

Ventilatory management

All infants at risk of RDS and those with RDS should be closely monitored for clinical and biochemical evidence of respiratory failure. Each unit that undertakes care of such infants should have consultant paediatricians with an up to date knowledge of the principles of mechanical ventilation, who should be responsible for providing a clear respiratory management protocol for all the staff working on that unit.

Ventilation techniques

Continuous positive airways pressure (CPAP)

During CPAP support, a constant pressure is applied to the airway of a spontaneously breathing infant. CPAP improves oxygenation by increasing the functional residual capacity, through recruitment of collapsed alveoli. It also promotes redistribution of lung liquid and reduces upper airway resistance. CPAP is now applied via an endotracheal tube (ETT CPAP), a single nasopharyngeal or binasal (Hudson) prongs; previously used techniques (Gregory box, face chamber or face mask) are associated with more adverse effects. The devices are connected via a T-piece circuit to a standard neonatal ventilator or to a specific device (eg. EME infant flow driver), either system gives gas mixing, pressure setting and humidification facilities. It is important to ensure appropriate attachment of the dual nasal prong system, as nasal deformities have been described presumably due to pressure necrosis (1). Continuous and variable flow CPAP devices are used, comparison of the devices has

demonstrated better lung recruitment and a lower work of breathing with variable flow (2,3). A disadvantage of the variable flow device, is the possibility of lung overdistension at CPAP levels greater than 6 cm H₂O (2).

In non-randomised trials, introduction of nasal CPAP soon after birth has been associated with a reduction in both the need for intubation and ventilatory support and bronchopulmonary dysplasia (4,5). The results of randomised trials have demonstrated that early use of CPAP compared to intubation and ventilation is associated with a reduction in the duration of mechanical ventilation, but no significant differences in long-term outcomes (6). Meta-analysis of the results of randomised trials has demonstrated extubation on to nCPAP rather than into an oxyhood is associated with a decreased incidence of post extubation failure and requirement for supplementary oxygen at 28 days (7).

Indications for CPAP

- At birth (B)
 - infants at high risk of RDS ie birthweight < 1000 gms
 - infants at high risk of RDS (ie. birthweight < 1000 gms) following extubation and administration of surfactant.
- Infants with worsening respiratory distress (B)
 - FiO₂ > 0.40 with PaO₂ < 6.7 kpa and pH < 7.25
- Post-extubation (A)
 - infants < 1500 gms in birthweight and maintained until the FiO₂ ≤ 0.25.

NB There is no evidence to suggest alternating CPAP with increasing periods in an oxyhood increases the likelihood of extubation success.

- Infants with mixed or obstructive, but not central apnoea (8), as the mechanism of CPAP's action in improving apnoea is via distending and maintaining the upper airway rather than on central drive (B).

Using CPAP (B)

Starting levels of 3-4 cm H₂O are recommended in infants with RDS who have had a positive response to surfactant administration (9), in some infants this level may be insufficient and need to be raised (C). The level should be elevated incrementally to 8 cm H₂O in infants with a poor response to surfactant administration, as indicated by a high work of breathing (subcostal recession) and high supplementary oxygen requirements. Higher levels of CPAP (6-8 cm H₂O) should be used in infants beyond the first week after birth with small volume hazy lung fields (9).

Criteria for failure of CPAP (C)

- $FiO_2 > 0.6$ and $PaO_2 < 6.7$ kpa and/or $pH < 7.25$ with $paCO_2 > 7.5$ kpa.
- A major apnoea or frequent (more than 4 per hour) requiring bag and mask ventilation for at least one minute.

Mechanical ventilation

Conventional ventilators can deliver pressure or volume controlled ventilation, pressure controlled ventilation has been most frequently used and studied. During

pressure limited time cycled ventilation mode, a peak inspiratory pressure is set and, during inspiration, gas is delivered to achieve the target pressure. After the target is reached the remainder of the gas volume is released into the atmosphere. Although the peak pressure may remain constant, the tidal volume delivery will vary according to the compliance of the lungs. During volume controlled ventilation, a pre-set volume is delivered with each breath regardless of the pressure required; thus the volume delivery will remain constant, but the peak pressure will vary depending on the compliance of the lung. To date, there have only been a few small randomised trials comparing pressure to volume controlled ventilation, their results suggest that volume controlled ventilation may have advantages including being associated with less hypotension (10) and a shorter duration of ventilation (11). Positive results are required from an appropriately powered study with long-term outcomes before routine volume controlled ventilation can be recommended for preterm infants with RDS.

Conventional mechanical ventilators delivery intermittent mandatory ventilation (IMV) and positive pressure ventilation (IPPV); they may also deliver triggered ventilation modes (see later). During IMV/IPPV, the clinician sets the required rate, inspiratory time, peak inspiratory pressure (PIP) and positive end expiratory pressure (PEEP). The ventilator then delivers inflation breaths at regular intervals irrespective of the baby's breathing activity, the baby thus may breathe either with (in synchrony) or against the ventilator (asynchrony or fighting the ventilator) (1) (see later).

Indications for mechanical ventilation: (C)

- Infants at high risk of RDS ie birthweight < 1000 gms
- Deteriorating blood gases ie $\text{PaO}_2 \leq 7$ kpa in an $\text{FiO}_2 = 0.6$ and/or a $\text{PaCO}_2 \geq 7$ kpa with a $\text{pH} < 7.25$
- Persistent apnoeas and bradycardias or a major apnoea and desaturation.
- Cardiorespiratory collapse.

Using conventional ventilation

Hypoxaemia in RDS is usually due to ventilation-perfusion (V/Q) mismatching or right to left shunting, although diffusion abnormalities and hypoventilation may also be additional factors. Oxygenation is directly related to FiO_2 and the mean airway pressure (MAP). MAP can be increased by changes in peak inspiratory pressure (PIP), positive end expiratory pressure (PEEP) or by changing the inspiratory-expiratory (I:E) ratio by prolonging the inspiratory time when the rate is kept constant. The most effective method of increasing MAP is by increasing the PEEP level. A very high MAP (>15 cm H₂O), however, may cause over distension, and oxygen transport may decrease due to reduced cardiac output. CO₂ elimination is proportional to minute ventilation, providing the tidal volume is greater than the deadspace. Minute ventilation is determined by the product of tidal volume (minus dead space ventilation) and inflation rate. For the same minute ventilation, changes that alter tidal volume delivery rather than the inflation rate are usually more effective in changing CO₂ elimination, because dead space ventilation remains constant.

Peak Inspiratory Pressure (PIP) (C)

Changes in PIP affect oxygenation (by altering the MAP) and the PaCO₂ (by altering the tidal volume and alveolar ventilation). An increase in PIP decreases PaCO₂ and improves oxygenation. PIP requirements are determined by the compliance of the respiratory system and not by the weight of the infant; the stiffer the lungs the greater PIP required. The lowest PIP that adequately ventilates the patient, as assessed by the clinical examination (chest movement and breath sounds) and blood gas analysis, should be used. Inappropriately excessive PIP may cause lung over-distension and increase the risk of baro/volutrauma and hence air leak.

Positive End Expiratory Pressure (PEEP) (B)

PEEP prevents alveolar collapse and, by maintaining lung volume at end-expiration, improves V/Q matching. Increasing PEEP augments mean airway pressure and thus improves oxygenation. Use of a very elevated PEEP (> 8 cm H₂O), however, may impair oxygenation by worsening lung compliance due to overfilled alveoli and induce hypercarbia by reducing tidal volume delivery. Tidal volume delivery is determined by the difference in pressure between the peak and positive end expiratory pressure ($\Delta P = PIP - PEEP$). A high level of PEEP (> 8 cm H₂O) can also have adverse haemodynamic effects due to lung over-distension causing reduced venous return and hence reduced cardiac output. Levels of 3 cm H₂O improve oxygenation in newborns with RDS without compromising lung mechanics, CO₂ elimination or haemodynamic stability (9).

Rate (A)

Two strategies regarding rate are used: the slow rate strategy during which babies are started on the ventilator at rates of 30-40 breaths per minute (bpm) and the fast rate strategy during which babies are started at rates of 60 bpm, the rate may then be increased to 120 bpm if the baby is breathing at a faster rate than the ventilator (12).

The expiratory time usually exceeds the inspiratory time regardless of the rate strategy used, this is to prevent inadvertent alveolar over-distension. Inspiratory times (T_i) should be limited to a maximum of 0.5 sec throughout the duration of mechanical ventilation, except in unusual circumstances. If a mature infant has severe disease, then T_i may be increased up to 1.0 sec and reverse I:E ratios used (see below) to increase MAP and oxygenation. If such manoeuvres are used a neuromuscular blocking agent should be administered, as babies are more likely to fight the ventilator if a long T_i is used. Randomised controlled trials have shown a lower pneumothorax rate in infants ventilated at fast (≥ 60 bpm) compared to slow rates (13), perhaps because at the faster rates ventilator inflations are more likely to synchronize with the infant's own respiratory effort (1).

Inspiratory and expiratory times (B)

During the acute phase of RDS, the time constant is short and an inflation time between 0.3 to 0.4 seconds is adequate. Prolonging the inflation time will increase the MAP and hence improve oxygenation and is an alternative to other manoeuvres such as increasing PIP. A prolonged inflation time, however, will predispose to lung over-distension and gas trapping, as it is likely to reduce the expiratory time unless the rate is altered to account for the change.

Flow rate (C)

Although, a minimum ventilator flow rate of at least twice an infant's own mechanical ventilation should prove adequate, in practise a flow rate of between 4 to 10 l/min is used. If high respiratory rates or short inspiratory times are used, flow rates at the upper end of the range may be needed to ensure delivery of the intended volume. A high flow rate is more likely to produce a square waveform, which compared to a saw tooth waveform, will increase MAP and hence oxygenation. Some valveless ventilators, however, have a fixed flow rate of 5 L/minute and are able to maintain their volume delivery at fast rates and short inflation times (14).

The infant's respiratory activity (A)

Breathing out of phase with the ventilator inflation (sometimes called "fighting the ventilator" or "asynchrony") causes ineffective gas exchange and is a risk factor for pneumothorax (15) and intraventricular haemorrhage. To avoid such adverse outcomes, although routine muscle relaxants for all ventilated babies are not advisable (16), selective administration of neuromuscular blocking agents to infants who are fighting the ventilator reduces the incidence of pneumothorax (17). Infants, however, who receive neuromuscular blocking agents for prolonged periods become oedematous and more difficult to ventilate. As a consequence many clinicians prefer to use analgesics and/or sedatives to cause respiratory depression, as well as to minimise any discomfort infants may experience during respiratory support. There are, however, no controlled trials demonstrating that use of either analgesics or sedatives prevent pneumothoraces. Alternatively, to reduce asynchrony, either the ventilator rate can be increased to try and 'capture' the respiratory rate of the baby (1) or patient triggered ventilation (PTV) may be tried (see below).

Using conventional ventilation

- PIP sufficient to cause chest wall exclusion subsequently modified by blood gas analysis.
- PEEP of 3 cm H₂O, elevated in increments (C) to 8 cm H₂O if the infant has poor oxygenation (C).
- Initial rate 60 bpm (A), rate increased if the infant is asynchronous in an attempt to capture the infant's spontaneous respiratory rate (B).
- A physiological I:E ratio, with an inspiratory time of 0.3 to 0.5 seconds (B).
- Flow rate 5-6 l/min (C).

Patient-Triggered Ventilation (PTV)

During PTV, ventilator delivered breaths are initiated in response to a signal derived from the patient's inspiratory effort. A variety of triggering devices, including those which detect changes in airway impedance, pressure, flow or abdominal movement, have been used. Each has inherent advantages and disadvantages (18). Two PTV modes have been extensively investigated: synchronized intermittent positive pressure ventilation (SIPPV) or assist/control (A/C) and synchronized intermittent mandatory ventilation (SIMV). During SIPPV any number of positive pressure inflations can be triggered providing that the infant's inspiratory effort exceeds the critical trigger level, during SIMV only the preset number of inflations can be triggered regardless of the infant's respiratory rate. Physiological studies (18) demonstrated that SIPPV and SIMV compared to conventional ventilation generally reduced asynchrony, improved blood gases and lowered the work of breathing. Meta-analysis of the results of

randomised trials, however, has demonstrated no long-term advantages of SIPPV/SIMV when used during acute RDS (13). SIPPV/SIMV may be useful during the recovery stage of RDS, as randomised trials have demonstrated that, if employed then, SIPPV/SIMV was associated with a shorter duration of ventilation (13).

Indications for SIPPV/SIMV

- Infants who are asynchronous on conventional ventilation despite use of sedation/analgesics (B)
- Weaning (A). If SIMV is used, a minimum ventilator rate of 20bpm should be employed otherwise the infant's work of breathing due to the resistance of the endotracheal tube will be increased.

Alternative PTV modes

Pressure support ventilation (PSV): During PSV, the infant's inspiratory efforts trigger a positive pressure inflation at a preset level but, in addition, the end of spontaneous inspiration dictates termination of inflation. The infant's inspiratory flow is measured by the ventilator and inflation terminated when the inspiratory flow reduces to a certain proportion of the maximum inspiratory flow. Employment of PSV can reduce the asynchrony rate by reducing the inflation time, whether this is associated with a reduction in airleaks remains to be tested. During PSV, minute ventilation is maintained by a greater contribution from the infant, whether this is possible throughout an infant's ventilatory career requires testing before this ventilatory mode can be recommended as a primary method of respiratory support. Preliminary evidence suggests PSV with SIMV compared to SIMV alone may be a better method of weaning.

Volume guarantee (VG): During VG, the PIP is servo-controlled so that the volume preset by the clinician is delivered during triggered ventilation (SIPPV, SIMV, PSV). Increased patient effort results in less applied pressure and vice versa. Physiological short-term studies have demonstrated that adequate gas exchange can be achieved at lower peak pressures when VG is used during the acute and the recovery stage of RDS (19,20). Preliminary evidence suggests that the level of VG applied may influence its effectiveness.

Proportional assist ventilation (PAV): During PAV the applied pressure is servo-controlled on a continuous input from the patient, thus the infant controls the timing, frequency and magnitude of lung inflation (21). In addition, negative ventilator resistance and elastance can be applied to relieve the infant's resistive and elastic work of breathing respectively, this is termed "unloading". The degree of unloading can be determined by the clinician, but if excessive unloading is applied then oscillations and runaway ventilator pressures occur; studies then are required to determine accurate and easy to use methods of identifying the optimum levels of unloading. There are few data on PAV in prematurely born infants; results from a short-term crossover study suggest compared to SIPPV and conventional ventilation, gas exchange during PAV can be maintained at lower MAPs (22).

Indications for using the newer triggered modes

- In the absence of information from randomised trials with positive long-term outcomes, none of the newer modes of patient triggered ventilation can be recommended for routine use in preterm infants with RDS.

High frequency oscillation (HFO)

HFO differs from other forms of positive pressure support in that it has both an active expiratory as well as an active inspiratory phase. Frequencies usually in excess of 10Hz are used. HFO is usually delivered on a background of a constant MAP, but it can be added to either or both the inspiratory or expiratory components of conventional ventilation. There is no evidence from randomised trials to suggest that combined HFO and conventional ventilation offers any advantages over HFO alone, indeed by increasing transpulmonary pressure swings such combinations may be disadvantageous. HFO has been increasingly used for the management of RDS either as a “rescue” mode of ventilation for babies not responding to conventional ventilation or as a primary mode of ventilation. Use of a high volume strategy (see below) can improve oxygenation in infants with severe RDS (23). Evidence from observational studies suggests that if the oxygenation does not improve as the MAP is increased that is a predictor of poor outcome, affected infants being more likely to die or survive with handicap (23,24). There has only been one randomised trial comparing HFO to conventional ventilation in infants with severe respiratory failure. Use of HFO was associated with a significant reduction in the development of new airleaks, but an the rate of any ICH was increased (25). There have been a number of trials assessing whether “prophylactic” HFO ie starting the modality within 12 hours of birth will be associated with a lower incidence of CLD than conventional ventilation. Meta-analysis (26), of those trials, has highlighted that there is no clear evidence that HFOV, as compared to conventional ventilation, offers any advantages or disadvantages as an initial ventilation strategy for preterm infants with RDS.

Indications for HFO

- Infants whose respiratory failure has failed to respond to surfactant therapy and optimisation of conventional ventilation, thus their FiO_2 remains >0.60 and their $PIP > 30\text{cmH}_2\text{O}$. A short trial (2 hours) of a high volume strategy is recommended and if after increasing the MAP oxygenation has not improved, then consideration should be given to administering additional therapy or changing to an alternative form of respiratory support (B).
- Prophylactic HFO has not been shown to have advantages over conventional ventilation (A).

Use of HFO

Oscillator performance (B)

A variety of techniques have been used to generate HFO, the technique applied influences the airway pressure waveform (varying from asymmetrical and complex to sinusoidal) and the volume delivered. As frequency is increased, volume delivery tends to fall with all oscillators (27); this has implications for carbon dioxide elimination. Some oscillators have a fixed inspiratory: expiratory ratio and others only a fixed inspiratory time; one oscillator allows a variable inspiratory:expiratory ratio from 1:1 to 1:1 to 1:2.

Oxygenation (B)

During HFO, oxygenation is controlled by the inspired oxygen concentration and the mean airway pressure; MAP, as during conventional ventilation, determining lung volume. Two strategies have been pursued; a low MAP (low volume) strategy which

may necessitate a high inspired oxygen concentration to maintain oxygenation and a high MAP (high volume) strategy. The former strategy is used with the aim of reducing trauma to the lung and the latter to ensure lung recruitment and optimise lung volume. There have been no randomised comparisons of these two strategies in infants, but in animal models such comparisons demonstrated that the high volume strategy was associated with higher levels of oxygenation and less lung damage (28). In addition, only trials where a high volume strategy had been used have demonstrated that HFO compared to conventional ventilation might reduce BPD, but this is not a consistent finding. A high volume strategy is then recommended; the MAP should be increased in increments (2cmH₂O), whilst the infant's oxygenation is continuously monitored. After each change in MAP it might take between 10 to 20 minutes for the lung volume to equilibrate (29), it is, therefore, important not to increase to the next MAP level until the oxygenation has stabilised.

Amplitude (B)

Carbon dioxide elimination is affected by the frequency and the delivered volume (squared). The delivered volume is mainly influenced by the amplitude. When transferring an infant to HFO the amplitude should be increased until there are visible chest wall vibrations. The PaCO₂ level should be checked within 20 minutes of transfer to HFO to avoid the possibility of undetected hypocarbia and its undesirable consequences.

Frequency (B)

Volume delivery by commercially available oscillators falls as frequency is increased, but between 10 and 20 Hz any adverse effect this would cause on carbon dioxide elimination is offset by being closer to the resonant frequency of the respiratory

system. Thus, there are no clinical advantages with regard to carbon dioxide levels of oscillating and 10 or 15Hz, however, reducing the frequency below 10Hz increases the volume delivery (30) and can be a useful method of increasing carbon dioxide elimination in an infant with severe respiratory failure despite use of a high amplitude.

Inspiratory: expiratory ratio (B)

Inspiratory: expiratory ratios of 1:2 have been recommended, as there has been concern that, despite an active expiratory and inspiratory phase, there may be gas trapping at the very fast frequencies used during HFO. A study in infants with RDS, however, failed to reveal any evidence of gas-trapping when the ratio was changed from 1:1 to 1:2 (31) and in another physiological study, altering the I:E ratio from 1:2 to 1:1, increased the volume delivery and MAP with improvements in blood gases (32).

Nitric Oxide

Nitric oxide is a vasodilator substance, which relaxes vascular smooth muscle. When NO is inhaled, it diffuses across the alveolar capillary membrane and activates guanylate cyclase in the pulmonary arteriolar smooth muscle. The resulting increase in cGMP causes smooth muscle relaxation. NO then binds rapidly to haemoglobin and once bound is inactivated. Administration of NO to infants with RDS and pulmonary hypertension can improve oxygenation, but not all babies respond. A poor response, which occurs in infants with severe parenchymal disease, systemic hypotension, myocardial dysfunction or structural pulmonary abnormalities such as pulmonary hypoplasia or dysplasia, is predictive of a poor outcome. Only one of five randomized trials has demonstrated that inhaled NO has any significant long-term benefit for preterm babies (33). Current evidence might suggest that iNO may be

helpful with regard to long term outcome in preterm infants with mild rather than severe disease; whether prophylactic iNO will reduce BPD needs testing in an appropriately sized trial with long-term outcomes.

Indications for iNO

- The infant born at or near term with RDS with proven pulmonary hypertension (A)
- There is insufficient evidence to recommend routine use of INO in preterm infants and it should be administered within the context of a randomised controlled trial (A)

Use of NO

- Levels of up to 80 ppm have been used, but in term infants 5 ppm appears as effective as higher doses (34).
- NO has side-effects, it reacts rapidly with oxygen to form nitrogen dioxide, which is toxic to the lung. The nitrosylhaemoglobin produced by NO binding to haemoglobin is rapidly converted to methaemoglobin, which is then reduced by methaemoglobin reductase in erythrocytes. Immature infants and those of certain ethnic groups have low levels of methaemoglobin reductase. These problems are more likely if high concentrations of NO are used for prolonged periods in high inspired oxygen concentrations, emphasising the importance of using low doses of iNO.
- NO administration has been associated with an increased bleeding time.
- Other potential side-effects include surfactant dysfunction and mutagenicity.
- It is important to wean inhaled NO as soon as oxygenation has improved and the infant stabilized, otherwise tolerance may occur.

References

- 1 Robertson NJ, Hamilton PA, Moss AL. Nasal deformities resulting from flow driver continuous positive airway pressure. *Arch Dis Child Fetal Neonatal Ed.* 1996;73(3):F209-212.
- 2 Courtney SE, Pyon KH, Saslow JG, Arnold GK, Pandit PB, Habib R. Lung recruitment and breathing patten during variable versus continuous flow nasal CPAP in premature infants: an evaluation of 3 devices. *Pediatrics* 2001;107(2):304-8.
- 3 De Paoli AG, Davis PG, Faber B, Morley CJ. Devices and pressure sources for administration of nasal continuous positive airway pressure (NCPAP) in preterm neonates. *Cochrane Database Systemic Review* 2002;(4):CD002977
- 4 Avery ME, Tooley WH, Keller JB. Is chronic lung disease in low birthweight infants preventable? A survey of eight centres. *Pediatrics* 1987;79:26-30
- 5 Kamper J, Wulff K, Larsen C, Lindeqvist S. Early treatment with nasal continuous positive airways pressure in very low birthweight infants. *Acta Paediatrica* 1993;82:193-197
- 6 Thomas MA on behalf of the IFDAS Study Group. Early nasal continuous positive airways pressure (nCPAP) with prophylactic surfactant for neonates at risk for RDS. The IFDAS multi-centre randomised trial. *Archives of Disease in Childhood* 2002;86:A7
- 7 Davis PG, Henderson-Smart DJ. Nasal continuous positive airways pressure immediately after extubation for preventing morbidity in preterm infants. *Cochrane Database System Review* 2003;(2): CD000143.

- 8 Miller MJ, DiFiore JM, Strohl KP, Martin RJ. Effects of nasal CPAP on supraglottic and total pulmonary resistance in preterm infants. *J Appl Physiol* 1990;68(1):141-6
- 9 Greenough A, Chan V, Hird MF. Positive end expiratory pressure in acute and chronic respiratory distress. *Arch Dis Child* 1992;67:320-323.
- 10 Piotrowski A, Sobala W, Kawczynski P. Patient-initiated, pressure-regulated, volume-controlled ventilation compared with intermittent mandatory ventilation in neonates: a prospective, randomised study. *Intensive Care Medicine* 1997;23:975-981
- 11 Sinha SK, Donn SM, Gavey J, McCarty M. Randomised trial of volume controlled versus time cycled, pressure limited ventilation in preterm infants with respiratory distress syndrome. *Archives of Disease in Childhood* 1997;77:F202-F205
- 12 Greenough A, Morley CJ. Fighting the ventilator – are fast rates an alternative to paralysis. *Early Hum Dev* 1986;13:189-194
- 13 Greenough A, Milner AD, Dimitriou G. Synchronised mechanical ventilation for respiratory support in newborn infants. In: *Cochrane Library*, Issue 2, 2004.
- 14 Dimitriou G, Greenough A. Performance of neonatal ventilators. *British Journal of Intensive Care* 2000;10:186-188
- 15 Greenough A, Morley CJ. Intraoesophageal pressure monitoring and the severity of the respiratory distress syndrome. *J Pediatr* 1983;140: 71-73
- 16 Shaw NJ, Cooke RWI. Randomised trial of routine versus selective paralysis during ventilation for RDS. *Arch Dis Child* 1993;69:479-482.

- 17 Greenough A, Wood S, Morley CJ, Davis JA. Pancuronium prevents pneumothoraces in ventilated premature babies who actively expire against positive pressure inflation. *Lancet* 1984;1:1-3
- 18 Greenough A. Update on patient-triggered ventilation. *Clin Perinatol* 2001;28(3):533-546.
- 19 Cheema IU, Ahluwalia JS. Feasibility of tidal volume-guided ventilation in newborn infants: A randomised, crossover trial using the volume guarantee modality. *Pediatrics* 2001;107(6):1323-1328
- 20 Herrera CM, Gerhardt T, Claire N, Everett R, Musante G, Thomas C, Bancalari E. Effects of volume-guaranteed synchronized intermittent mandatory ventilation in preterm infants recovering from respiratory failure. *Pediatrics* 2002;110(3):529-533
- 21 Schulze A, Bancalari E. Proportional assist ventilation in infants. *Clinics in Perinatology* 2001;28:561-578
- 22 Schulze A, Gerhardt T, Musante G, Schaller P, Claire N, Everett R, Gomez-Marin O, Bancalari E. Proportional assist ventilation in low birth weight infants with acute respiratory disease. A comparison to assist/control and conventional mechanical ventilation. *Journal of Pediatrics* 1999;135:339-344
- 23 Chan V, Greenough A, Gamsu HR. High frequency oscillation for preterm infants with severe respiratory failure. *Archives of Disease in Childhood* 1994;70:F44-F46
- 24 Cheung PY, Prasertsom W, Finer NN, Robertson CMT. Rescue high frequency oscillatory ventilation for preterm infants: neurodevelopmental outcome and its prediction. *Biology of the Neonate* 1997;71:282-291

- 25 HIFO Study Group. Randomised study of high-frequency oscillatory ventilation in infants with severe respiratory distress. *Journal of Pediatrics* 1993;122:609-619
- 26 Henderson-Smart DJ, Bhuta T, Cools F, Offringa M. Elective HFO ventilation vs conventional ventilation in preterm infants with acute pulmonary dysfunction. *Cochrane issue 2*, 2004.
- 27 Laubscher B, Greenough A, Costeloe K. Performance of four neonatal high frequency oscillators. *British Journal of Intensive Care* 1996;6:148-152
- 28 McCulloch PR, Fokert PG, Froese AB. Lung volume maintenance prevents lung injury during high frequency oscillatory ventilation in surfactant deficient rabbits. *American Review of Respiratory Disease* 1988;137:1185-1192
- 29 Thome U, Toepfer A, Schaller P, Pohlandt F. Effect of mean airway pressure on lung volume during high frequency oscillatory ventilation of preterm infants. *American Journal of Respiratory and Critical Care Medicine* 1998;157:1213-1218
- 30 Laubscher B, Greenough A, Costeloe K. Performance of four neonatal high frequency oscillators. *British Journal of Intensive Care* 1996;6:148-152.
- 31 Alexander J, Blowes R, Ingram D, Milner AD. Determination of the resonant frequency of the respiratory system during high frequency oscillatory ventilation. *Early Human Development* 1993;35:234

- 32 Dimitriou G, Greenough A, Kavvadia V, Milner AD. Comparison of two inspiratory:expiratory ratios during high frequency oscillation. *European Journal of Pediatrics* 1999;158:796-799
- 33 Schreiber MD, Gin-Mestan K, Marks JD, Huo D, Lee G, Srisuparp P. Inhaled nitric oxide in premature infants with the respiratory distress syndrome. *New England Journal of Medicine* 2003;349:2099-2107
- 34 Davidson D, Barefield ES, Kattwinkel J, Dudell G, Damask M, Straube R, Rhines J, Chang CT. Inhaled nitric oxide for the early treatment of persistent pulmonary hypertension of the term newborn: a randomized, double-masked, placebo-controlled, dose-response, multicenter study. *Pediatrics* 1998;101:325-334