Introduction

Respiratory distress syndrome (RDS) is the most common respiratory diagnosis in preterm infants. Surfactant therapy and mechanical ventilation using conventional or high-frequency ventilation have been the standard of care in the management of RDS ***(Ramanathan & Sardesai, 2008).*** However, lung protective ventilatory strategies, including non-invasive ventilation as a primary therapy or following surfactant administration in very preterm infants with RDS, were developed in order to reduce the adverse effects associated with invasive ventilation via an endotracheal tube ***(Davis et al., 2009).***

Sustained inflation to establish functional residual capacity, followed by noninvasive ventilation to minimize lung injury and subsequent development of bronchopulmonary dysplasia (BPD) were recently approved ***(Ramanathan & Sardesai, 2008).***

Nasal continuous positive airway pressure (NCPAP), as one of the non-invasive modes of ventilation, is accepted in supporting the recently extubated preterm infant and in the management of apnea of prematurity ***(Millar & Kirpalani, 2004).*** Moreover, its role in reducing the adverse effects of prolonged intubation – such as BPD, sepsis and trauma to the upper airways – is now well established ***(Mahmoud et al., 2011).***

However, despite the well-known beneficial effects of CPAP, there are also some drawbacks, such as lung over-inflation, air leaks, nasal septum injury, and gastric distention ***(Mahmoud et al., 2011).***

Aim of the Work

The aim of this study is to compare nasal continuous positive airway pressure as a non-invasive mode of ventilatory support with the invasive modes of intermittent positive pressure ventilation either synchronized or not, regarding risk factors and complications associated with their use.

Chapter (1)
Neonatal Assisted Ventilation

Introduction

In the last decade the role of mechanical ventilation in the neonatal intensive care unit (NICU) has been evolving. Invasive mechanical ventilation, although often necessary for supporting neonates with lung disease, has been implicated as a major cause of lung injury and inflammation, and is now considered a primary risk factor for neonates developing bronchopulmonary dysplasia (BPD). As such, institutions with better outcomes appear to be taking a different approach to mechanical ventilation ***(Heron et al., 2010)*.**

Physiological aspects of respiration

One of the most critical events in life is the switch from dependence on placental gas exchange in utero to air breathing at birth. In utero several processes take place to ensure an effective transition. However, full respiratory adaptation to extra uterine life takes weeks to complete. The primary function of the lungs is to arterialize mixed venous blood. This is achieved by pulmonary gas exchange and involves three important processes: ventilation, diffusion، and perfusion ***(Ali et al., 2007)*.**

Post natal Physiology of Respiration

The lungs primarily have two functions – the movement of oxygen (O_2) and carbon dioxide (CO_2) to and from the alveoli (through convection) and the provision of a surface for gas exchange (through diffusion). The lungs consist of approximately 300 million alveoli, surrounded by a network of capillaries, providing a large surface area for the transfer of gases. These gases reach the alveoli though a complex tree like structure of airways, starting from the trachea, which divides into the bronchi ***(Hardman, 2001)*.**

These further divide into bronchioles, terminal bronchioles, alveolar ducts and finally the alveoli. Gas flow to and from the alveoli depends on the airway resistances and the pressure gradient (between the mouth and the lungs) created by the respiratory muscles, which causes the expansion and deflation of the lungs. The pulmonary artery brings deoxygenated blood to the lungs from the heart and divides into the pulmonary capillaries. Here O2 is diffused to the blood and CO2 is diffused to the alveolar units. The pulmonary capillaries containing the oxygenated blood converge into the pulmonary vein. This blood is transported to the heart which pumps the oxygenated blood into systemic circulation ***(Hardman, 2001)*.**

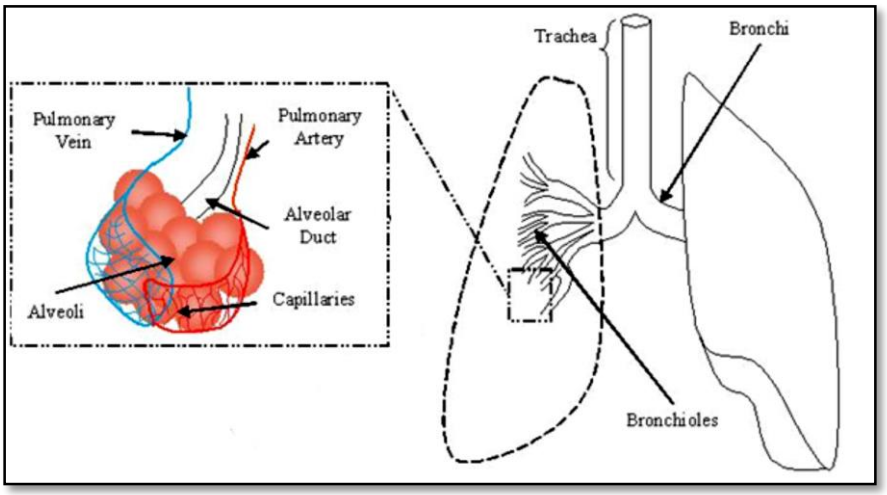

Figure (1): Lung structure ***(Hardman, 2001)***

The physiological makeup of the lungs maintains the delicate balance between these disparate anatomic entities. Several terms have been developed to describe the various physiological capacities of the respiratory tract ***(Reynolds, 2004).***

The amount of air that the lung inhales, exhales or holds under different conditions can be described by specific lung volumes and capacities. Figure (2) introduces various lung volumes and capacities which are important clinically as their values can be affected by pathological processes. When compared to normal physiological ranges, they can help physicians in making diagnoses regarding the underlying pathological conditions ***(Gatinoni and Pesenti, 2005).***

Total lung capacity (TLC) is defined as the volume of gas in the lungs following maximal inspiration. Functional residual capacity (FRC) is the volume of gas in the lungs at the end of normal expiration. The residual capacity (RC) is comprised of the expiratory reserve volume (the amount of air that can be expelled with maximal expiratory effort) and the residual volume (the volume of air in the lungs after maximal expiration) ***(Reynolds, 2004).***

Tidal volume (TV) is the volume of gas in any normal breath, whereas vital capacity is the maximal volume of air that can be expelled following maximal inspiration. These volumes can be measured by spirometry ***(Myers, 2001).***

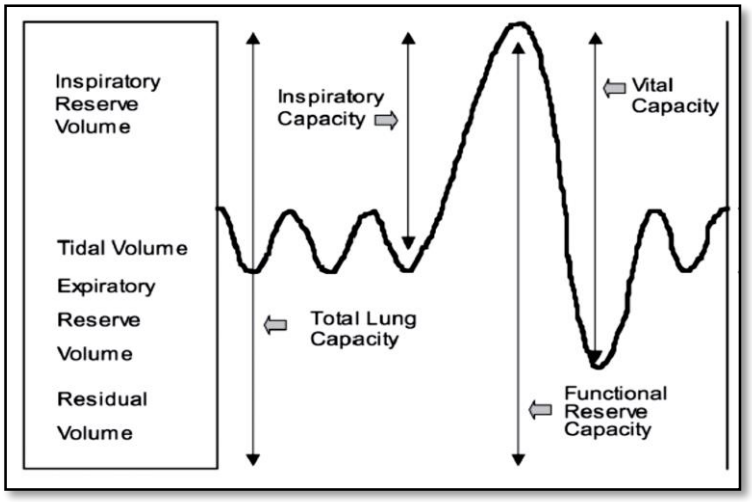

Figure (2): Lung volumes ***(Gatinoni and Pesenti, 2005)***.

The three main physiological functions of the respiratory tract are ventilation, perfusion, and diffusion.

Ventilation is the process of procuring air from the external environment via inspiration to supply the alveolus, after which it is subsequently returned to the outside of the body through expiration ***(Beers et al., 2006).***

The elastic nature of the lungs and chest wall permit pressure difference without which inspiration and expiration could not occur. The lungs are distended by pressure exerted by the airways and alveoli (positive internal pressure) or by pressure outside the lungs (negative external pressure). The chest wall's elasticity allows it to act as a spring. When the pressures exerted on it are altered, the chest wall moves and breathing occurs ***(Myers, 2001).***

The stimulus for respiration comes mainly from the medulla and pons. The carotid bodies detect changes in PaO2, PaCO2, and pH, whereas the medullary chemoreceptor monitors PaCO2 and pH alone. All of this information is combined to determine ventilatory needs, which increase in illness, exercise, or other physiological states in which tissue oxygen needs are increased. The responses of these receptors can be blunted and lead to decreased ventilation as well ***(Weinberger and Drazen, 2005).***

The ventilatory drive is stimulated by PaO_2 and $PaCO_2$ levels, although the body demonstrates far greater sensitivity to $PaCO_2$ levels. In normal individuals at rest, the $PaCO_2$ level

is tightly controlled. If the $PaCO_2$ level raises slightly, to 42 mmHg, the rate of ventilation quickly increases. However, the PaO_2 generally must decrease to around 65 mmHg for a similar ventilatory response to be initiated via hypoxemic stimulus. Hypercapnia is therefore the primary drive for ventilation ***(Weinberger and Drazen, 2005).***

Another main physiological responsibility of the respiratory tract is diffusion. This is measured by diffusion capacity for carbon monoxide, which tests how well the gas in inspired air can cross the wall of the alveolus and enter the capillary ***(Myers, 2001).***

This entails crossing the alveolar type 1 epithelial cells, the interstitial space, and the vascular endothelial cells. Carbon monoxide is used for measuring the diffusing capacity of the lung, generally by use of the single breath determination ***(Beers et al., 2006)***.

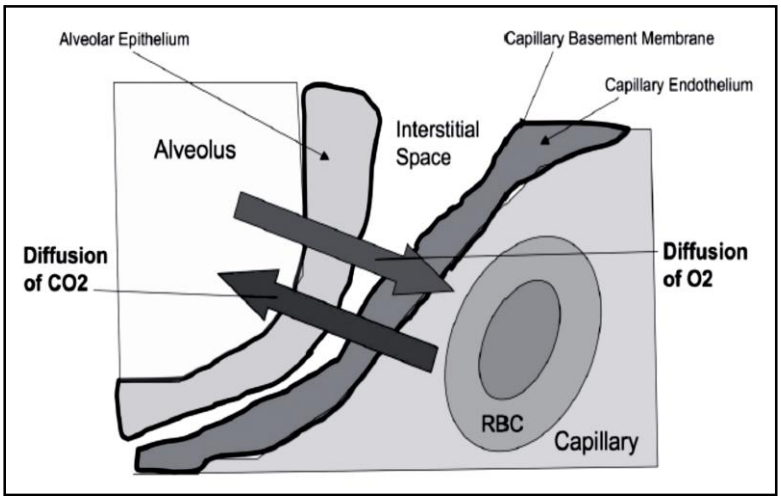

Figure (3): Diffusion of gases across the alveolar–capillary membrane. RBC, red blood cell ***(Myers, 2001)***

Perfusion is the final responsibility of the respiratory tract, and is necessary to maintain ventilation and diffusion of its anatomical components. Each division and subdivision of the respiratory tract has its own blood supply. Perhaps most valuable, however, are the pulmonary artery capillaries that surround the alveoli and provide the physiological proximity necessary for the transport of oxygen and other gases into the blood supply and carbon dioxide from the blood back into the lungs for expulsion. Because of gravitational forces, perfusion is greater at the lung bases than at the lung apices, leading to a slight normal physiological mismatch of perfusion compared with ventilation ***(Weinberger and Drazen, 2005).***

Lung function is most commonly tested using a spirometer which measures the volume and flow of air entering and leaving the lung during a breath. The spirometer is thus used to determine the lung volumes of Vtidal, IRV, ERV and VC ***(Gatinoni and Pesenti, 2005).***

Other tests of lung functionality such as the nitrogen washout technique (NWT) can be used to approximate FRC. In NWT, a patient breathes air with 100% oxygen while the concentration of nitrogen is monitored in expired air using a nitrogen analyzer. When the nitrogen is completely 'washed out' of the expired air, the amount of nitrogen at the beginning of the test can be approximated by multiplying total volume of expired air with percentage of nitrogen in the expired air. As the air in the lung at the beginning of the test consisted of 80% nitrogen, the total volume at the beginning of the test can be approximated. Using FRC, RV can simply be calculated as RV = FRC - ERV ***(Cotes et al., 2006).***

Clearing Lung Liquid

In utero, the lungs are filled with a liquid that is secreted by the lung epithelium. The volume of liquid in the lung before birth is controversial, but the available evidence indicates that it is greater than the FRC measured soon after birth. The high prenatal lung volume is due to adduction of the glottis restricting lung liquid efflux promoting its

accumulation within the airways and increasing lung expansion. The high degree of lung expansion provides an essential physiological stimulus for fetal lung development ***(Hooper and Wallace, 2006)***.

Although the precise mechanisms for airway liquid clearance at birth are unclear, the process starts just before or with the onset of labour. It is well established that limited intra-uterine space (as occurs during labour), impose changes in fetal posture that alter fetal chest wall configuration, increase transpulmonary pressure and lead to the loss of large volumes of liquid from the lung ***(Lines et al., 1997)***.

In addition, a large release of fetal adrenaline occurs late in labor, which stimulates pulmonary epithelial cells to stop secreting and start reabsorbing lung liquid due to the activation of luminal surface sodium channels ***(Barker and Olver, 2002)***.

Many studies have focused on the role of epithelial sodium channels in lung liquid re-absorption. At birth the pulmonary epithelium switches from facilitated Cl- secretion to active Na+ reabsorption with the opening of amiloride-sensitive Na+ channels on the apical surface. This is thought to reverse liquid movement across the pulmonary epithelium, promoting liquid uptake from the airways into the interstitium ***(Jain and Dudell, 2006)***.

Diminished activity or immaturity of this process may reduce the adaptation of the newborn lung to air breathing contributing to wet lung syndrome and hyaline membrane disease. However, the specific role of Na channel activation in lung liquid reabsorption at birth is still unclear ***(Jain and Eaton, 2006).***

Many commentaries have highlighted the considerable evidence supporting a role for Na+ uptake in alveolar fluid clearance, particularly under stimulated conditions, and the role of glucocortioids, catecholamines and oxygen in regulating the activity of this uptake. But it has also been noted that additional mechanisms, that are independent of amiloride sensitive Na+ uptake, are likely to be involved ***(Jain and Eaton, 2006).***

Vyas et al. (1986) measured intra-thoracic pressures during birth and found the maximum pressure averaged 145 cm H2O (range 88 to 265 cm H2O), but failed to show any loss of lung liquid. However, they reported liquid escaped from the mouth before they could place a mask on the infant's face. They also compared infants born by elective caesarean section and vaginal delivery and found the esophageal pressure changes were halved during caesarean section. Furthermore, although the initial inspiratory volumes recorded in the two groups were similar, significantly fewer infants born by caesarean section retained air at the end of their first breath.

This may reflect greater liquid retention within a lung of an infant born by caesarean section that had not been exposed to labour, thereby limiting the entry of air into the lower airways ***(Brewerton et al., 2005)*.**

Many studies suggested that "vaginal squeeze" during the progression of the chest through the birth canal was the predominant mechanical factor influencing lung liquid loss at birth. However, uterine contractions during labour impose fetal postural changes, leading to compression of the thorax, that could account for the high intra-thoracic pressures, causing expulsion of lung liquid early in labour. Indeed, large volumes of lung liquid can be lost shortly after the first signs of labor, before the onset of second stage ***(Flecknoe et al., 2002)*.**

Whatever the mechanism for removal of liquid from the airways before birth, liquid still fills the airways after birth until the infant takes its first breath. A study used phase contrast X-ray imaging to observe the rate and spatial pattern of lung aeration at birth in rabbit pups delivered by caesarean section. They demonstrated that the distal movement of the air/liquid interface only occurred during inspiration, indicating that the transpulmonary pressure generated by inspiratory efforts also plays a critical role in airway liquid clearance. They also noted that thoracic volume increased during lung aeration indicating that the gas volume of the

lung increased faster than the liquid could be cleared from the thorax ***(Hooper et al., 2007)***.

They concluded that the trans-pulmonary pressure gradient during inspiration promoted the movement of liquid into the interstitial tissue compartment from which it was gradually cleared, probably by the pulmonary circulation and lymphatics. This suggestion is consistent with the finding that interstitial tissue pressures transiently increase at birth and accounts for the increase in thoracic lymph flow observed in immature and term fetal sheep after the initiation of ventilation ***(Hooper et al., 2009)***.

Physiological principles of mechanical ventilation

Gas moves within the respiratory tract because of a pressure gradient, i.e. gas flows from a higher pressure to a lower pressure. Normal inspiration is accomplished by the integrated contraction of the respiratory muscles resulting in an expansion of the thoracic cavity with a decrease in alveolar pressure (Fig. 4) ***(Chifetz, 2003)***.

If the alveolar pressure (Palv) is lower than the pressure at the mouth or nose, then air flows into the lung with a change in lung volume. At all ages, including premature infants, a normal Pdr for the respiratory system during spontaneous ventilation is about 8 cmH2O (0.8 kPa) ***(Pilbeam, 2006)***.