CLINICAL PREDICTION SCORE FOR NASAL CPAP FAILURE IN PRE-TERM NEONATES WITH RESPIRATORY DISTRESS

Thesis
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List of Abbreviations

- A-a DO2: Alveolar-arterial oxygen tension gradient
- ACMV: Assist Control Mode Ventilation
- ANS: Antenatal Steroids
- AUC: Area Under Curve
- BPD: Bronchopulmonary Dysplasia
- CCAM: Congenital Cystic Adenomatoid Malformation
- CDP: Continuous Distending Pressure
- CHD: Congenital Heart Disease
- CLD: Chronic Lung Disease
- CLE: Congenital Lobar Emphysema
- CMV: Conventional Mechanical Ventilation
- CNEP: Continuous Negative Expiratory Pressure
- CPAP: Continuous Positive Airway Pressure
- CPIP: Chronic Pulmonary Insufficiency of Prematurity
- EA: Esophageal atresia
- ECMO: Extra-Corporeal Membrane Oxygenation
- ERV: Expiratory Reserve Volume
- ETT: Fraction of Inspired Oxygen
- FRC: Functional Residual Capacity
- FVC: Forced Vital Capacity
- GA: Gestational Age
- GBS: Group B Streptococci
- GDM: Gestational Diabetes Mellitus
- GHTN: Gestational Hypertension
- HFV: High Frequency Ventilation
- HMD: Hyaline Membrane Disease
- ICH: Intracranial Hemorrhage
- IMV: Intermittent Mandatory Ventilation
- iNO: Inhaled Nitrous Oxide
- MAP: Mean Arterial Pressure
- MAS: Meconium Aspiration Syndrome
- MIS: Minimal Invasive Surgery
- NCPAP: Nasal Continuous Positive Airway Pressure
- NPCPAP: Nasopharyngeal Continuous Positive Airway Pressure
- NRS: Non Invasive Respiratory Support
- OR: Odds Ratio
• PaCo2 arterial partial pressure of carbon dioxide
• PaO2 arterial partial pressure of oxygen
• PCA Post Conceptional Age
• PCV Packed Cell Volume
• PDA Patent Ductus Arteriosus
• PEEP Positive End Expiratory Pressure
• PIE Pulmonary Intersitial Emphysema
• PIP Positive Inspiratory Pressure
• PPHN Persistent Pulmonary Hypertension of the Newborn
• PROM Premature Rupture Of Membranes
• PTV Patient Triggered Ventilation
• RDS Respiratory Distress Syndrome
• ROC Receiver Operation Characteristics
• RV Residual Volume
• TTNB Transitional Tachypnea of the Newborn
• TRH Thyrotopin- releasing hormone
• VLBW Very Low Birth Weight
• SGA Small for Gestational Age
• SIMV Synchronized Intermittent Mandatory Ventilation
ABSTRACT

In recent years, the use of continuous positive airway pressure (CPAP) has gained immense popularity as the primary mode of respiratory support. CPAP use has been associated with the reduced need for mechanical ventilation and associated lung injury. CPAP improves ventilation-perfusion relationships and reduces oxygen requirements.

However, failure of CPAP has variable incidence as shown in previous studies on predictors of CPAP failure which concluded; gestational age <28 weeks, PROM, lack of exposure to antenatal steroids (ANS), product of CPAP pressure and FiO2 ≥1.28, alveolar-arterial oxygen tension gradient (A-a DO2) >180 mmHg on the first arterial blood gas (ABG) and small for gestational age (SGA).

We performed a prospective study on 100 preterm neonates who were initiated on nasal continuous positive airway (CPAP) for respiratory distress to predict causes leading to this failure.

CPAP failed in 48.5% of the cases. Neonates with lower birth weight, higher FiO2 at initiation of CPAP and Product of CPAP pressure & FiO2 at initiation ≥2.45 were at higher rates of CPAP failure.

However, in multivariate analysis, only sepsis was a statistically significant cause of CPAP failure. The odds ratio for CPAP failure in cases who have clinical sepsis are 11.1 times higher than in cases who do not have sepsis with Confidence Interval (3.2-38.5%). And therefore, clinical sepsis can be considered as an associated or risk factor for CPAP failure.

Key words:

Antenatal Steroids - Hyaline Membrane Disease.
Basic Mechanisms of Lung Development

To understand the mechanisms that possibly explain the morbidity in preterm neonates, it is necessary to understand lung physiology at this stage of their development. *(Joshi and Kotecha, 2007)*

Stages of Lung Development

Normal lung development is characterized by a carefully choreographed series of prenatal and postnatal events that can be compromised by a variety of factors. *(Joshi and Kotecha, 2007)*

Early growth and development of the human lung is a continuous process that is highly variable between individuals but, nonetheless, has traditionally been divided into 5 stages.

The first is the embryonic phase (26 days to 6 weeks’ GA), followed by the pseudoglandular (6 –16 weeks’ GA), canalicular (16 –28 weeks’ GA), saccular (28 –36 weeks’ GA), and alveolar (36 weeks’ GA to term) phases. This final phase continues into childhood. *(Langston et al, 1984)*

Interference with this stepwise process of lung development during any of these phases may render the lung less effective as a gas exchanger and more susceptible to disease. *(Maritz et al, 2005)*

The formation of conducting airways and terminal bronchioles occurs during the canalicular period and establishes the platform for gas exchange. Bronchial branching to roughly the 16th generation of the bronchial tree is complete by 16 weeks’ GA. *(Kotecha, 2000)*

During the embryonic phase (26 days to 6 weeks gestation), an endoderm-lined outpouching or “lung bud” derived from the primitive foregut divides and branches dichotomously to form the early tracheobronchial tree (Figs 1,
2). Initially, the primitive airways are surrounded by loose mesenchyme supplied by primitive systemic arteries. The pulmonary arteries arise from the sixth aortic arch near the end of the embryonic period, penetrate the mesenchyme, and ultimately replace the systemic vessels. (Langston, 1989)

(Figure 1.)
Normal development of the major airways. Schematic shows induction of dichotomous branching of the lung bud (arrow) by contact with primitive mesenchyme (Langston, 1989)

(Figure 2.)
Embryonic phase of normal respiratory tract development. Photomicrograph (original magnification, _100; [H-E] stain) of the developing lungs of a 4-mm embryo at approximately 30 days gestation shows the primary bronchial buds (arrows) surrounded by primitive mesenchyme.) (Joshi and Kotecha, 2007)
The pseudoglandular phase (6–16 weeks gestation) includes the development of the airways to the level of the terminal bronchioles. At gross examination, the external morphology of the immature lungs is similar to that of neonatal lungs at term. However, at microscopic examination, the bronchioles end blindly within primitive stroma, a histologic feature reminiscent of glandular tissue (Fig 3). Recently, the traditional understanding that only conducting airways are formed during this period of lung development has been challenged. Nevertheless, a deficient number of true alveolar saccules during this developmental stage prevents meaningful gas exchange, and extrauterine survival is not possible. (Tschanz and Burri, 1997)

(Figure 3)
Immature lung in the pseudoglandular phase.
Photomicrograph (original magnification, _15; H-E stain) of the lungs at 13 weeks gestation shows blind-ending terminal bronchioles (arrows) surrounded by immature lung parenchyma, which has begun to organize into lobules and clusters of primitive acini (arrowheads). (Tschanz and Burri, 1997)

During the canalicular or acinar phase (16–28 weeks gestation), multiple alveolar ducts arise from respiratory bronchioles (Fig 4). Alveolar ducts are lined by type II alveolar cells, which are capable of surfactant synthesis. Thin type I alveolar lining cells differentiate from type II cells. Toward the end of this developmental phase (24–28 weeks), primitive distal saccules (primitive alveoli) begin to form through a process known as primary septation. Progressive thinning of the pulmonary interstitium allows gas exchange as the walls of proliferating
capillaries and type I alveolar lining cells approximate. (Agrons and Harty, 1998)

(Figure 4.) Immature lung in the canalicular (acinar) phase. Photomicrograph (original magnification, ×425; H-E stain) of the lungs shows blood-filled capillaries (arrow) that lie immediately beneath the surface of alveolar duct structures lined by cuboidal epithelium (early type II pneumocytes (arrowhead). (Agrons and Harty, 1998)

The 28- to 36-week-GA period, termed the saccular period, is a transitional phase before full maturation of alveoli occurs characterized by an increased number of saccules, primitive alveoli that become gradually more effective as gas exchangers and may be sufficient in number and quality to sustain life in the preterm infant. The alveolar walls in the saccular stage are more compact and thick than the final thin walls of alveoli. They also include a double capillary structure that is reduced to a single one in the mature alveolus (Fig.5). However, the blood vessels are well oriented to the epithelium and protrude into air spaces, forming many thin airblood interfaces that are capable of carrying out the function of gas exchange that fully matures in the alveolar phase. Although alveoli may form during the saccular phase, mature alveoli are not uniformly present until 36 weeks’ GA. (Kotecha, 2000)
(Figure 5).
Saccular phase of lung development. Photomicrograph (original magnification, ×350; H-stain) of the lungs reveals saccules subdivided by secondary crests (arrows) composed of thinning type I cells immediately adjacent to capillary beds.

During the alveolar phase, the epithelium and interstitium decrease in thickness, air-space walls proliferate, and the capillary network matures to its final single-capillary network. (Fig.6) (Copland and Post, 2004)

Blood-vessel development, which begins at the earliest stages, continues throughout lung development. It is important to note that these structural changes not only affect gas exchange but have profound effects on the mechanical properties of the lung and, hence, the respiratory system as a whole. As noted, premature birth during this critical period may result in significant alteration in lung function and physiology. (Stenmark and Gebb, 2003)

(Figure 6.)
Alveolar phase of lung development. Photomicrograph (original magnification, ×25; H-E stain) of the normal lung at 38 weeks gestation shows mature alveolar ducts and alveolar saccules with delicate septa, resulting in a thin air-blood barrier.
Stable Functional Residual Capacity and Effectiveness of Gas Exchange

Maintenance of a stable and adequate functional residual capacity (FRC) is important for securing stable gas exchange. FRC is determined by the balance between the opposing forces of the chest wall and lung and, thus, is a direct function of their respective mechanical properties. In early life, a compliant chest wall offers little outward recoil to the respiratory system; thus, the elastic characteristics of the respiratory system approximate those of the lung. The lung is also more compliant (ie, has less elastance) in premature and newborn infants. The lung becomes less compliant (ie, increases in elastance) as it undergoes alveolarization, and the interstitium becomes more intricately woven. Compliance of the chest wall declines over the first 2 years of life. (Papastamelos et al, 1995)

In early life, the lung–chest-wall equilibrium results in a mechanically determined FRC that is low relative to older children and adults and is an important determinant of age-related vulnerability to hypoxia. To circumvent this limitation, infants actively elevate their FRC by using laryngeal braking during tidal expiration and by initiating inspiration at an end-expiratory volume above that determined by the mechanical properties of the chest wall and lung. (Kosch et al, 1988)

An additional mechanism is persistence of inspiratory muscle activity into the expiratory phase, thereby modulating the expiratory flow. The transition from an actively maintained FRC to one that, as in adults and older children, is mechanically determined occurs in term infants late in the first year and into the second year of life. (Colin et al, 1989)

The timing of this transition coincides with the declining compliance (stiffening) of the chest wall and its gradually increasing contribution to the overall stabilization of the respiratory system. Chest-wall compliance is particularly elevated in premature infants, with the slope of change toward reduced compliance being the steepest between 28 and 40 weeks’ GA compared with that at any stage in postnatal life. (Gerhardt et al, 1980)

Thus, it is reasonable to assume that breathing with an overly compliant chest wall, high lung compliance, and reduced number of aircontaining units is a challenge for infants delivered before term. The challenge of maintaining an FRC that permits stable gas exchange is likely compounded in the premature infant by apneic events, which have been shown to drive the system to critically low lung volumes and result in rapid desaturation. (Kosch and Stark, 1984)
Airway Tethering

An additional crucial mechanism that secures airway patency and, thus, adequate maintenance of FRC is airway-tethering. Tethering is mediated through the elastic components in alveolar walls that surround bronchi. These elastic fibers are anchored to each other, creating an extended mesh that exerts a circumferential pull on the intraparenchymal airways. This complex elastic network transmits tension from the pleural surface to the individual bronchi. (Gomes et al, 2001)

The tension on the system increases during inspiration, resulting in increased airway caliber. The cross-sectional area of the airway decreases with decline in lung volume. Thus, tethering couples lung volume changes to airway caliber. Tethering of airways is less effective in infants born prematurely, because alveolarization and the associated development of the parenchymal elastic network are still in the saccular stage of development at 32 to 36 weeks’ GA. The effect of reduced tethering is decreased airway stability, increased tendency to closure, increased airway resistance, and, ultimately, a tendency to collapse alveolar units in the lung periphery. (Henschen et al, 2006)

Changes in Lung Volume During the Last Trimester of Gestation

Total lung volume undergoes rapid changes during the last trimester of gestation. Calculations by Langston et al revealed that at 30 weeks’ GA, the lung volume is only 34% of the ultimate lung volume at mature birth, and at 34 weeks only reaches 47% of the final volume at maturity. In contrast, the airspace walls decrease in thickness such that at 30 and 34 weeks, they are 164% (28 _m) and 135% (23 _m), respectively, relative to the ultimate wall thickness at mature birth (17 _m). In parallel, dramatic increases in airspace surface area occur. Surface area increases from 1.0 to 2.0 m2 at 30 to 32 weeks’ GA and to 3.0 to 4.0 m2 at term. These volume changes likely have direct mechanical implications in reducing the vulnerability caused by a low and unstable FRC. Maturation of the alveolar network improves parenchymal elastance and, therefore, airway-tethering. (Langston et al, 1984)
ASSOCIATION OF PRETERM BIRTH WITHOUT CLINICAL LUNG DISEASE WITH ALTERED LUNG DEVELOPMENT AND FUNCTION

Lung development occurs mostly in utero. At term, the lung is in its final stage of development: the alveolar stage. Normal in utero lung development occurs according to a highly programmed sequence in a stable milieu, one that is significantly more hypoxic relative to the atmosphere (at a fraction of inspired oxygen of 2%–3% at 10–12 weeks’ GA, which rises to 8%–10% thereafter). (Burri, 1997)

This hypoxic environment represents the norm for lung organogenesis, including vascular development. (Groenman et al, 2007)

Early events of trophoblast differentiation are oxygen regulated. It is now recognized that postnatal hyperoxia plays a key role in the development of BPD. Premature birth interrupts normal in utero lung development and results in an early transition from the hypoxic intrauterine environment to a comparatively hyperoxic atmospheric environment. An inhaled oxygen concentration of 21% represents significant hyperoxia for the preterm infant. Although this relative hyperoxia has not been directly demonstrated to be an independent cause of altered lung maturation, it may play a role in the subsequent development of chronic lung dysfunction. (Caniggia et al, 2000)

There is increasing evidence to support the hypothesis that preterm delivery, even in the absence of any neonatal respiratory disease, may have adverse effects on subsequent lung growth and development and that these alterations may persist and worsen during the first 5 years of life. Results of a limited number of studies have shown that premature infants of varying GAs, but born without clinical lung disease, have altered pulmonary function. (Greenough, 2007)

Reduced airway function in the absence of neonatal respiratory disease was demonstrated at 1 year of age in a population of healthy infants born at 29 to 36 weeks’ GA. (Hoo et al, 2002)

Mansell et al reported lower airway conductances and maximum expiratory flows in a group of 5- to 7-year old children who had been born prematurely but without respiratory problems, which suggests that airway dysfunction persists into childhood. (Mansell et al, 1987)
These effects may not be dissimilar to those experienced by very preterm infants (32 weeks’ GA), who have generally been the focus of attention because of the severity of their respiratory problems immediately after birth and frequent development of BPD. (McEvoy et al, 2004)

A direct association between premature birth and reduced expiratory flows was demonstrated recently by using the raised-volume rapid thoracic-compression technique. (Friedrich et al, 2006)

In these studies, healthy preterm infants (30 –34 weeks’ GA [mean: 33.4 weeks’ GA]) studied at a mean corrected age of 8 weeks had reduced airway flows in the presence of normal forced vital capacity (FVC) compared with term infants. In a follow-up analysis, the reduced flows did not normalize in these children by 16 months of age, thus demonstrating a lack of “catch-up growth in airway function by early in the second year of life .This result led the authors to conclude that preterm birth was associated with altered lung development. These longitudinal studies that used the raised volume method confirmed the results of previous studies that suggested a similar conclusion. (Friedrich et al, 2007)

The long-term significance of reduced airway function early in life was recently emphasized in a longitudinal study that involved a large group of nonselected (enrolled at birth without any specific criteria) infants who had participated in the Tucson Children’s Respiratory Study. The study’s results showed that infants whose pulmonary function was in the lowest quartile also had pulmonary function in the lowest quartile through the years of follow-up until early adulthood. These findings in a normal unselected population suggest that level of pulmonary function in early life tracks and changes little with growth. Data from Weiss and Ware have suggested that deficit in lung function during early life, especially if associated with lower respiratory illnesses, increase the risk of chronic obstructive pulmonary disease later in adult life. Of particular importance in this context is the role played by RSV, which is known to affect most children during their first year of life. (Stern et al, 2007)
Respiratory distress is a common emergency responsible for 30-40% of admissions in the neonatal period. A diagnosis should be made in the first few minutes of seeing the baby and immediate life-saving measures should be undertaken till further management plans are drawn up. (*NNF Recommended Basic Perinatal-Neonatal Nomenclature, 1998*)

Respiratory distress in the neonate is diagnosed when one or more of the following is present; tachypnoea or respiratory rate of more than 60/minute, retractions or increased chest in drawings on respirations (subcostal, intercostal, sternal, suprasternal) and noisy respiration in the form of a grunt, stridor or wheeze. The distress may or may not be associated with cyanosis and desaturation on pulse oximetry. (*NNF Recommended Basic Perinatal-Neonatal Nomenclature, 1998*)

**CAUSES OF RESPIRATORY DISTRESS**

The common causes of respiratory distress in neonates:

A. Respiratory Distress Syndrome
B. Other Causes

**A. Respiratory Distress Syndrome (RDS), Hyaline Membrane Disease (HMD)**

Respiratory distress syndrome results from immaturity of the lungs and surfactant deficiency. Approximately 1% of all newborns and 10% of the preterm population develop RDS (*Rubaltelli et al., 1998*).

Untreated, the condition worsens up till 48 h after birth, after which the infant’s surfactant synthesis commences. The infant’s respiratory problems then improve and this is associated with a spontaneous diuresis. Nowadays, with the early use of exogenous surfactant, the classical signs of RDS are rarely seen. Nevertheless, the course of a very prematurely
born infant is frequently associated with respiratory complications and they may remain ventilator and/or oxygen dependent for weeks or even months as they develop chronic lung disease, which is now usually termed BPD. The initial histological finding in RDS is alveolar epithelial cell necrosis. The epithelial cells become detached from the basement membrane and hyaline membranes form on the denuded areas, hence, RDS was originally known as hyaline membrane disease. The hyaline membranes are formed by coagulation of plasma proteins that have leaked onto the lung surface through damaged capillaries and epithelial cells. RDS is now the preferred term as hyaline membrane disease requires histological confirmation, which is now uncommon as only the minority of infants with RDS die. (Rubaltelli et al, 1998)

Pathophysiology

Surfactant is a mixture of phospholipids (the most important are phosphatidylcholine, which is most effective in reducing surface tension in its disaturated form [DPPC] and phosphatidylglycerol, which is required as a spreading agent), neutral lipids and four surfactant-associated proteins, SP-A, SP-B, SP-C and SP-D. SP-A and SP-D are collectins and interact with bacteria and other microorganisms to promote phagocytosis and killing of microorganisms by alveolar macrophages. SP-A and SP-D polymorphisms have been associated with severe respiratory syncytial virus infection. SP-B is important for surface activity. SP-B deficiency is an autosomal recessively inherited disorder and causes lethal hypoxemic respiratory failure. SP-C enhances spreading of phospholipids. SP-C deficiency has been associated with interstitial lung disease. Compression of the surfactant monolayer results in an insoluble surface film, which reduces the surface tension and work of breathing and prevents transudation of fluid. The ‘solid’ monolayer formed in expiration promotes alveolar stability. DPPC is relatively rigid at body temperature and, hence, phosphatidylglycerol is required as a spreading agent. (Hamvas et al, 2007)

Premature infants with RDS have low levels of DPPC and absent phosphatidylglycerol. As a consequence, the surfactant monolayer formed in expiration is unstable and does not effectively reduce surface tension, and affected infants have stiff (noncompliant), low-volume lungs. As a result of the increased surface tension and hypoxic damage to the integrity of the alveolar capillary membrane, protein-rich fluid flows from the intravascular space into the alveoli creating hyaline membranes; the plasma proteins inhibit surfactant function. (Hamvas et al, 2007)