INTRODUCTION

Preterm birth continues to be one of the major challenges in perinatal medicine. The prematurity and its associated complications are not only associated with high morbidity and mortality but also lead to a great burden on the health care system due to prolonged stay of these preterm neonates in NICU [(1)].

The incidence of preterm birth is rising despite years of research in the cause, epidemiology and prevention of preterm labor. According to the WHO the rate of preterm births worldwide is over 9.5 % of all births. In USA, the rate is between 12-13% while in Europe and other developed countries; the rate is between 5% and 9%[(2)].

Many developing countries have reported rates between 12-20%. However in developing countries accurate and complete population data and medical records usually do not exist, Furthermore, a range of factors influences the estimation of the rate of preterm birth in developing countries. These factors include varying scoring systems used to determine gestational age, national differences in birth registration processes, heterogeneous definitions used for preterm birth and differences in perceptions of the viability of preterm infants. These issues make measurement of preterm birth and comparisons across and among developing countries difficult. Unfortunately, multiple factors related to the circumstances of these countries have been identified and linked to a higher risk of a preterm birth as low socio-economic standard, bad hygienic habits, poor antenatal care, as well as extreme of ages [(1-6)].

Complications of preterm birth are the single direct cause of neonatal deaths, responsible for 35% of the world's 3.1 million deaths a year, and the second most common cause of under-5 deaths after pneumonia. In almost all high and middle-income countries of the world, preterm birth is the leading cause of child death. Being born preterm also increases a baby's risk of dying due to other causes, especially from neonatal infections, with preterm birth estimated to be a risk factor in at least 50% of all neonatal deaths.[(1-6)]

For preterm birth, International Classification of Disease (ICD) encourages the inclusion of all live births. This definition has no lower boundary, which complicates the comparison of reported rates both between countries and within countries over time since perceptions of viability of extremely preterm babies change with increasingly sophisticated neonatal intensive care. In many high and middle-income countries, the official definitions of live birth or stillbirth have changed over time. [(1-6)]

Preterm birth is a syndrome with variety of causes which can be classified into 2 broad subtypes *spontaneous preterm birth* (spontaneous onset of labor or prelabor premature rupture of membrane) and *provider initiated preterm birth* (defined as induction of labor or elective caesarean section before 37 completed weeks of gestation for maternal or fetal indications or other non- medical reasons. [(1-6)]

Risk factors for spontaneous preterm birth includes adolescent pregnancy, advanced maternal age, short inter-pregnancy interval, multiple gestation, urinary tract infections, symptomatic or asymptomatic chorioamniotis, congenital infections (TORCH), cervical incompetence, intrauterine growth retardation, family history, under nutrition, smoking, excess alcohol consumption, excess physical work...etc. While indications for provider initiated preterm birth includes prior caesarean section, preeclampsia, eclampsia, placenta accreta and fetal distress…etc. [1-6]

Four different pathways have been identified that can result in preterm birth and have considerable evidence: precocious fetal endocrine activation, uterine over distension, premature decidual activation, and intrauterine inflammation/infection. Activation of one or more of these pathways may occur gradually over weeks, even months. One of the recent causes implicated in preterm birth is the assisted reproductive technology, which has contributed to an increase in multiple gestations. [1-6]

Although marked improvement in perinatal care has been achieved, prematurity is still the number one cause of infant mortality accounting for 24-35% of all neonatal deaths.[1-6]

As regard preterm morbidity, a major proportion of this population is at higher risk of early complications, including respiratory distress, intraventricular hemorrhage, necrotizing entercolitis, sepsis and late complications including, chronic lung disease (CLD), retinopathy of prematurity, cerebral palsy, developmental delay, deafness and learning disabilities [6].

Respiratory distress (RD) is a leading cause of morbidity and mortality in preterms and remains a major problem for clinicians and researchers in neonatology.it accounts for nearly half of all neonatal deaths. [7]

Admission policy and definition of RD were introduced in the early seventies in routine care in neonatology and are still in use today without modification. RD differs from the more restrictive terms 'respiratory distress syndrome' and 'hyaline membrane disease' which are related to surfactant deficiency due to lung immaturity and which require specific X-ray changes. Respiratory distress is defined by the Swiss Society of Neonatology as a clinical picture based on five symptoms and signs (tachypnea >60/min, central cyanosis in room air, nasal flaring, retractions and expiratory grunting). This definition is entirely based on clinical observation irrespective of the etiology of RD and is used on all neonatal units since 1972. In Switzerland, The number of infants hospitalized with RD increased from 1.9% in 1974 to 3.8% in 2004 of all liveborn infants and from 29.7% in 1974 to 52.8% to of all admitted infants. [8]

To study the development and pathogenesis of respiratory distress in preterm infants, normal development of the lung and the consequences of its disruption with preterm birth should be in concern. Typically lung development has been divided into five stages: embryonic, pseudoglandular, canalicular, saccular, and finally the alveolar stage. However, more recently the alveolar stage has been split in two stages and the sixth stage has been defined as the period of microvascular maturation. [9,10]

Human lung development is initiated during the early embryonic period of gestation (0-6 weeks of gestation) as a small ventral bud of the foregut called the respiratory

diverticulum. During the subsequent pseudoglandular stage of lung development (6-16 weeks of gestation), formation of the conducting airways, i.e., the tracheobronchial tree occurs by elongation and repetitive branching of the primitive bronchial tubules. Vascular development is complete by the end of this stage. Vascularization of the surrounding mesenchyme with formation of the alveolar-capillary membrane occurs during the canalicular stage of lung development (16-24 weeks of gestation). The beginning of the saccular period (24-36 weeks of gestation) represents the current limit of viability for premature birth. At the beginning of this period the airways end in clusters of thin-walled terminal saccules. These saccules produce, by term, the last generations of airways, alveolar ducts and at the periphery the alveolar sacs. [9,10]

True alveoli can be seen as early as 32 weeks however are generally more recognizable at 36 weeks. Alveolar number increases from about 32 weeks' gestation, and the term human lung contains between about 50 and 150 million alveoli. For comparison, the adult human lung has about 500 million alveoli. The most rapid rate of accumulation of alveoli occurs between 32 weeks' gestational age and the first months after term delivery. The potential lung gas volume and surface area increases from about 25 weeks' gestation to term. This increase in lung volume, and the surface area of saccules establishes the anatomic potential for gas exchange and thus for fetal viability. While the initial part of alveolarization in human development occurs in utero, late lung development consisting of alveolarization and microvascular maturation occurs predominantly after parturition in an air-breathing environment. [9,10]

A number of factors that can interfere with alveolarization have been identified. Mechanical ventilation of the lung in saccular phase, repeated course of antenatal glucocorticoid, overexpression of proinflammatory mediators in the pulmonary epithelium, postnatal steroid, hyperoxia and poor nutrition can interfere with alveolarization. Because lung growth following the completion of alveolarization is by increase in airway and alveolar size, any event that decreases alveolar number could impact lung function as the individual ages. [11-12]

In the last 30 years several improvements in preterm newborn ventilation along with wide spread use of antenatal steroids and exogenous surfactant have been introduced aiming at reducing the incidence and severity of RD as well as the mortality caused by RD.[8]

Mechanical ventilation (MV) remains an essential tool in NICUs, especially in extremely low gestational age infants (ELGANTs). In a large cohort analysis of extremely preterm infants, 89% were mechanically ventilated during the first day after birth, and nearly 95% of survivors were ventilated at some point during their hospital stay. The Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) trial found that 83% of infants assigned to noninvasive support required intubation at some point during their hospitalization. [13]

The introduction of modern mechanical ventilation for neonatal respiratory failure as a rescue therapy in the 1960s was subsequently extended to premature infants with RD and resulted along with other interventions in a dramatic increase in survival of critically ill preterm newborns. However, this was accompanied by the appearance of complications as Bronchopulmonary dysplasia (BPD), air leaks, ventilator associated pneumonia, intraventricular hemorrhage and periventricular leukomalacia.

BPD is a chronic pulmonary disorder that is the consequence of abnormally repaired lung damage. Despite great advances in neonatal care in general and respiratory care in particular BPD still affects 20 to 40% of survivors and remains a major cause of morbidity and mortality in preterm infant. [14-15] The affected infants have both short and long-term clinical issues, including very complicated initial neonatal intensive care course, prolonged hospital stay, increased financial cost, poor growth, neurodevelopmental handicaps, and repeated hospitalizations in the first years of life. Furthermore, infants with severe BPD have a higher risk of mortality than unaffected infants or those with mild disease. Death usually is caused by respiratory failure, unremitting pulmonary hypertension with cor pulmonale, and/or sepsis. [16-17]

Mechanical ventilation is the main cause of the development of BPD. Animal and clinical data indicate that lung injury is affected, in large part, by the ventilatory strategies used. [18] Lower incidence of BPD has been associated with less frequent use of mechanical ventilation. [19]

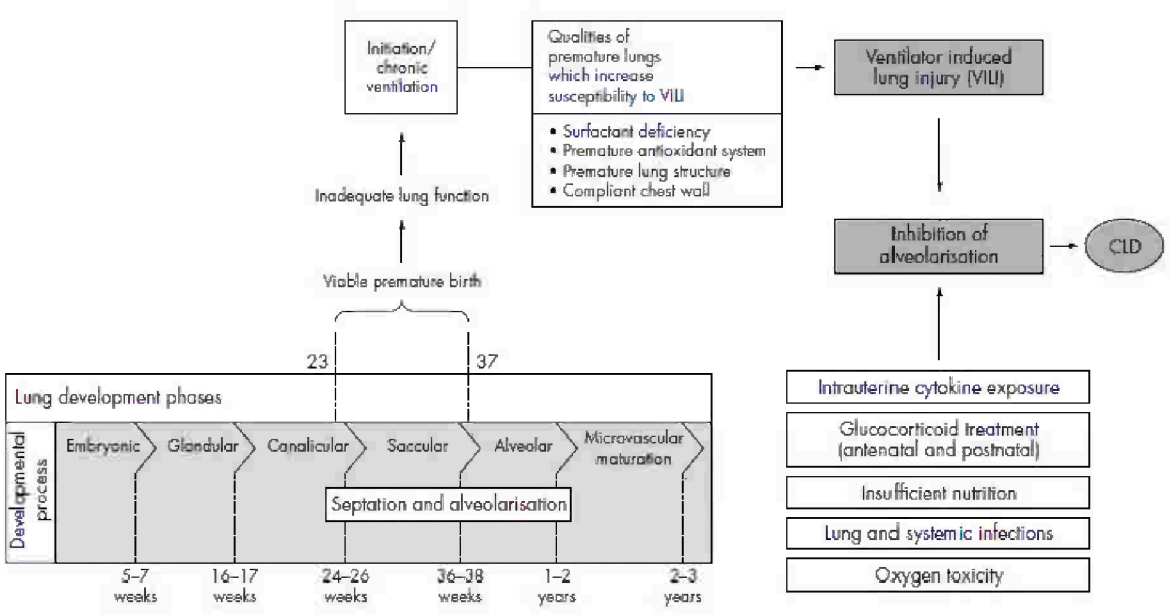

Figure (1): The pulmonary injury sequence. The diagram illustrates the effect of ventilator-induced injury and other factors on lung development and their relation to chronic lung disease (CLD). Reproduced from Attar MA, Donn SM. Mechanism of ventilator-induced lung injury in premature infants. Semin Neonatol 2002;7:353–60, with permission from Elsevier.

Bronchopulmonary dysplasia (BPD) is directly correlated with the occurrence of ventilator induced lung injury (VILI) in preterm infants. Premature infants are most vulnerable to VILI in the period immediately following birth because their lungs are partially filled with fetal lung fluid, they are not uniformly ventilated, and their surfactant content is often deficient. Illustration of the pulmonary injury sequence in preterm infants can be seen in figure (1)[20-22]

The known direct mechanisms of VILI are barotrauma, volutrauma, atelectotrauma, and more recently, biotrauma. Barotrauma occurs when high pressures are used in ventilation, thus increasing the risk of air leak syndromes, such as interstitial emphysema, pneumothorax, and pneumomediastinum, which in turn activate the inflammatory cascade. In PLV, the volume of gas supplied to the lungs is not controlled. Volutrauma alludes to inadequate lung inflation caused by localized or generalized hyper-expansion of the lung parenchyma. Lungs are injured when they are inflated to a volume larger than the total lung capacity because of the structural damage caused by stretching, the migration of leukocytes to the lungs, the increase in capillary permeability in the lungs, and interstitial and alveolar edema. However, volutrauma might also occur with lower tidal volumes (V_T) that over distend the ventilated portions of a partially collapsed lung. An overdistension-induced injury promotes the production of lung cytokines, including IL-6 and IL-8. In newborn infants, an overdistension-induced injury may appear after just a few inflations with high V_T and after periods as short as 30 minutes, which indicates the importance of performing resuscitation in the delivery room with appropriate positive end-expiratory pressure (PEEP). [20-22]

Atelectotrauma results from regionally or totally reduced lung parenchyma expansion. Pulmonary injury is associated with alveolar instability as shown in figure (2). The successive collapsing and reopening of the alveolar walls cause the lysis of the structural elements that compose the lung interstitium, triggering local and systemic inflammation. Biotrauma results from the release of inflammatory mediators secondary to injuries caused by volutrauma or atelectotrauma, magnifying the initial mechanical injury and also causing damage in distant organs. The presence of a lung injury increases the number of inflammatory cells and mediators in systemic circulation and also favors bacterial translocation and the release of endotoxins into the air space, which aggravates lung inflammation.

Therefore, MV promotes inflammation and direct damage to the lungs in premature infants. For that reason, strategies for preventing ventilator-induced injuries are needed. Clinical investigation has not yet defined the best way to avoid lung injury in preterm infants requiring mechanical ventilation. The reality is that some CLD may be inevitable in those infants delivered at a time when the lung is still in the saccular phase of development. [20-22]

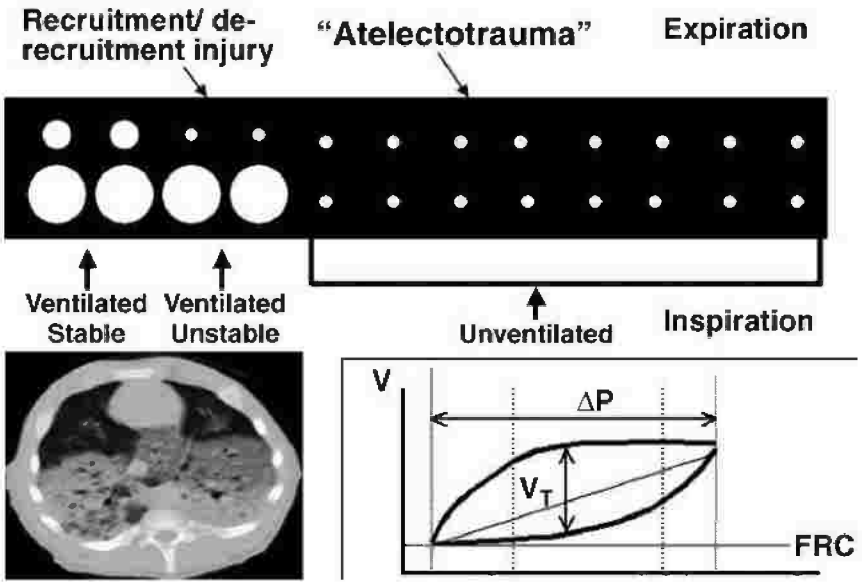

Figure (2): Non-homogeneous aeration in RDS. Extensive atelectasis is often present in surfactant deficient lungs as illustrated on the Computer Tomography view in lower left corner (courtesy of Anastasia Pellicano, MD). This situation is schematically represented in the middle panel. The corresponding pressure–volume loop is shown in the lower right portion of the figure. In the absence of extrapulmonary right-to-left shunting, poor oxygenation strongly suggests that atelectasis is present. If this situation is allowed to persist, a normal, physiologic tidal volume entering only the small proportion of open alveoli will inevitably lead to over-expansion and lung damage.

Ventilator associated pneumonia (VAP) is defined as nosocomial pneumonia in mechanically ventilated patients that develops more than 48 hours after initiation of mechanical ventilation. [23] VAP accounts for up to 30% of nosocomial infections in NICU patients and complicates the course of 8 to 28% of patients receiving mechanical ventilation. The incidence of VAP in developed countries oscillates between 2.7 and 10.9 episodes per 1000 ventilator days while in developing countries it may reach up to 37.2 cases per 1000 ventilator days. US reported the incidence of VAP at 28.3% or 6.5 cases/1000 days of mechanical ventilation in preterm neonates with gestational ages < 28 weeks. A report from Thailand has quoted the incidence of VAP at 50% (70.3 cases/1000 days on the ventilator). Figures from other countries are as follows: China (20.1%), India (30.6%), and Egypt (57.1%)[23-24]

VAP arises from aspiration of secretions, colonization of the aero- digestive tract, low nursing to patient ratio, or medications. Risk factors for VAP include prematurity, very low birth weight, severe underlying disease, prolonged duration of mechanical ventilation, use of wide spectrum antibiotics, prolonged hospital stay, inadequate pulmonary toilet, and extensive use of invasive devices and procedures [24]

Air leak syndrome includes pulmonary interstitial emphysema, pneumothorax, pneumomediastinum, pneumopericardium, pneumoperitoneum, subcutaneous emphysema, and systemic air embolism. All the clinical variations of air leak syndromes originate in overdistended alveoli, which ultimately rupture. Overdistension may follow initial

spontaneous vigorous respirations (usually larger term babies) at birth, high pressure with mechanical ventilation (either PEEP or peak inspiratory pressure), vigorous ventilatory resuscitation, and air trapping in the presence of a ball valve mechanism. Although most of the syndromes have long been known to occur spontaneously, their incidence increased as the use of ventilatory support became widespread, particularly since the advent of PEEP Ventilation. The occurrence of air leaks has diminished considerably since the advent of surfactant treatment, and the use of less intense pressure settings for ventilator support. Besides BPD, air leak syndromes are the most frequent life-threatening complications of ventilatory assistance. [25]

There is an intimate relationship between cardiorespiratory disease and an increased risk for brain injury in the premature infant. The mechanisms leading to this association include vulnerable capillary beds, the immature differentiating oligodendrocyte, perturbations in cerebral blood flow (CBF), and a pressure-passive cerebral circulation. Multiple factors including pneumothorax and PDA, physiologic variables such as acid-base disturbances in the form of extremes of PaCo2, ventilatory support and commonly used respiratory medications, in combination or singularly may increase the risk for brain injury. Thus in the management of a sick newborn infant with respiratory distress, the potential risk/benefit ratio of any intervention as it relates to hemorrhagic ischemic injury should be considered in each case to minimize such injury and thus improve long-term neurodevelopmental outcome. [26]

Mechanical ventilation can directly or indirectly affect CBF via modulating cardiac output by impeding venous return or via changes in the acid-base balance. Impedance of venous return may result from elevated mean airway pressure, which can result in increased central venous pressure and, therefore, increased intracranial venous pressure. It can also decrease cardiac output. This puts the premature brain at risk of hypoperfusion, especially in the vulnerable regions such as the periven- tricular white matter. [26]

Prolonged exposure to these fluctuations of cerebral blood flow with prolonged mechanical ventilation presumably results in repeated insults throughout the course of intensive care. [26]

Moreover mechanical ventilation can result in hypocapnic and hypercapnic episodes, Hypocapnia is a risk factor for potential damage to the central nervous system, such as periventricular leukomalacia, intraventricular hemorrhage, cerebral palsy, cognition developmental disorder, and auditory deficit. Permissive hypercapnia can improve lung injury caused by diseases of the respiratory system, lessen mechanical ventilation-associated lung injury, reduce the incidence of bronchopulmonary dysplasia and protect against ventilation-induced brain injury, However severe hypercapnia can induce intracranial hemorrhage and even consciousness alterations. [27]

And so many ventilatory strategies have been established in aim of decreasing these complications starting from the neonatal resuscitation including early CPAP even in the delivery room, positive pressure ventilation using pressure limiting or monitoring devices, use of pulse oximetry to guide use of Oxygen therapy, use of surfactant replacement therapy, patient triggered ventilation…. etc.

Lung protective ventilation strategies:

Resuscitation in the delivery room (DR):

Once a preterm infant with immature lungs is born, some form of assisted ventilation with supplemental oxygen is usually required to sustain life. The goal in providing ventilatory assistance to a preterm infant at risk of BPD is to deliver these life-saving measures, but without lung injury from high airway pressures, high tidal volumes and high FiO2. One approach to this dilemma has been the early initiation of nasal CPAP in the delivery room. In fact, Wung and colleagues have used nasal CPAP as a primary ventilatory strategy and have reported a low incidence of BPD relative to comparable neonatal centers [28,29].

There is good evidence that 100% oxygen is harmful to most neonates and potentially more so in extremely preterm infants. [30] Recently there is increased evidence for the beneficial effects of low inspired oxygen concentration in resuscitation of preterm infants. Pulse oximetry at resuscitation gives a continuous, non-invasive measure of both oxygen saturation and heart rate. It may help to wean inspired oxygen and prevent hyperoxic peaks. [31,32] If positive pressure breaths are required during resuscitation, either by mask or endotracheal tube, peak inspiratory pressure limiting or monitoring devices e.g. Neopuff should be used to help avoid excessive tidal volumes. [33] Another recent approach during resuscitation of preterm infants is the use of sustained inflation instead of repeated manual inflations (PIP of 25 cmH20 for 15 sec.) for recruiting the alveolar spaces in order to help the clearance of the fetal lung fluid and facilitate the formation of the functional residual capacity (FRC). Moreover the premature infants whose clinical condition requires emergency intubation in the DR, it is a good practice to administer exogenous surfactant as early as possible. [33] The advantage of giving surfactant early is to help establishing of FRC before the occurrence of lung damage.

Pragmatically, there is now increasing emphasis on minimizing ventilation-induced lung injury (VILI) and its consequence, in the delivery room.

Early nasal CPAP;

Use of CPAP in neonates during the 1970s was welcomed with enthusiasm as the "missing link" between supplemental oxygen and mechanical ventilation to treat RDS. [34] CPAP is positive pressure applied to the airways of a spontaneously breathing baby throughout the respiratory cycle. CPAP support has re-emerged as a potentially 'gentler' and less invasive modality to stabilize preterm neonates in the delivery room. This is reflected in several surveys of centers showing that a practice of early CPAP is linked to a favorable outcome. [34-37]

During the immediate postnatal period the preterm, surfactant-deficient lung is highly susceptible to tissue injury and an exaggerated, unchecked inflammatory reaction can be triggered with the first manual breaths during resuscitation [38-42].

Starting CPAP immediately after birth in spontaneously breathing extremely preterm infants is crucial because the non-compliant lung will otherwise collapse and positive pressure is more likely to be required to open the lung with the subsequent risk of injuring the lung.

This modality appears to be beneficial for infants born with hemodynamic stability but who are slow to establish FRC and effective spontaneous respiration. The data from animal studies suggest that providing positive end-expiratory pressure (PEEP) during resuscitation reduces the alveolar-arterial oxygen gradient proportional to the level of PEEP applied, lowers indicators of acute lung injury, improves alveolar surfactant pool size, and improves oxygenation and ventilation/perfusion matching. [43,44]

CPAP reduces the likelihood of upper airway collapse and decreases upper airway resistance by mechanically splinting it open. It increases the pharyngeal cross-sectional area. CPAP also alters the shape of the diaphragm, increases its activity and improves lung compliance. CPAP also seems to conserve surfactant on the alveolar surface, and therefore may have a synergistic effect. Early application of CPAP in preterm infants at risk for or with respiratory distress syndrome reduces the risk of developing CLD, because it prevents atelectasis and decreases the need and duration of mechanical ventilation. The avoidance of endotracheal intubation should decrease the likelihood of damage to the tracheal mucosa, altered mucociliary function, and increased risk of infection [45].

Although adequate levels of CPAP may be useful in decreasing pulmonary edema or left-to-right cardiac shunting, high levels of CPAP can increases intrathoracic pressure, which may further decrease venous return to the heart leading to reduction in cardiac output, reduced pulmonary perfusion, and enhanced ventilation-perfusion mismatch, resulting in a lower PaO2.Excessive PEEP may ultimately lead to serious consequences, such as air leak syndromes, increased dead space ventilation and Alveolar Overdistension which cause the CO2 retention. [46] Renal adverse effects of CPAP in preterm infants are notable at higher levels of pressure. These effects on the kidney may be due to decreased cardiac output. [47,48] In addition, CPAP and PEEP are known to increase intracranial pressure. [49]

Despite its widespread use, a number of problems still persist. Nasal prongs rarely fit tightly into the nostrils, thus resulting in gas leak and inability to maintain a baseline pressure. Selection of appropriate size prongs, constant nursing vigilance, and attention to correct positioning are necessary to prevent nasal injury during NCPAP.

There is no universally accepted definition of CPAP failure however, the following failure criteria were set for infants randomized to NCPAP in the COIN trial: FiO2>0.6 or pH<7.25 with a pCO2>60 mmHg or more than 1 apneic episode per hour requiring stimulation [50-51]. Infants who required intubation secondary to failure of CPAP had lower gestational ages and lower Apgar scores. Successful use of CPAP in the delivery room increases with staff experience. Combination of a sustained inflation and early CPAP may be an effective and potentially less injurious way of recruiting the lung in preterm neonates at birth. Indeed, very low birth weight (VLBW) newborns, whose mothers were not antenatally supplemented with glucocorticoids, are at the highest risk of early intubation in the delivery room and prolonged mechanical ventilation.

Surfactant replacement therapy

Surfactant therapy for RDS is standard of care for preterm infants, based on numerous randomized controlled trials and epidemiologic data demonstrating decreased mortality following its introduction in treatment of RDS [52-54].

In 1929 Kurt von Neergaard performed experiments suggesting the presence of pulmonary surfactant and its relevance to the newborn's first breath. About 30 years later Mary Ellen Avery and Jere Mead published convincing evidence that preterm neonates dying of respiratory failure had a deficiency of pulmonary surfactant (hyaline membrane disease). The first trials of nebulized synthetic (protein-free) surfactant to prevent RDS were published soon after Patrick Bouvier Kennedy (son of President John F Kennedy) died of this disorder after treatment in Boston. These trials were unsuccessful; however, Goran Enhorning and Bengt Robertson in the early 1970s demonstrated that natural surfactants (containing proteins) were effective in an immature rabbit model of RDS. During the 1980s there were numerous randomized controlled trials of many different natural and synthetic surfactants, demonstrating reductions in pulmonary air leaks and neonatal mortality

Surfactant is lung recruitment tool that, when used early, decreases lung injury. Oxygenation improves in most infants within minutes of surfactant administration. This response is associated with an increase in lung inflation, improved ventilation-perfusion matching, and a decrease in intrapulmonary shunting. Surfactant helps stabilize recruited lung volume and prevents atelectasis.

Pulmonary surfactant is primarily composed of phospholipids (85%) and proteins (10%). Surfactant proteins especially the low molecular weight SP-B and SP-C, are essential for structural organization and functional durability of surfactants. They both promote the rapid dispersion of phospholipids at the air–liquid interface and account for the sustained low surface tension activity after dynamic compression. [55-57]

The surfactant phospholipids are produced by alveolar type II cells. The production of surfactant phospholipids by alveolar type II cells is stimulated by antenatal steroids via the fibroblast-pneumocyte factor. The fibroblast pneumocyte factor stimulate the formation of citdyltransferase directly in the type II cell which is the rate limiting enzyme in the formation of lethicin. Moreover antenatal steroids enhance the expression of surfactant-associated proteins, reduce microvascular permeability, and accelerate overall structural maturation of the lungs. [55-57]

Surfactant synthesis can be compromised by cold stress, hypovolemia, hypoxemia, and acidosis. Other unfavorable factors, such as exposure to high-inspired oxygen concentration and the effects of volutrauma from assisted ventilation, can trigger the release of proinflammatory cytokine resulting in reduced surfactant synthesis and function. The leakage of proteins such as fibrin in the intra-alveolar space further aggravates surfactant deficiency by promoting surfactant inactivation. Finally, intrauterine inflammation may disrupt lung development or endogenous surfactant metabolism. The net effect is decreased surfactant function for a given amount of surfactant and so the need for intubation and exogenous surfactant administration. [55-57]

Combining a noninvasive ventilation approach with a strategy for surfactant administration is important, but questions remain about the optimal timing, mode of delivery and the value of predictive tests for surfactant deficiency. Timing of surfactant treatment is defined as prophylactic when administered in the DR, usually within 15 min from birth. The term rescue administration is used to describe later, selective surfactant treatment to infants with progressive signs of RD. [58-59]

All regimens of surfactant therapy appear to decrease the incidence of air leaks and improve oxygenation of ventilated preterm infants. Early selective surfactant administration (within 2 hours after birth) given to infants with RDS requiring assisted ventilation leads to decreased risk of pneumothorax and pulmonary interstitial emphysema and a decreased risk of neonatal mortality and chronic lung disease compared with delaying treatment until RDS is well established [58-59]. However, it is unclear whether a preventive dose administered endotracheally in the delivery room (prophylactic) has any advantage over treatment given after the patient has been resuscitated and stabilized (early treatment)[60]. Prophylactic surfactant has been recommended only for infants of less than 27–28 weeks of gestation especially if no antenatal steroids were given to the mother. For infants of >28 weeks of gestation, early CPAP is recommended with surfactant given as early rescue treatment. If intubation at birth is needed for resuscitation, surfactant should be given at that time [61-62].

To date, surfactant needs to be administered as a tracheal instillation to be effective. The Scandinavian model, the so-called INSURE (Intubation SURfactant Extubation) procedure, has now been used for almost two decades and has proven to reduce the need for MV. [63,64]

NICU management

Physiologic principles of neonatal ventilation

Neonatal ventilation aims at maintaining adequate oxygenation and controlling the PaCO2.Achievement of adequate oxygenation does not require gas to move regularly in and out of the lungs and so does not need rhythmic ventilation. [65]

Three factors control oxygenation:

1. Oxygenation is proportional to the exposed alveolar surface area. If the lung volume is abnormally low, oxygenation will also be low. Improving lung volume improves oxygenation. Applying a positive pressure to the lungs by altering the mean airway pressure (MAP) if the infant is ventilated, or continuous positive airway pressure (CPAP) if the infant is spontaneously breathing, is an important way to improve oxygenation.
2. Increase the inspired oxygen concentration (FiO2).
3. Increase blood flowing through the lungs, particularly to the aerated areas. This flow can be improved by ensuring a reasonable blood pressure or by using pulmonary arterial dilating agents such as nitric oxide. Therefore, oxygenation is improved by ensuring adequate lung aeration. It does not need gas to move in and out and is unrelated to the tidal volume.

To control PaCO2, gas-containing CO2 has to move out of the lungs. Mechanical ventilation is primarily about controlling PaCO2. Assuming there is sufficient blood passing the aerated alveoli and the dead space is not too large, the 2 functions that control the PaCO2 are the tidal volume and the rate of breathing or ventilation. The tidal volume is the volume of gas that moves in and out of the lungs with each respiratory cycle. [65]

Therefore, the primary function of mechanical ventilation is to control the PaCO2 by controlling the tidal volume and ventilator rate. It seems logical to control the PaCO2 by directly controlling the tidal volume rather than the PIP. [65]

Non-invasive respiratory support (NRS);

Noninvasive respiratory support (NRS) is becoming increasingly more popular as a method of respiratory support in sick newborn infants. NRS refers to respiratory support provided without use of an endotracheal tube. Noninvasive ventilation spans the range from flow-only devices to CPAP with a variety of synchronized or non-synchronized ventilation modes. In the future, augmented frequency CPAP (nasal high frequency ventilation) may substitute for mechanical ventilation. [66-67]

High-flow nasal cannula therapy

High-flow nasal cannula therapy typically denotes flow rates greater than 1 L/min. Recent studies have used heated, humidified, high-flow nasal cannula (HHHFNC) with flow rates greater than 2 L/min in preterm infants. HHHFNC is beneficial over low-flow nasal cannula: as it results in (1) washout of nasopharyngeal dead space leads to improved CO2 clearance and increased FiO2 in alveolar regions of the lungs; (2) reduction in inspiratory resistance;(3) improved lung compliance with warmed and humidified gas;(4) decreased metabolic cost of gas conditioning; and (5) provision of distending pressure. Commercially available HHHFNC products and those made locally typically include an oxygen blender, a gas heater and humidification unit, and a pressure pop-off valve. Similar to NCPAP, HHHFNC has been used in preterm infants as an initial mode of respiratory support, to reduce apnea events, or to help in weaning from mechanical ventilation. HHHFNC has grown in popularity, especially in units not comfortable with performing CPAP. The CPAP devices deliver pressure more reliably, but are more difficult to maintain in position on the infant than HHHFNC. [67]

Bi-Level CPAP

Bi-level CPAP, known by different acronyms such as SiPAP™ or biphasic CPAP or nasal BIPAP, is another type of CPAP that allows spontaneous breathing at two levels of CPAP.A sigh level of CPAP is reached for a preset defined interval of time (set as inspiratory time) and a low level, the baseline CPAP is maintained continuously. The number of sighs is determined and preset by the caregiver. The difference created by these two levels of pressure is minimal, however; it may be associated with small changes in volume and associated increases in functional residual capacity (FRC), which can be integral to recruitment. The goal of this bi-level CPAP is to achieve some higher level of alveolar recruitment and prevent alveolar collapse, and it implies some assumption that it will decrease the work of breathing required by the infant. In addition, the higher mean airway pressure generated by two levels of CPAP maybe responsible for accelerating the

surfactant production of a spontaneously breathing infant and also stimulating the respiratory center of very low birth weight infants. Recommendations for using the SiPAP version of bi-level CPAP are to use low frequencies of about 5-6 breaths per minute and a minimum of1-second duration for sigh breaths. When it was introduced into practice, bi-level CPAP showed clinical evidence of greater improvement in gas exchange compared to CPAP alone. However, in the incidence of extubation failure, bi-level CPAP and CPAP remain similar. The ability to achieve bi-level CPAP requires either a ventilator or a specific flow generator that can function as a bi-level CPAP generator. [67]

Nasal positive pressure ventilation (NPPV)

Nasal intermittent positive pressure ventilation (NIPPV) combines the use of nasal continuous positive airway pressure (NCPAP) with intermittent ventilator breaths. NIPPV is typically performed using nasal prongs with any of the ventilators currently available in the NICU. NIPPV can be used in synchronized (SNIPPV) or non- synchronized modes (NIPPV). SNIPPV can decrease spontaneous breathing effort compared with NIPPV. The technique was widely used in the 1980s but became less popular when reports appeared linking its use to gastrointestinal perforation. [68] The availability of ventilators that provided inflations synchronized with the infant's own efforts led to renewed interest in NIPPV [69]

Nasal intermittent mandatory ventilation (IMV) may be able to augment an ELBW infant's inadequate respiratory effort without the complications associated with endotracheal intubation. NV could be used as a non-invasive alternative to CPAP both in early RDS and post-extubation. NV may have advantages over NCPAP in stabilizing a borderline functional residual capacity, reducing dead space, preventing atelectasis, and improving lung mechanics. Moreover, NV would avoid potential complications of prolonged ventilatory support via an endotracheal tube (volutrauma, subglottic stenosis and infections). [66-71]

Nasal Neurally Adjusted Ventilatory Assist

Nasal neurally adjusted ventilatory assist (NAVA) is a novel form of non-invasive respiratory support that uses the electrical activity of the diaphragm (EAdi) to determine the timing and magnitude of inspiratory pressure delivery during spontaneous breathing. The EAdi signal is obtained with an indwelling 5.5 French feeding tube equipped with 10 electrodes. The tube is placed in the esophagus so that the electrodes are at the level of the diaphragm. When positioned properly, the electrodes and consequent EAdi signal can accurately and reliably trigger and cycle a positive-pressure breath, independent of airway leak. Additionally, the magnitude of the inspiratory pressure assist is a product of the EAdi signal and the preset NAVA level.

NAVA is currently commercially available only on the Servo-i ventilator. Nasal NAVA requires frequent bedside attendance, and is relatively expensive. Studies with large numbers of neonates will help to assess outcomes to evaluate NAVA as a standard NIV approach for supporting neonates with lung disease. [67]

expiratory valve opens, allowing circuit pressure to fall rapidly to the level of PEEP. The valve remains open with circuit pressure at the PEEP level with fresh gas flowing in the circuit available for spontaneous breathing, until the end of T_E, at which point the valve closes again and the cycle repeats. The next figures (3,4) illustrate the working principle of TCPLV continuous flow ventilator and Factors influencing tidal volume during PLV.

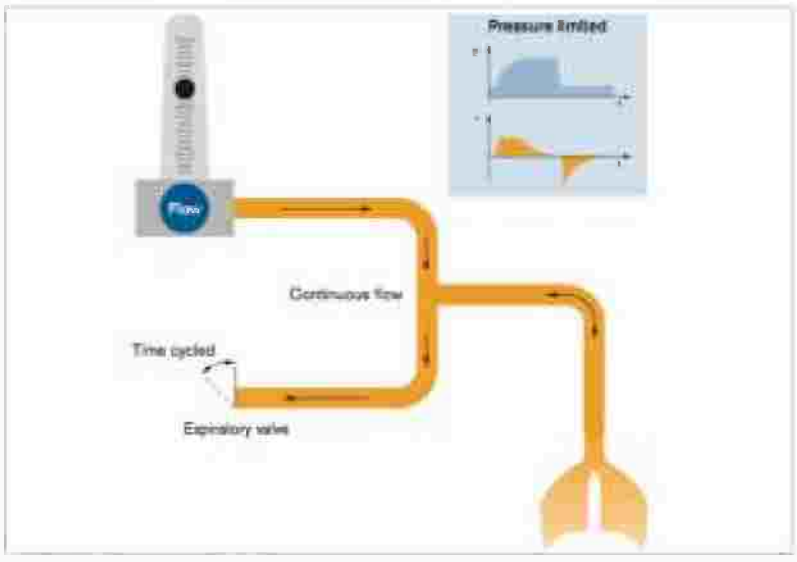

Figure (3): Working principle of a pressure limited time cycled continuous flow ventilator[13]

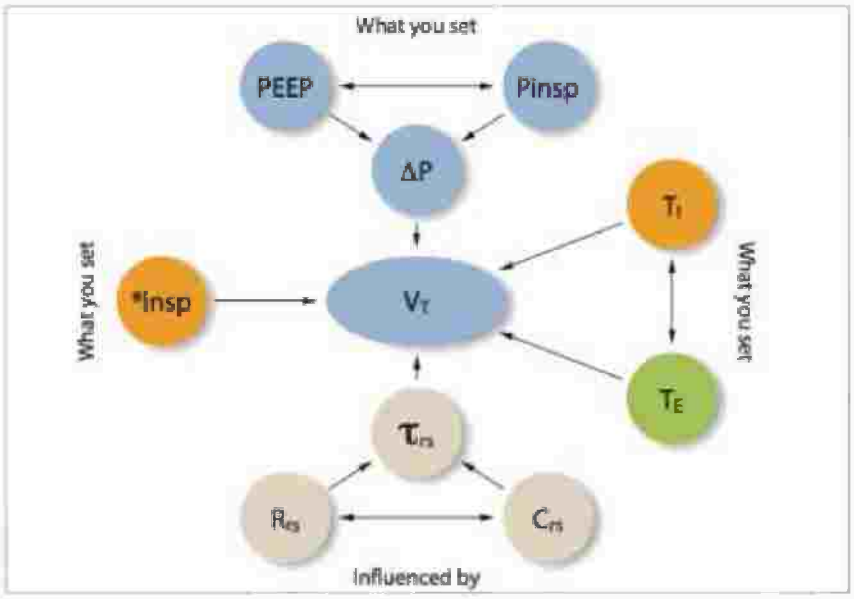

Figure (4): Factors influencing tidal volume during pressure-limited, continuous flow ventilation. V_T (tidal volume), T_{rs} (time constant), Crs (compliance), Rrs (resistance), T_I (inspiratory time), T_E (expiratory time), Pinsp. (Peak inspiratory pressure) [13]

There is no single PIP or PEEP that can be used for all babies under all circumstances. It is usual to maintain a PEEP of between 4 and 6 cm H2O to avoid alveolar de-recruitment during expiration. Higher PEEP may be desirable in the presence of large left-to right ductal shunts, pulmonary hemorrhage or severe RDS and high oxygen requirement. Higher PIP improve lung inflation and oxygenation but carry the risk of lung damage and pulmonary air leak. Tidal volume is generally proportional to the difference between inspiratory and expiratory pressures.

The major disadvantage of pressure-limited ventilation is that the V_T varies with changes in lung compliance. Such changes may occur as a result of clearing of lung fluid, recruitment of lung volume and surfactant replacement therapy, partial ETT obstruction...etc.

Lack of ventilation monitoring was common in the earlier IMV devices. Monitoring was limited to visual assessment of chest expansion and breathing rate, thus lacking the ability to accurately detect inadequate or excessive lung inflation, hypoventilation, gas trapping and impaired lung mechanics.

Patient-ventilator asynchrony occurs frequently during IMV since mechanical breaths of a fixed duration delivered at fixed intervals interferes with the infant's spontaneous breathing and reflex activity.

Asynchrony can adversely affect gas exchange and it has been associated with the occurrence of air leaks. [72] Concerns also exist regarding its effects on fluctuation of cerebral blood flow and the possible increased risk of intraventricular hemorrhage (IVH). [73] Earlier reports of elimination of asynchrony by heavy sedation or neuromuscular paralysis suggested a reduction in IVH and air leaks. [74-77]. However, these interventions resulted in greater dependence on respiratory support, lack of respiratory muscle training, generalized edema and inability to assess the neurological status. Increasing the ventilator rates was also suggested to prevent asynchrony and avoid the need for paralysis. [77,78] This may not be desirable for the preterm infant in whom hypocapnia has been associated with increased CNS and lung injury.

Introduction of patient triggered ventilation mostly solved the problem of patient ventilator asynchrony, However its use in neonatal care lagged far behind its use in adults due to technological challenges imposed by the small size of preterm infants. [79-81]

Patient-triggered respiration requires a machine with a rapid and sensitive response time, and it also demands sufficient inspiratory effort by the infant. Abdominally triggered techniques have been less satisfactory than airway sensors. [82,83] Clinical and laboratory experience has shown that flow triggering using a flow sensor at the airway opening (at the ETT adaptor) is ultimately the best compromise currently available [84,85]. At this time, most infant ventilators in common use utilize this triggering mode. However, it is important to be aware of the potential problems of this mode of triggering. The interposition of the flow sensor adds approximately 1 ml of dead space to the breathing circuit, which becomes a larger proportion of the V_T in the tiniest infants. The second problem is susceptibility to auto-triggering in the presence of a leak around the ETT. Any substantial leak flow during the expiratory phase will be misinterpreted by the device as inspiratory effort and would trigger the ventilator at an excessively rapid rate. That can be

corrected by decreasing trigger sensitivity. However, the magnitude of the leak often changes quite rapidly, requiring frequent adjustment.

Comparison of triggering methods [13]

Method	Advantages	Disadvantages
Pressure	No added dead space, leak tolerant	Poor sensitivity, long trigger delay, high WOB
Airflow	Very sensitive, rapid response	Added dead space, leak sensitive
Diaphragm EMG	Sensitive, most rapid response, leak tolerant	Requires careful positioning of probe

Basic ventilator terminology/general classification of ventilation modes [13]

Basic modes of mechanical ventilation are best classified on the basis of three factors: as shown in figure(5)

A) How is each breath initiated?
B) How is gas flow controlled during breath delivery?
C) How is the breath ended?

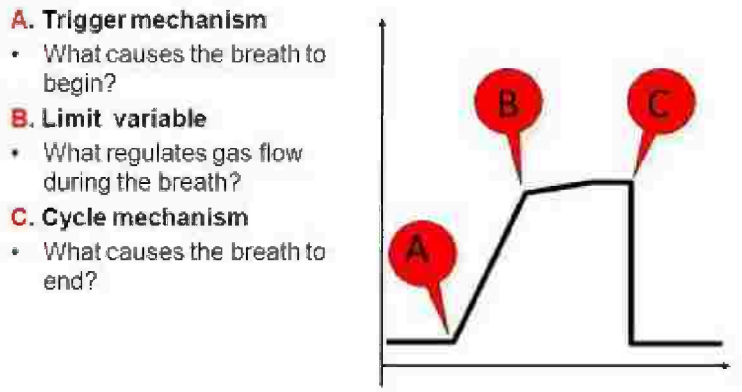

Figure (5): Classification of ventilator modes

Breaths can be initiated by a timing mechanism without regard to patient inspiratory effort. These modes are known as controlled ventilation. Alternately, breaths may be triggered by the patient's inspiratory effort, in which case we refer to assisted, also known as synchronized or patient-triggered ventilation.

The primary control variable for gas flow during the breath may be pressure (pressure-controlled/pressure-limited ventilation) or delivered VT (volume-controlled ventilation, VCV).

Breath termination may occur based on elapsed time (time cycled), or based on cessation of inspiratory flow (flow or volume cycled).

In addition to these basic modes, a variety of hybrid modes have been developed that combine features of several of the basic types.

Patient-triggered ventilation (PTV)

PTV is characterized by the delivery of a mechanical breath in response to a signal derived from the patient representing spontaneous respiratory effort and includes synchronized intermittent mandatory ventilation (SIMV), assist/control (A/C) ventilation, and Pressure Support Ventilation (PSV).

A. Synchronized intermittent mandatory ventilation

Synchronized intermittent mandatory ventilation is a mode in which the onset of mechanical breaths is synchronized to the onset of spontaneous breaths if the patient begins to breathe within a timing window. SIMV provides a preset number of mechanical breaths as in standard IMV, but these are synchronized with the infant's spontaneous respiratory effort if present [86]. Spontaneous breaths in excess of the set rate are supported with PEEP and FIO2 only. That unassisted breath results in uneven V_T's and high work of breathing (WOB) during weaning, an important issue particularly in extremely small and immature infants to overcome the resistance of the narrow ETT. In addition high airway resistance of narrow ETT, limited muscle strength and mechanical disadvantage conferred by the infant's excessively compliant chest wall typically result in small, ineffective V_T. Synchrony between mechanical and spontaneous breathing occurs only during inspiration, therefore expiratory asynchrony may occur if the inspiratory time for both mechanical and spontaneous breaths is different.

B. Assist control

In the A/C mode, the ventilator delivers a mechanical breath each time the patient's inspiratory effort exceeds the preset threshold criterion. Assist/control is a TCPL mode that supports every spontaneous breath, providing more uniform V_T delivery and lower work of breathing. The clinician still sets a ventilator rate for mandatory 'backup' breaths, which provides a minimum rate in case of apnea. This rate should normally be below the infant's spontaneous rate to allow the infant to trigger the breaths. The goal here is to have the infant and the ventilator work together, resulting in lower PIP. Because the infant controls the effective ventilator rate, weaning is accomplished by lowering the PIP rather than ventilator rate. In this fashion, the amount of support provided to each breath is decreased, allowing the infant to gradually take over the WOB.

C. Pressure support ventilation

Pressure support ventilation (PSV) is a flow cycled, rather than TCPL mode that supports every spontaneous breath just like A/C but also terminates each breath when inspiratory flow declines to a prethreshold, usually 10 to 20% of peak flow.

PSV differs from A/C in that every breath is patient triggered and cycled (by means of a flow- cycle criterion). In PSV the patient controls the start of inspiration, the start of expiration, the inspiratory time, the breathing frequency, and the minute volume, so the patient has complete control of the breath, which enhances patient comfort and patient-ventilator synchrony. It is important to note that to use PSV, the neonate must have sufficient respiratory drive. While newer PSV modes have an apnea backup mode, it takes time for the ventilator to sense apnea before mandatory backup breaths are delivered. Patients with persistent and frequent apnea may be better served by A/C or SIMV. A large

ETT leak can also pose a problem for PSV, because the leak may not allow the patient to flow-cycle to exhalation.

PSV may be particularly useful in patients who are difficult to manage with a fixed inspiratory time and respiratory rate (e.g. A/C). This is especially true in infants with high airway resistance (i.e. chronic lung disease), who are prone to developing gas trapping.

Despite years of routine use, there is no consensus regarding the relative merits of A/C and SIMV, the two most widely used modalities of synchronized ventilation. There are no large prospective trials with important clinical outcomes, such as incidence of air leak, chronic lung disease or length of ventilation to prove the superiority of one mode over the other. Short-term clinical trials have demonstrated smaller and less variable V_T, less tachypnea, more rapid weaning from mechanical ventilation and smaller fluctuations in blood pressure with A/C, when compared to SIMV. [87-92]

Rationale for volume targeted ventilation

Dreyfuss and Saumon demonstrated 20 years ago that severe acute lung injury occurred in small animals ventilated with large VT, regardless of whether that volume was generated by positive or negative inspiratory pressure. In contrast, animals exposed to the same high inspiratory pressure but in whom the movement of the chest wall and diaphragm were limited by external binding experienced much less acute lung damage. This landmark paper and other similar experiments clearly show that excessive VT, not pressure by itself, is primarily responsible for lung injury. [93-95]

As a result of the overwhelming evidence that excessive tidal volume, rather than high inspiratory pressure, is the primary determinant of lung injury, most clinicians at least now monitor the delivered tidal volume (VT) when using pressure-limited ventilation. It is critical to recognize that optimizing lung volume improves lung compliance. [93-95]

Moreover insufficient VT also causes significant problems. At any level of inspiratory pressure, insufficient VT may develop because of decreasing lung compliance, increasing airway resistance, airway obstruction, air-trapping or decreased spontaneous respiratory effort. Inadequate VT leads to hypercapnia, increased WOB, increased oxygen consumption, agitation, fatigue, atelectasis and possibly increased risk of intraventricular hemorrhage (IVH). Low VT also leads to inefficient gas exchange due to increased dead space to VT ratio. It should thus be obvious that relatively tight control of VT delivery during mechanical ventilation is highly desirable. [13]

Unique challenges in volume controlled ventilation of newborn infants. [13]

Measurement of tidal volume (V_T)

The importance of very accurate V_T measurement in any sort of volume-controlled/volume-targeted ventilation of ELBW infants should be self-evident, given that infants weighing 400 to 1000 g require V_T's in the range of 2 to 5 ml.

Flow and volume measurement has traditionally been performed at the junction of the breathing circuit and the ventilator. This placement is convenient and avoids extra

wires and the added instrumental dead space (IDS). However, in neonates this remote placement results in major inaccuracy of the V_T measurement as shown in figure (6). When the V_T is measured at the ventilator end of the circuit, the value does not account for compression of gas in the circuit and humidifier, distention of the circuit or leak around the ETT. In large patients with cuffed ETT, the volume injected into the circuit correlates reasonably well with the actual V_T entering the lungs and the volume loss to compression of gas in the circuit can be readily corrected by available algorithms. In small infants whose lungs are tiny and stiff, compared to the volume and compliance of the circuit/humidifier, the loss of volume to the circuit is not readily corrected, especially in the presence of significant ETT leak.

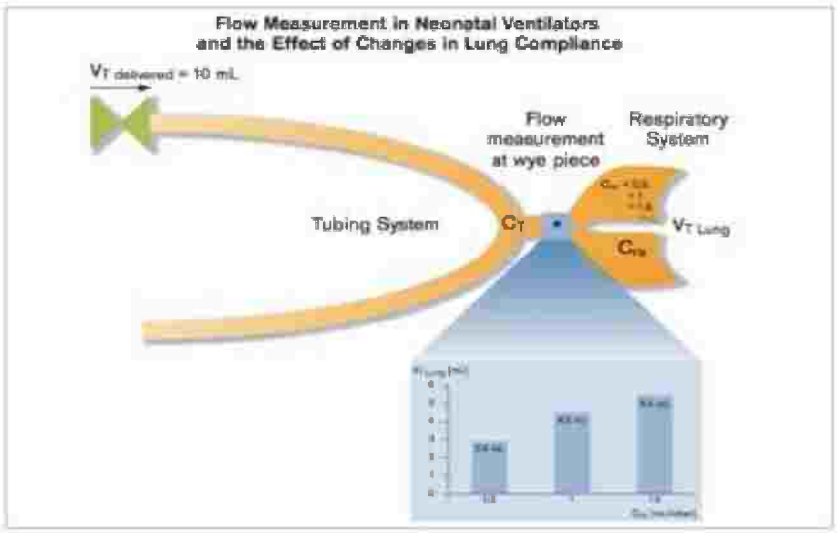

Figure (6): Flow measurement in neonatal ventilators and the effect of changes in lung compliance. A volume measurement, which is not situated at the Wye piece, reflects a volume displacement distributed in the ventilator breathing circuit tubing and the patient's lungs (V_T delivered). The actual delivered tidal volume into the patient's lung is markedly affected by changes in respiratory compliance. The lower the respiratory compliance C_{rs} at a constant tubing compliance, the greater the fraction of V_T "left behind" in the breathing circuit, and less volume delivered to the patient. For example, a total delivered tidal volume into the ventilator breathing circuit of 10 mL at a constant tubing compliance of 1.2 mL/mbar and a constant C_{rs} of 0.5 mL/mbar will result only in a tidal volume V_T lung of 2.9 mL.

Lung mechanics

Small infants who have poorly compliant lungs have very short time constants and normally have rapid respiratory rates with very short inspiratory times to match their lung mechanics. They have limited muscle strength and cannot develop strong inspiratory flow or pressure. This situation imposes great technological challenges on de- vice design, especially in terms of triggering ventilator inflations, inflation termination, and VT measurement. Suboptimal trigger devices may lead to excessive trigger delay with asynchrony, failure to trigger or terminate inflation, and errors in VT measurement or delivery.

Uncuffed endotracheal tubes (ETTs) have traditionally been used in newborn infants, because of concern about pressure necrosis of the neonatal tracheal mucosa and the small size of the tubes that makes inflatable cuffs more difficult to incorporate. As a consequence, majority of infants have some degree of leak around the ETT, especially later on in their course as the larynx and trachea progressively dilate as a result of exposure of these immature structures to cyclic stretch at a rate of as much as 3600 times per hour or more than 86 000 times per day. The leak is always greater during inspiration than in expiration. Therefore, it is important to measure both inspiratory and expiratory VT, with the latter more closely approximating the volume of gas that had entered the patient's lungs. It is critical to appreciate that the magnitude of the leak (or indeed its presence) varies from moment to moment. Leak around ETT also imposes additional challenges in breath triggering and termination.

Advances in the neonatal ventilators were accelerated in the 1990s with the use of microprocessor and sensing technology for control and monitoring the ventilator. Many modern neonatal ventilators allow not only the monitoring of proximal airway pressure, but also flow within the T- piece. This has many potential advantages, including an ability to target desired tidal or minute volumes by adjusting inspiratory and expiratory pressures and times, to display pressure–volume loops and assess dynamic lung compliance, and synchronize the ventilator to the infant.

Traditional volume controlled ventilation

Volume-controlled/volume-cycled ventilators deliver a constant; preset tidal volume (V_T) with each ventilator breath. In theory, these volume ventilators allow the operator to select V_T and frequency and therefore directly control minute ventilation. The ventilator delivers the preset V_T into the circuit generating whatever pressure is necessary, up to a set safety pop off, generally set at a pressure >40 cm H_2O. A maximum T_I is also set as an additional safety measure. Inspiration ends when the preset V_T has been delivered or when the maximum T_I has elapsed. The latter ensures that with very poor lung compliance, the ventilator does not maintain inspiration for a prolonged period trying to deliver the set V_T.

The major limitation of volume-controlled ventilators is that what they actually control is the volume injected into the ventilator circuit, not the V_T that enters the patient's lungs. This limitation is based on the fact that, as discussed previously, the V_T measurement does not account for compression of gas in the circuit and humidifier and distention of the compliant circuit. Most importantly, the variable leak around uncuffed ETTs used in newborn infants makes accurate control of delivered V_T very difficult with traditional volume-controlled modes. However Singh *et al.* did demonstrate the feasibility of VCV when special measures are taken to compensate for these problems. In that study, the set V_T was manually adjusted at frequent intervals to achieve a target exhaled V_T measured by a proximal flow sensor at the airway opening. [96]

Volume-targeted ventilation (VTV)

The recent full appreciation of the importance of volutrauma and the dangers of inadvertent hyperventilation has brought renewed interest in directly controlling V_T during neonatal ventilation. [96].

Because TCPLV and VCV have specific advantages, a hybrid form of ventilation (volume targeted ventilation) has been developed in an attempt to combine the best features of each. The development of VTV has been facilitated by the introduction of microprocessor-based ventilators, the development of sensitive and accurate flow sensors and the development of servo-controlled mechanics that allow accurate measurement and tracking of gas flow [97-100]

Volume-targeted ventilation is an essentially pressure-limited mode of ventilation that uses dual loop control to maintain tidal volume delivery in the target range. VTV uses a computerized servo controlled algorithm that adjusts the rise and fall of pressure to produce tidal volume delivery within a set range. In VTV, the delivered volume is an independent parameter whereas the PIP depends on respiratory system compliance. The ventilator uses the tidal volume of previous breaths as a reference, after which follow-up adjustments in PIP take place. VTV includes Volume Guarantee (VG), Pressure Regulated Volume Control (PRVC), Targeted Tidal Volume (TTV) and Volume Assured Pressure Support (VAPS). [101-103] These hybrid forms try to achieve the same goal, the optimization of tidal volume delivery, although each has a different mechanism. Clinicians must familiarize themselves with the specific features of individual machines in order to maximize safety and efficacy.

The proposed beneficial effects of volume-targeted ventilation are based on *first*, avoidance of excessive lung inflation and so preventing volutrauma and maintenance of a stable lung volume to prevent alveolar de-recruitment (atelectotrauma). *Second*, Decreasing V_T fluctuations, and reducing variations in minute volume, leads to a more stable PaCO2 and that leads to decreased fluctuations in cerebral blood flow and so decreases the risk of brain injury. Moreover, VTV would allow the ventilator to respond to rapid changes in lung compliance without clinician intervention and is potentially a self-weaning modality of ventilation, possibly facilitating faster weaning from mechanical ventilation.

Current evidence regarding the use of volume-targeted ventilation points towards beneficial effects in the preterm neonate [103,104]. A proposed benefit of volume-targeted ventilation is avoidance of excessive V_T believed to contribute to lung injury by promoting an inflammatory cascade. Analysis of tracheo-alveolar fluid from preterm infants with RDS showed lower levels of pro-inflammatory cytokines among infants ventilated with PSV+VG compared to PSV during the first week [105-107].

Unfortunately, the critical importance of distributing the V_T evenly into an optimally aerated lung has not been widely appreciated yet and requires special emphasis. The "open-lung concept" (OLC) is central to optimize the impact of volume-targeted ventilation: its benefits cannot be realized without ensuring that this V_T is distributed evenly throughout the lungs. In practical terms, the open lung is achieved by applying adequate PEEP. For a variety of reasons, including poorly conceived animal studies where moderate to high levels of PEEP were applied to animals with normal (that is, very

compliant) lungs, resulting in significant hemodynamic impairment, many clinicians fear using adequate levels of end-expiratory pressure. This 'PEEP-o-phobia' is only slowly being overcomed and remains one of the most important obstacles in optimizing the way conventional mechanical ventilation is practiced. So it is important to understand that there is no single 'safe' PEEP level. Optimal PEEP must be tailored to the degree of lung injury (that is, lung compliance). For infants with healthy lungs and thus normal lung compliance, PEEP of 3 cm H2O is adequate and PEEP of 6 cmH2O may result in overexpansion of the lungs with circulatory impairment and elevated cerebral venous pressure. On the other hand, atelectatic, poorly compliant lungs may require PEEP levels up to 8 to 10 cmH2O or more to achieve adequate alveolar recruitment and improve ventilation/perfusion ratio.

In conclusion, the application of a lung protective strategy in patients should be based on the use of reduced tidal volumes to avoid volutrauma and the use of adequate PEEP to prevent atelectotrauma. Such an approach would theoretically promote ventilation in a "safe zone" as shown in figure (7).

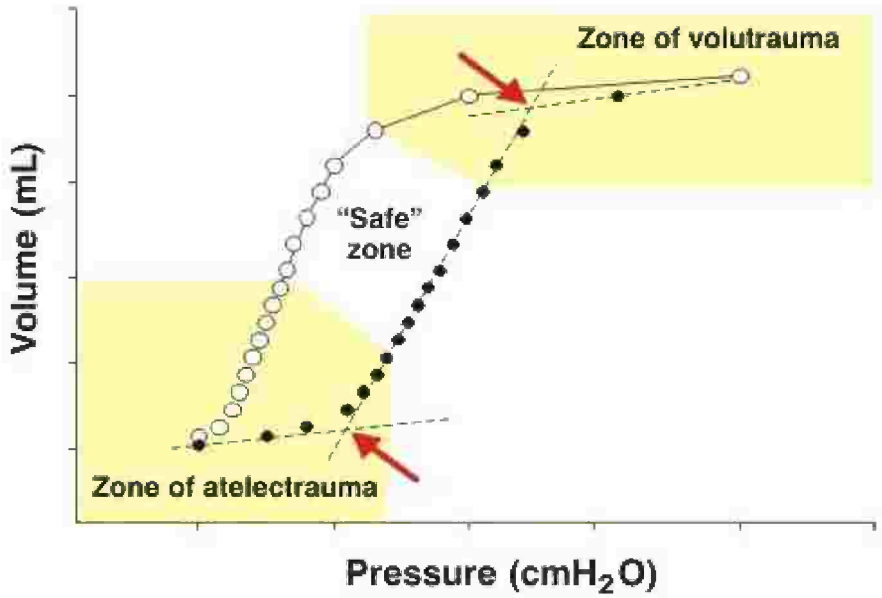

Figure (7): Static volume-pressure relationship of the respiratory system, indicating the zones of ventilator-induced lung injury and the theoretical safe zone. The arrows indicate the lower and upper inflection points

Mechanisms of volume targeted ventilation

There are 2 main ways by which ventilators target tidal volume control. Each has its strengths and weaknesses [108-115].

Control of the Inflation Tidal Volume

With this technique, the ventilator controls the tidal volume entering the baby's lungs and when the set inflation tidal volume has been reached, inflation is stopped. The obvious advantage is that it controls the tidal volume as it is delivered. The disadvantage is that as it measures the tidal volume going into the ETT, it cannot accurately compensate for how much is lost through leak around the ETT. If the leak is 50% then the tidal volume

delivered to the lung would be half that entering the ETT. Some ventilators may have a mechanism whereby the staff can adjust the ventilator setting for ETT leaks, but the technology cannot accurately respond to the ETT leak, as it varies inflation by inflation.

With some older volume-targeted ventilator modes, the set tidal volume is the inflation tidal volume leaving the ventilator and entering both the circuit and the baby. The main disadvantage is that the circuit has a relatively large compressible gas volume compared with a baby's tidal volume, so clinicians have to adjust the volume leaving the ventilator with each inflation to take this into account. If there is a flow sensor at the Wye connector measuring and displaying the tidal volume in and out of the baby, care providers have to adjust the tidal volume leaving the ventilator to control the delivered tidal volume. Although this is probably better than no volume control, it is not directly responding to the tidal volume delivered to the baby and cannot directly adjust the tidal volume for variable ETT leaks.

Control of the Expired Tidal Volume

With this technique, the tidal volume is regulated by the expired tidal volume, which makes intuitive sense, because the gas leaving the lung most closely represents the tidal volume that entered the lung when ETT leak was present. The problem is that the ventilator has to measure the expired tidal volume following an inflation and then use those data to determine the PIP needed to achieve the set expired tidal volume for the next inflation. Therefore, it is always working one inflation behind. An advantage is that the ETT leak in the previous breath has been calculated (inflation tidal volume minus expired tidal volume) and so the ventilator automatically adjusts the PIP to deliver a higher inflation tidal volume to compensate for the ETT. As ETT leak is almost always present and varies from inflation to inflation, this may be the better way to control the delivered tidal volume.

Some ventilators have 2 programs controlling the PIP used to deliver the tidal volume for each inflation that depend on whether the inflation was or was not triggered by the baby. This aspect is important because if the inflation is triggered, the baby has created some of the tidal volume and so a lower PIP is needed to deliver the set tidal volume. If the inflation is not triggered, the baby is probably apneic and so a higher PIP is required to ensure an adequate tidal volume. If a ventilator uses one program to control triggered and untriggered inflations, it will be difficult to control the tidal volumes accurately.

Modes of volume targeted ventilation:

Volume limit

Volume limit is a function of the Bear Cub 750 PSV (Viasis Medical Systems Conshohocken, PA). This is not true volume-targeted ventilation, as the only enhancement over simple pressure-limited ventilation is a volume limit setting; when the limit VT is exceeded, the device terminates inspiration thus avoiding excessive tidal volume. There is no automatic adjustment of inspiratory pressure and no provision to ensure that adequate VT is delivered when compliance or patient effort decreases. The reliance on inspiratory VT measurement means that significant leak around the ETT may lead to inadequate VT delivery.

Pressure regulated volume control (PRVC)

PRVC is a pressure-limited time-cycled assist/control mode that adjusts inspiratory pressure to target a set tidal volume, based on the tidal volume of the previous breath. Breath to breath increment is limited to 3 cm H2O, up to 5 cm H2O below the set upper pressure limit. Because pressure adjustment is based on the previous breath, variable patient respiratory effort will cause fluctuations in delivered VT. The main problem with the PRVC mode of the Maquet Servo 300 and the newer Servo-i (Maquet Inc., Bridgewater, NJ, formerly Siemens, Solna, Sweden) for newborn infants is the major inaccuracy of VT measurement performed at the ventilator end of the circuit, rather than at the airway opening. Recently, a second flow sensor that permits monitoring of actual VT has been made available, though the VT regulation is still based on the volume measured at the ventilator outlet.

Volume Guarantee (VG)

The Draeger Babylog 8000-plus (Dräger, Lübeck, Germany) offers a Volume Guarantee (VG) option that may be combined with any of the standard ventilator modes (A/C, SIMV, PSV). The VG mode is a volume-targeted, time- or flow-cycled, pressure-limited form of ventilation. The operator chooses a target tidal volume and selects a pressure limit up to which the ventilator operating pressure (the working pressure) may be adjusted.

The microprocessor compares the tidal volume of the previous breath, using exhaled tidal volume to minimize possible artifact due to air leak, and adjusts the working pressure up or down to try to achieve the set tidal volume. The algorithm limits the pressure increment from one breath to the next to 3 cm H2O, in order to avoid over-correction leading to excessive tidal volume. This, and the fact that the exhaled tidal volume of the prior breath is used, means that with very rapid changes in compliance or patient inspiratory effort, several breaths may be needed to reach target tidal volume. In order to minimize the risk of excessively large tidal volume, the microprocessor opens the expiratory valve, terminating any additional gas delivery if the inspired tidal volume exceeds 130% of the previous breath. The algorithm is designed to make slower incremental adjustment for low tidal volume and more rapid adjustment for excessive, potentially dangerous tidal volume. The auto-regulation of inspiratory pressure makes Volume Guarantee a self-weaning mode. Because weaning occurs in real-time, rather than intermittently in response to blood gases or intermittent observation of delivered tidal volume, the VG mode has the potential to achieve faster weaning from mechanical ventilation. Though more tolerant of endotracheal tube leak than other volume-targeted modes because of the use of exhaled tidal volume measurement, VG becomes impractical in the presence of leak that substantially exceeds 40%, because the VT measurement increasingly underestimates the true value. The problem is easily corrected by re-intubating the infant with a larger endotracheal tube.

Volume assured pressure support (VAPS)

The Volume Assured Pressure Support mode on the Bird VIP Gold (Viasis Medical Systems Conshohocken, PA) is a hybrid mode, which seeks to ensure that the targeted VT is reached. Each breath starts as a pressure-limited breath, but if the set VT is not reached,

the breath converts to a flow-cycled mode by prolonging the inspiratory time with a passive increase in peak pressure. This may result in a rather prolonged inspiratory time leading to expiratory asynchrony. Targeting tidal volume based on inspiratory tidal volume is susceptible to under-ventilation and the presence of significant endotracheal tube leak. Furthermore, there is no provision for automatically lowering inspiratory pressure as lung compliance improves. Therefore, the focus is on ensuring a large enough VT, but no provision is made to avoid excessive tidal volume and inadvertent hyperventilation, or to allow for automatic weaning.

The new Avea ventilator by Viasis shares the basic features of VAPS, but adds a Volume Limit function that will terminate inspiration if the upper limit of tidal volume is exceeded. The algorithm used to assure delivery of the target VT has been refined to try to avoid excessive inspiratory time. The ventilator calculates the decelerating inspiratory flow required to deliver the set volume in the set inspiratory time. When a pressure control breath is delivered and peak flow decelerates to this calculated peak inspiratory flow, if the set volume has not been delivered, the ventilator will automatically transition to a continuous flow mode until the set volume has been delivered (volume cycling). If the set volume is met or exceeded during delivery of the pressure control breath, the ventilator will complete the breath as a normal Pressure Control breath.

The addition of a volume limit should reduce the risk of volutrauma and hyperventilation, but still does not provide for automatic weaning of inspiratory pressure. No clinical studies are available at this time to validate the performance of this device in newborn infants. As with the other approaches, the interaction of an actively breathing infant with the device will make the achievement of a stable VT much more difficult than in bench tests.

Targeted tidal volume (TTV^{plus})

The targeted tidal volume mode is a hybrid mode of ventilation available on the SLE 4000 and 5000 (Specialised Laboratory. Equipment Ltd, South Croydon, UK). When TTV^{plus} is on, the user sets the targeted inspiratory VT that is appropriate for the patient, as well as the maximum PIP. The SLE 4000/5000 measures the inspiratory and expiratory VT of every assisted breath and compares it to the target inspiratory VT. If necessary, the algorithm adjusts the delivered PIP, only up to a maximum PIP setting. Therefore, even if there is a change to the lung mechanics, such as change in the resistance and compliance of the lung or a change in the respiratory effort of the patient, the ventilator will ensure that the appropriate PIP is used. . The inspiratory time is controlled by inspired VT. Ti may vary, but is maintained within 75% to 100% of the set Ti. In Neonatal patients, it is very common to have gas leak around the ET tube, due to the use of un-cuffed ET tubes. It is therefore very important for the ventilator to be able to compensate for leakage. The SLE TTV software version 4.3 can manually compensate for leaks of up to 20%, ensuring that the appropriate tidal volume is achieved. Of note that the new TTV software version 5 measures and targets the expiratory VT and can automatically compensate for leaks of up to 50%.

There are several reports about the accuracy of VTV. McCallion and colleagues studied the tidal volumes delivered to ventilated preterm babies with both triggered and untriggered inflations during volume guarantee ventilation with the Drager Babylog. On

average, both triggered and untriggered inflations were found to be almost identical to the set target expired tidal volume; however, there was a wide variation from 0% to 300% of the set volume. On careful examination of detailed recordings, the very high tidal volumes were found to be due to the baby taking a large breath such as crying, and the very low tidal volumes were due to the infant having a forced expiration against inflation. [113] Using the SLE5000 (SLE Ltd, South Croydon, UK), Patel and colleagues demonstrated that the delivered tidal volumes were 10% to 20% higher than the set tidal volume with a wide range. [115]

VTV can be very useful as soon as mechanical ventilation is started, because all the clinician has to do is set the tidal volume to approximately 4-6 mL/kg and the ventilator will adjust its settings to try and ensure that the set volume is delivered. Using this method may result in much better control of PaCO2 and tidal volume than using a set PIP, observing the chest-wall movement and intermittent blood gases.

VTV can also be useful when surfactant is given because surfactant has been shown to cause some obstruction to the airway. With VTV the ventilator will adjust the PIP to ensure that the set tidal volume is delivered. [112]

Despite the last 10 years researches in VTV, dilemmas still remain whether pressure limited or volume targeted ventilation should be the standard ventilatory mode in preterm infants. Therefore it is of great significance to evaluate the efficiency of the use of volume targeted versus pressure-limited ventilation for preterm neonates in our clinical practice.