MVM=

Whilst on ET CPAP

Time (in minutes)	Heart Rate	Respiratory Rate	FiO$_2$	Saturations	Tidal Volume	Minute ventilation (MVS-mls/kg/min)
End of 1st minute						
End of 2nd minute						
End of 3rd minute						
End of 4th minute						
End of 5th minute						
						Average MVS=

Baby is ready for extubation only when
- MVS/MVM is more than 50% and
- No bradycardia needing IPPV and
- Rise in FiO_2 of no more than 10%

MVS/MVM	_____%
Minute ventilation test	Pass/failed
Date and time when extubated	

Test done by

Name		
Designation		
Signature		Date:

Appendix 5 Data collection form

Data collection form   POST TRIAL

Hospital Identifier NHS No Time of Birth	
Date and time of admission to the NNU	
Maternal Contact Details	
Parity	
Contact telephone no	
Antenatal steroids given	Yes/No
Antenatal steroids	Date Full course / Partial course Date Full course / Partial course
Antenatal events	1. Prelabour ROM 2. PROM 3. Chorioamnionitis 4. Pregnancy induced Hypertension 5. Diabetes in pregnancy needing treatment 6. Antepartum haemorrhage 7. Maternal Pyrexia 8. Intrapartum antibiotics
Birth Order	Singleton Twins Higher
Antenatal scan abnormalities	Yes/NO
If Yes	Known upper airway anomaly Complex congenital heart problem Neuromuscular disorder Syndromic diagnosis
Comments	
Cord blood gas	Arterial pH BE Venous pH BE

Mode of delivery	NVD	
	Breech Delivery	
	Emergency LSCS in labour	
	Emergency LSCS not in labour	
	Elective LSCS Instrumental delivery	
LMP		
EDD by dates		
EDD by scan		
Agrees gestation		
Birth weight		
Gender	Male/ Female	
Place of delivery	Inborn/ Outborn	
If outborn, referring hospital details		
Transferred at	_____Hours of life	
Date and time of admission to the NNU		
Condition at birth	No support needed	
	Oxygen via face mask	
	CPAP	
	Ventilation via ETT	
	External cardiac compression	
	Drugs	
Time heart rate more than 100		
Time to first gasp		
Time to establish spontaneous respiration		

APGAR score	At 1 minute	
	At 5 minutes	
	At 10 minutes	
Temperature on admission to the NNU		
Worst base deficit in the first 12 hours		
CRIB2 score		
Mechanical ventilation from birth	Yes/No	
If No	Non invasive respiratory support for _____Hours	
Age mechanical ventilation commenced	_____Hours from birth	
Endotracheal tube size on commencing mechanical ventilation	2.0mm	2.5 mm
	3.0mm	3.5mm
Primary mode of ventilation	Volume modality/ Pressure modality/ HFOV	
Date and time of commencing mechanical ventilation		
Maximum OI		
First blood gas upon mechanical ventilation	pH pCO2 BE	
Other adjuncts of ventilation	Nitric Oxide Duration Maximum dose	
Surfactant	1st dose _____mg/kg 2nd dose _____mg/kg 3rd dose_____mg/kg	
Problems of ventilation	Air leaks needing treatment	
	PIE	
	Pneumonia	
Inotropic support	_____hours	

Mean airway pressure on commencing mechanical ventilation	
Maximum peak inspiratory pressure	
Maximum FiO$_2$ at admission to the NNU/ commencing mechanical ventilation	
Respiratory rate at admission to the NNU	
Date and time when randomised	
Date and time to achieve the trial entry criteria	
Time to achieve the trial entry criteria	_____Hours
Duration of primary mode of ventilation before randomisation	_____Hours
Date and time of commencing randomised mode	
Randomised to	PSV/SIMV

Stratified to	Very very prem	
	Very prem	
	Prem	

Caffeine citrate loading dose administered before / at commencing randomisation	Yes/No
Maintenance dose	a. 5mg/kg b. 10mg/kg
Adjuncts to maintain weaning – diuretics administered	Yes/No

| ETT at commencing weaning | 2.0 mm | 2.5mm |
| | 3.0mm | 3.5mm |

Length of the ETT tube	
Mean airway pressure at the time of commencing weaning	
FiO$_2$ at the time of commencing weaning	
pCO2 at commencing weaning	
Vti/kg at commencing weaning	
MVT (Ve) at commencing weaning	
Blood gas at commencing weaning	pH pCO2 BE
Postnatal steroid	Yes/No
If yes	No of courses
MVT performed	Yes/No

If yes	First MVT	
	Second MVT	
	Third MVT	

	Fourth MVT	
	Fifth MVT	
Average MVM Vti		
Average MVS VTi		
Respiratory rate at MVM		
Respiratory rate MVS		
pCO2 at MVT		
Average of the PCO2 in the assigned mode during the weaning period		
FiO2 at MVT	MVM	MVS
RSBI	MVM	MVS
PEFR/Tube Resistance		
Haemoglobin at MVT		
No. of times MVT failed		
Date and time of passing MVT		
Date and time of extubation		
If MVT not performed	Comments:	
Need of re intubation in 72 hours	Yes/No	
Date and time of maintaining extubation for 72 hours		
Date and time of re intubation		
Date and maintaining extubation for 7 days		
Date of transfer to other hospital		
Primary outcome: Duration of weaning in the assigned mode/passing MVT	_____Hours (Includes time from commencing randomised mode to passing the final MVT before extubation)	
Total duration of mechanical ventilation through ET tube		
Non invasive respiratory support upon extubation	1. CPAP_____hours 2. SiPAP_____hours 3. High Airflow_____hours	
Need for oxygen at 28 days of life	Yes/No	
Need for oxygen at 36 weeks of life	Yes/No	
Modified Jones Test performed	Yes/No	
If yes	Need for oxygen to maintain saturations 91-93% confirmed? Yes/No	

Total duration of respiratory support including non invasive respiratory support	
Discharge on home oxygen	Yes/No
Date of discharge home	
Enteral feeding commenced on	____Days of life
Time to full enteral feeding	____days of life
Time to gain birth weight	_____days of life
Weight gain from admission to discharge	
Average weight gain per day	
Total duration of hospital stay	
Complications of prematurity	
Any IVH	
Intraventricular haemorrhage grade 3 or more	
Periventricular Leukomalacia	
Hydrocephalus needing intervention	
Retinopathy of prematurity requiring surgery	
ROP stage 2 or more	
Prophylactic PDA treatment	
Patent Ductus Arteriosus (PDA) medically treated after 72 hours of birth as per unit protocol	
PDA surgically ligated	
Necrotising Enterocolitis (NEC) stage 2 or above	
NEC requiring surgery	
Pneumothorax during weaning phase	
Chronic lung disease (need for supplemental oxygen at 36 weeks after failing room air challenge)	
Severity of CLD	Mild	
	Moderate	
	Severe	
Sepsis episodes (defined as need for antibiotics for >5 days/ positive blood culture) or other fluid culture	
Death before discharge	

BPD is classified as
- Mild BPD defined as need for supplemental oxygen at ≥ 28 days but not at 36 weeks postmenstrual age (PMA) or discharge
- Moderate BPD is oxygen supplementation for ≥28 days plus treatment with <30% oxygen at 36 weeks PMA
- Severe BPD as oxygen supplementation at ≥ 28 days plus ≥30% oxygen supplementation or positive pressure support at 36 weeks PMA

Appendix 6 Ventilation Practice survey

Poster presentation- Paediatric Academic Society, Denever 2011.

Current trends in Respiratory Care of Very Low Birth Weight (VLBW) Infants : Based on Evidence or Habit?

Prashant Mallya, MRCPCH[·], Samir Gupta, MD[·], C Harikumar, MD[·] and Sunil K Sinha, MD, PhD[·].

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Abstract

Background: The respiratory management of very low birth weight (VLBW) infants has changed over the last decade. This includes volume targeted and pressure support ventilation, use of non-invasive respiratory support at birth, oxygen saturation targeting and use of caffeine.

Objective: To study current trends in respiratory management of VLBW infants in level 3 neonatal units.

Methods: A structured questionnaire was designed and a senior staff at all level 3 units in England were contacted telephonically in November 2010. The data was collected by a single interviewer and all questions were validated.

Results: A total of 54 units were identified from British Association of Perinatal Medicine database. Of these 53 units (98%) responded.

Pressure limited ventilation was used as initial mode of mechanical ventilation in 69.8% units, volume targeted ventilation in 24.5% and High Frequency Ventilation in 5.7% units. Pressure support (PS) ventilation was used in 50.9% units, with 18.8% using PS of up to 50% and only 7.5% units used more than 50% PS. 69.8% units targeted tidal volume and 54.7% units aimed a tidal volume of 4-7mls/kg. Synchronised intermittent mandatory ventilation (SIMV) was most widely used for weaning on ventilator (64.2%), followed by SIMV with PS (18.9%) and Assist control (AC) mode (11.3%). Only 7.6% units used any objective criterion to assess readiness for extubation.

Most units (77.4%) used target oxygen saturation between 82 to 95%. Caffeine was used by 28.3% units in the acute phase of the respiratory distress syndrome, and 67.9% units preferred to give caffeine only when infant deemed ready for extubation.

81.1% units try CPAP at birth in babies less than 28 weeks gestation. Infant flow driver CPAP is used by 79.2% units, Bubble CPAP by 13.2% units and Bi-level CPAP by 69% units. Weaning CPAP by reducing pressure was practiced in 28.3% units, but 62.3% used cycling method by increasing time off on CPAP. High flow nasal cannula oxygen was also used in 47.2% units.

Conclusions: This survey highlights wide variation among England neonatal units for respiratory support of VLBW infants. This precludes generalisability of current research findings in clinical practice and there is an urgent need to drive for a consensus amongst neonatologists regarding their respiratory care protocols which can be used both for clinical practices and future research.

Background

- Advances in microprocessor technology and the perceived advantages of synchronised mechanical ventilation have led to availability of newer modes of patient triggered ventilation.
- Cochrane meta analysis on volume controlled ventilation has highlighted reduced death and chronic lung disease compared with pressure limited ventilation.
- Three large trials comparing CPAP and mechanical ventilation reported no difference in chronic lung disease at 36 weeks post menstrual age.
- Neonatologists worldwide continue practicing newer modes of respiratory support with no agreed consensus on ventilation practices. There is lack of evidence on superiority of one mode of ventilation over the other in neurodevelopmental outcome.

Aims

- To ascertain if the current practice of respiratory management of the preterm infants in level 3 neonatal units in England is guided by current evidence base.

Methods

- A structured telephone questionnaire was formulated and senior clinical team member in all level three neonatal units in England identified from British Association of Perinatal Medicine (BAPM) register were contacted by a single interviewer in September 2010.
- The questionnaire included aspects of invasive and non invasive modes of respiratory support.
- All questions were validated.

Results

Invasive ventilation

- Fifty four level 3 neonatal units were identified and 53 units responded (98%).
- 70% units provide initial ventilation using Pressure controlled ventilation (Fig.1)
- 83% of the units chose SIMV (64%) or SIMV with pressure support (18.8%) for weaning (Fig. 2)
- Only 4 units (7.5%) used an objective evaluation in form of spontaneous breath test or Minute ventilation test for extubation.
- 69.8% units targeted tidal volume delivery for mechanical ventilation (Fig. 3)
- Most units aimed to deliver a tidal volume between 4- 6mls/kg (Fig. 4).
- Caffeine was widely used for extubation (96%), however only 28.3% units administered caffeine in early phase of RDS.

Non invasive respiratory management (Table 1)

- 83% units have used non invasive mode of respiratory support at birth using CPAP or high flow nasal cannula oxygen.
- 47% units used high flow nasal cannula oxygen for respiratory support of the preterm infant.

Figure 1 — Initial mode of ventilation (Pressure Controlled, Volume Controlled, High Frequency)

Figure 2 — Weaning on mechanical ventilation (SIMV, Assist Control/ SIPPV, SIMV+PSV, Other)

Figure 3 — Tidal volume targeted? (Yes, No)
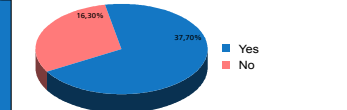
Figure 4 — Minimum Targeted Tidal Volume / Maximum Targeted Tidal Volume

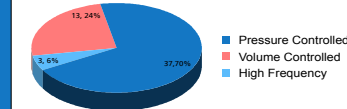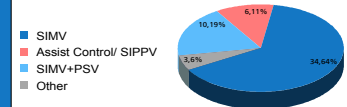| Type of non invasive respiratory support	Number of Units (%)
BiPAP	37 (69%)
Infant flow driver	42 (79%)
Ventilator derived CPAP	3 (5.6%)
Bubble CPAP	7 (13%)
Weaning CPAP	By pressure 15 units (28.8%) By cycling 33 units (63.4%)
High flow nasal cannula oxygen	25 (47.1%)

Table 1
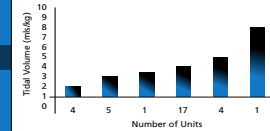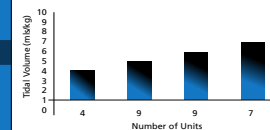
Conclusions

- Most units continue to use pressure controlled ventilation to provide the initial respiratory support despite convincing evidence in favour of volume controlled ventilation.
- Non invasive modes of respiratory support are increasingly used in infants less than 28 weeks gestation.
- The current survey highlights wide variation among UK neonatologists and precludes generalisability of current research findings in clinical practice.
- This requires consensus amongst neonatologists regarding their ventilatory management of the very low birth weight infants.

Appendix 7 In-vitro Endotracheal tube resistance experiment

Poster presentation- European Society of Pediatric Research Istanbul, 2012. (ADC 2012;97:A483)

Estimation of Neonatal Endotracheal Tube Resistance by Water Manometer

Prashant Mallya[1], Paul Webb[2], and Samir Gupta[1]
[1]Neonatal Unit, University Hospital of North Tees
[2]Regional Medical Physics, James Cook University Hospital

Background:
Endotracheal tube diameter, tube length, gas type and gas flow rates have an effect on mechanical ventilation and patient ventilator interaction. Understanding the physics and their interaction could help us in better understanding the effect of this on patient-ventilator interaction.

Aim/Objective:
1. To ascertain the resistance offered by the endotracheal tube commonly used in neonatal practice (2.5mm, 3.0mm, 3.5mm and 4.0mm) across different flow rates commonly used in volume controlled ventilation (4lt/min to 11lt/min).

2. To ascertain the effect of tube length (7 cm and 14 cm) and the effect of medical air and 100% oxygen on the observed pressure drop.

Methods:
An in-vitro laboratory based observational study was performed to ascertain endotracheal tube resistance using 100% hospital oxygen and medical air. We used a paediatric flow regulator to study the pressure drop across flow rates of 4 to 11lt/min. The flow meter had an accuracy of +/- 0.5lt/min. Water used as reference fluid was contained in a 'U' plastic tube. The proximal end of the plastic tube was used to connect the proximal end of the Portex endotracheal tube through the standard 1 mm side port using a connector and air flow directed as per usual practice to maintain laminar flow pattern. Menisci difference measured against the standard scale (range 0 - 300mm) from 8 observations for each flow rate was used to determine the pressure drop.

Results:
1. ANOVA was used to compare variation at different flow rates & tube diameters, and paired t test to compare variation at different type of gases and tube length.
2. Multiple regression of the various factors showed the p-values for the estimated coefficients of tube length, gas type and flow rate are all 0.000. The p-value for tube diameter is 0.161, at an α of 0.05. The R-sq value indicates that the predictors explain 66.4% of the variance in pressure drop.
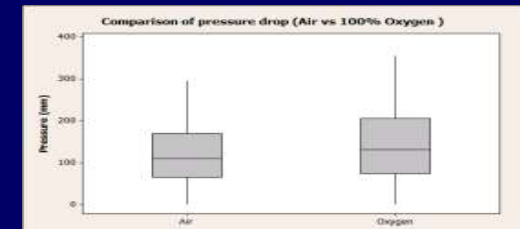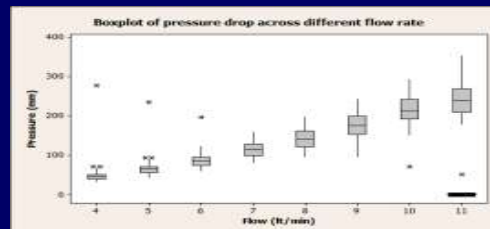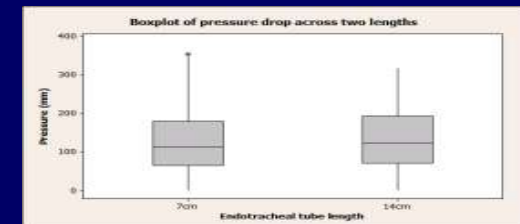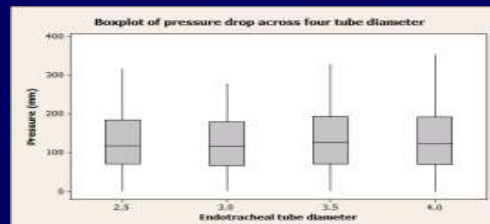
Conclusion:
- The regression model confirms endo tracheal tube diameter commonly used in neonatal respiratory support does not significantly impact the pressure drop.
- The results from this study could be utilised in setting the ventilator to achieve the desired pressure delivery at different flow rates using air / oxygen at varying ET tube sizes.

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