

OPTIMAL HOME OXYGEN FLOW RATE FOR INFANTS WITH BRONCHOPULMONARY DYSPLASIA

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By

AHMAD ALI IMRAN

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Saskatoon, Saskatchewan S7N 5C9
Canada

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LIST OF ABBREVIATIONS:

Abbreviation	Full Name
RDS	Respiratory Distress Syndrome
BPD	Bronchopulmonary dysplasia
IVH	Intraventricular Hemorrhage
ROP	Retinopathy of prematurity
NEC	Necrotizing enterocolitis
DV	Ductus Venosus
DA	Ductus Arteriosus
PDA	Patent Ductus arteriosus
RA	Right atrium
LA	Left Atrium
RV	Right Ventricle
LV	Left Ventricle
FO	Foramen Ovale
PFO	Patent Foramen Ovale
PO ₂	Partial Pressure of Oxygen
PCO ₂	Partial pressure of Carbon Dioxide
HbF	Fetal Hemoglobin
SVR	Systemic vascular resistance
Na/K ATPase	Sodium–Potassium adenosine triphosphatase
P	Pressure
R	Radius
T	Surface Tension
PI	Phosphatidyl inositol
PG	Phosphatidyl glycerol
ENaC	Epithelial sodium channels
ROS	Reactive Oxygen Species
PEEP	Peak End Expiratory Pressure
TV	Tidal Volume
RR	Respiratory rate
XR	X-Ray
pH	Potential of Hydrogen
CS	Caesarean Section
NIH	National Institute of Health
IUGR	Intrauterine growth Restriction/Retardation
VEGF	Vascular Endothelial growth factor
ELGAN	Extremely Low Gestational age Newborn
VILI	Ventilator induce lung injury
NIV	Non-Invasive ventilation
CPAP	Continuous positive airway pressure
CO ₂	Carbon Dioxide

FiO2	Fraction of Inspired Oxygen
NAVA	Neurally-adjusted ventilator assist
CAP	Caffeine for Apnea of prematurity
STOP ROP	Supplemental Therapeutic Oxygen for Pre-threshold ROP
PVL	Periventricular Leukomalacia
COT	Canadian Oxygen Trial
DNA	De-oxy ribonucleic acid
NICU	Neonatal intensive care unit
NIRS	Near Infrared Spectroscopy
SpO2	Saturation of peripheral Oxygen
BP	Blood Pressure
HR	Heart Rate
MABP	Mean arterial Blood Pressure
LED	Light Emitting Diode
O2Hb	Oxy hemoglobin
HHb	Deoxy-Hemoglobin
RcSO2	Regional cerebral saturation of Oxygen
SO2	Saturation Oxygen
FTOE	Fractional Tissue Oxygen extraction
MRI	Magnetic Resonance imaging
PIVH	Peri/Intraventricular Hemorrhage
MRP	Most Responsible Physician
RCT	Randomized control trial
GA	Gestational Age

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ABSTRACT

INTRODUCTION:

Bronchopulmonary dysplasia (BPD) is one of the most common morbidities related to preterm birth. Infants with moderate BPD are discharged on supplemental oxygen to maintain oxygen saturation between 90-96%, avoiding both hypoxia and hyperoxia, each with its own morbidity. Pulse oximetry (POX) is used to measure oxygenation in the blood. Near-infrared spectroscopy (NIRS) is a potential method to measure cerebral oxygenation and brain perfusion. To the best of our knowledge, there is a lack of normalized data for NIRS values in neonate infants going home with or without oxygen. We proposed that with combination of NIRS and pulse oximetry we could better identify a safe oxygen flow rate/concentration for babies with BPD. In doing so, we also sought to determine what the normative values of NIRS are in premature infants.

METHODS:

This was a prospective cohort study approved by the Bioethics Board, University of Saskatchewan. Infants were recruited from the NICU, Jim Pattison Children's Hospital after obtaining written informed consent. One group (Control group, n=22) of relatively healthy preterm infants were recruited for NIRS measurements in relation to standard POX. We then compared NIRS and POX values on varying flow rates (0.03, 0.06, 0.12 L/Min) for moderate BPD infants going on home oxygen (n=10).

RESULTS:

Of the control infants in room air, the average POX value was 97.8% with SD \pm 1.661 and SEM \pm 0.006. The average time of hypoxia with POX below 90% was 3.5%, while time above 96%

was 96.5%. The average NIRS value was 78.24% with SD \pm 7.705 and SEM \pm 0.027. The NIRS values for this group showed time at <60% was 1.4% of the time, 60%-80% was 50.75% and >80% was 47.9%. As expected, the difference of means between POX and NIRS (POX – NIRS) was 19.56% with the 95% confidence interval of 19.503 to 19.61. Cohen's correlation coefficient was 0.02 between the two variables Pulse Oximetry and Near-Infrared Spectroscopy. One-sided and two-sided p-tests values were 0.00.

For the group on oxygen, at the flow rate of 0.03 lpm the average time with POX <90% was 2.35%, with 90-96% was 15.52% and with > 96% was 82.13 %. Time for this group with NIRS values <60% were 0.01%, 60%-80% were 58.5% and > 80% were 41.5%. At oxygen flow rate of 0.06 lpm, the average time with POX <90% was 1.43%, 90-96% was 6.08% and > 96% was 92.49%. Time for this group with NIRS values <60% was 0.6%, 60%-80% was 65% and > 80% was 34.4%. At oxygen flow rate of 0.12 lpm, the average time with POX <90% was 1.46%, 90-96% was 11.54% and > 96% was 87.00%. Time for this flow rate with NIRS values <60% was 0.2%, 60%-80% was 64% and > 80% was 34.8%. Individually, we did not see POX desaturation events associate with NIRS desaturations.

CONCLUSION:

As expected, there is an approximate difference of 19.5% between the POX and NIRS values with POX being higher than NIRS in healthy infants. Individually, we could not find any correlation between POX and NIRS values for hypoxia events. On average, we did not see a dose response correlation between oxygen flow rate and time spent in the hyperoxemic range across different flow rates by POX or cerebral NIRS. While NIRS could play an important adjunct role in the NICU for brain oxygen saturation, NIRS data cannot serve as a stand-alone monitoring tool.

CHAPTER 1: REVIEW OF LITERATURE.

1.1: IMPACT OF PREMATURITY

In Canada, nearly 8% of all infants are born preterm before 37 weeks gestation (term=37-41 weeks) (1). Preterm infants are at higher risk of mortality and morbidity. The common morbidities include respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC) and nosocomial infections or sepsis (2-4). All these increase the risk of poor neurodevelopmental outcomes for these preterm infants (5). With advances in neonatal care, survival rates have increased for preterm infants, but we have also increased the number of infants with these co-morbidities.

Preterm infants develop respiratory distress syndrome (RDS) shortly after birth as their lungs have not developed fully as will be discussed below. Some of these infants that require mechanical ventilation and oxygen therapy after birth go on to develop bronchopulmonary dysplasia (BPD). BPD is a chronic lung disease that develops in preterm infants after suffering the effects of require mechanical ventilation and oxygen therapy after birth. BPD remains one of the most common causes of morbidity with incidence close to 40% in preterm infants \leq 28 weeks (6-7).

To understand respiratory distress syndrome and its progression to bronchopulmonary dysplasia, we need to understand the embryological stages of lung development, and fetal circulation.

1.1.1: UNDERSTANDING LUNG DEVELOPMENT:

There are five stages of lung development (figure 1) (8, 9).

- Embryonal stage between 0-7 weeks gestation.
- Pseudoglandular stage: from 7 weeks to 16 weeks gestation.
- Canalicular stage: From 16 – 25 weeks gestation
- Saccular stage: From 25- 36 weeks gestation
- Alveolar stage: From 36 weeks to 3-8 years after birth.

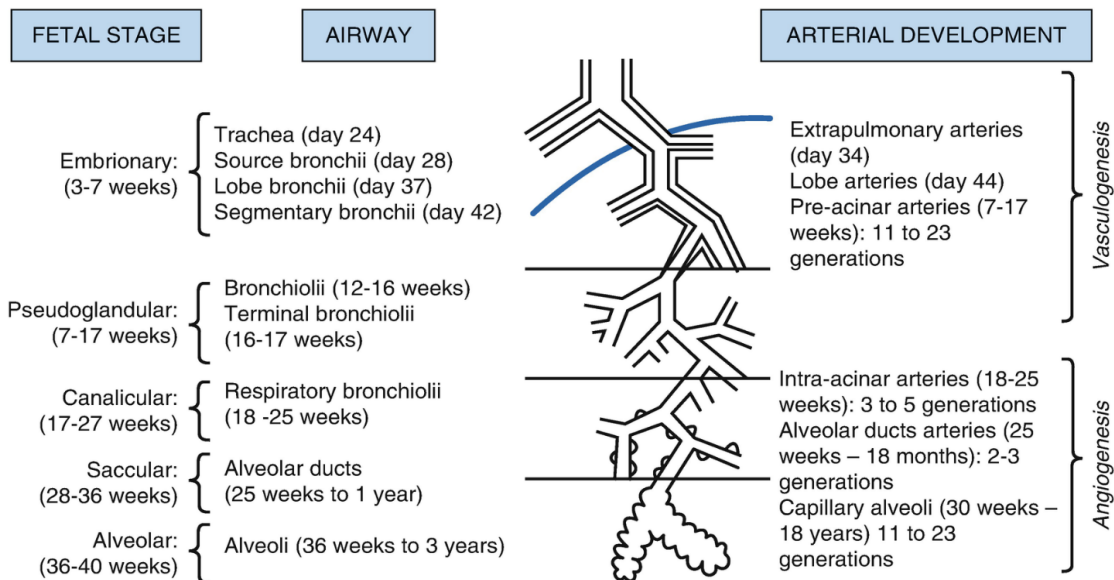


Figure 1: Stages of Lung Development (reprinted with permission)

Iñiguez Osmer, F., Sánchez, I. (2020). Development of the Respiratory System. In: Bertrand, P., Sánchez, I. (eds) Pediatric Respiratory Diseases. Springer, Cham. https://doi.org/10.1007/978-3-030-26961-6_2

Embryonal stage (first seven weeks of gestation):

Respiratory diverticulum arises from the ventral foregut endoderm and forms the primitive lung bud. The epithelium of the lung bud comes from foregut endoderm however the cartilage, smooth muscles, blood vessels and connective tissue are derived from the surrounding mesoderm.

By five weeks of gestation the lung buds branch and continue to grow into the surrounding mesenchyme. This is controlled by growth factors present in the mesenchyme. By the end of the embryonic phase there are development of five asymmetric bronchi for five lobes of the lungs. In addition, vascular inflow and outflow also begins to develop by the end of this stage.

Pseudo-glandular Phase (7-16 weeks gestation):

At the beginning of the pseudo glandular phase the airways are lined with cuboidal cells and surrounded by mesodermal mesenchymal cells. The differentiation of the airways continues to progress distally. By 10 weeks of gestation, cartilage and smooth muscle are formed. By 13 weeks of gestation the columnar ciliated epithelial cells, goblet cells and basal cells are present. By the end of this stage the conducting bronchial tree up to the terminal bronchi are established. The bronchopulmonary epithelium starts to produce amniotic fluid and type 2 pneumocytes precursors become evident. The pulmonary vasculature is developed in parallel with the differentiating airways. By the end of the pseudo glandular stage the primitive pulmonary vasculature is present.

Canalicular stage (week 16-25):

During this stage, functional unit of gas exchange, the lung acinus is formed which is composed of respiratory bronchioles and alveolar ducts. The adjacent vasculature which continues to differentiate, and the capillaries closely approximate with the acinus. Eventually the vascular and epithelial basement membranes begin to fuse and form an air-blood barrier for gas exchange. The primitive type 2 pneumocytes present at the end of the pseudo glandular stage begins to differentiate into type 1 pneumocytes. The type 2 pneumocytes begin to form lamellar bodies in the cytoplasm and surfactant synthesis begins at about 20

weeks. By the end of this stage the preterm lung has the potential to take part in gas exchange.

Saccular Stage (25 to 36 weeks):

During this stage terminal saccules, which are the branching alveolar ducts continue to differentiate. At the beginning of this stage the septa between the alveoli are thick. This continues to elongate and branch thus increasing the surface area. By 36 weeks all generations of the conducting and respiratory bronchioles are formed. Mature air-blood barrier is formed which contains type one pneumocytes, basal membranes of the epithelial cells and capillary and the capillary endothelium.

The Alveolar stage (36 weeks to approximately 3-8 years):

The septation of the alveolar sacs happens. Primary and secondary septation results in the formation of alveoli which is more efficient in gas exchange by increasing the surface area. There are approximately 50 million alveoli present at birth which increase to 500 million by adulthood.

1.1.2: UNDERSTANDING FETAL CIRCULATION:

The fetus lives in a physiological hypoxemic condition (10). Uterine arteries supply blood to the placenta. After oxygenating the walls of the uterus, the less oxygenated blood goes to the placenta where it mixes with the deoxygenated blood in the villi. From there the blood goes via the umbilical vein to the fetus. The average PO_2 in the umbilical vein is 27 mm Hg (16.5-40 mm Hg) with the saturation of 60% while the PO_2 in the umbilical artery is 15 mm Hg (6.2-27.6 mm Hg) with the saturation of 30%. Fetus can tolerate the relative hypoxemia due to:

1. The presence of hemoglobin F, which has an oxyhemoglobin curve shifted to the left allowing increased affinity for oxygen.
2. Increase hemoglobin concentration, further increasing the oxygen carrying capacity of the fetus.
3. The fetus has a unique circulatory system (discussed below).

Cardiovascular Adaptation in Fetal Life:

Fetal circulation has 4 major cardiovascular adaptations (see figure 2) with a goal to move relatively oxygen rich blood from the placenta to the brain (15):

1. Presence of Ductus Venosus (DV).
2. Foramen Ovale (FO)
3. Presence of Ductus Arteriosus (DA).
4. Right heart as the major side of blood flow.

1. Ductus Venosus (DV): The Ductus Venosus connects the umbilical veins to the inferior vena cava bypassing the portal circulation (11,15). Blood flows from the umbilical vein in the DV with a high velocity and has the highest oxygen concentration. Agenesis of the DV in fetal life may lead to demise of the fetus.

2. Foramen Ovale (FO): The FO is a flap-like connection between the right and the left atrium (12). The increased velocity of blood from the DV and lower pressures in the left atrium, keeps the flap-like foramen ovale open and the blood from the DV preferentially goes to the left atrium to supply the brain and upper part of the body. After birth, flow from the placenta is lost, and right sided pressures go down. After delivery more blood pressure comes into the left atrium through the pulmonary veins and the pressure in the left atrium

increases resulting in closure of foramen ovale. Patent Foramen Ovale is a very common neonatal finding and is of minimal clinical significance) (15).

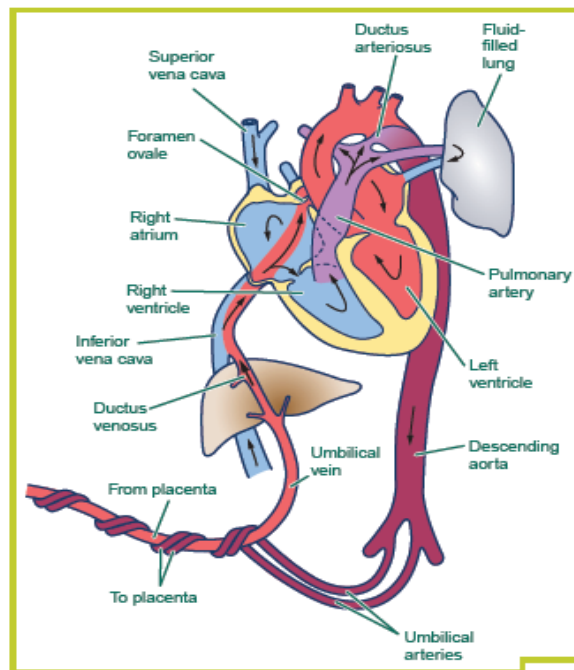
3. Ductus Arteriosus (DA): The lungs are filled with fluid during fetal life and do not take part in the gas exchange, which occurs totally by the placenta. The DA is a connection between the pulmonary artery and aorta (13-14). Most of the blood coming from the right ventricle to pulmonary artery is shunted via DA to the aorta as pressure in the right side of the heart is greater than the left side of the heart. This supplies blood to the lower part of the fetal body. Only 10-15% of the blood passes through the lungs and comes back through the pulmonary veins into the left atrium. The patency of DA is maintained by the prostaglandins which are mainly secreted from the placenta. After birth, the DA closes due to loss of prostaglandins from placenta. Drugs like indomethacin and ibuprofen given during pregnancy could result in premature closure of DA which can lead to persistent pulmonary hypertension in the neonate after birth. In addition, after birth especially in preterm infants, the DA may remain open, and causes left to right shunt. The resultant ductal steal from the hemodynamically significant PDA may result in pulmonary edema (due to increased pulmonary blood flow), intraventricular hemorrhage, necrotizing enterocolitis, and renal failure.

4. Right heart as the major side of blood flow in fetal life: Right sided chambers of the heart are the predominant chambers during the fetal life (15). Pressures in the right heart are greater than the left resulting in shunting of the blood from RA to LA through FO and pulmonary artery to aorta through DA (figure 2). Relatively oxygen rich blood from the

placenta goes to the umbilical vein and bypasses the portal circulation through the DV to the inferior vena cava (IVC) and then into the right atrium and through the patent FO it goes into the left atrium and finally to the left ventricle and aorta. So, the brain and upper part of the body

Figure 2: Fetal Circulation (reprinted with permission)

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 Edited by: Gary M. Weiner, MD,FAAP, Jeanette Zaichkin, RN,NNP-BC



receive oxygen rich blood. The blood from the superior vena cava comes to the right atrium, mixes with oxygenated blood, and goes to the right ventricle and to the pulmonary arteries. Most blood is shunted away from the lungs through the DA to the descending aorta where it mixes with the blood from the left side. This relatively oxygen poor blood supplies the lower part of the body. The deoxygenated blood is carried through umbilical arteries to the placenta thus making placenta as the major organ for gas exchange.

1.1.3: UNDERSTANDING LUNG GROWTH IN UTERO:

Lungs during the fetal life are filled with amniotic fluid and are not meant for gas exchange (16,17). They are predominantly a secretory organ. The fluid formed by the lungs keeps it distended and is required for the development of pulmonary architecture. Lack of fluid results in pulmonary hypoplasia. This fluid passes from the trachea through the glottis and enters the amniotic space making it part of the amniotic fluid.

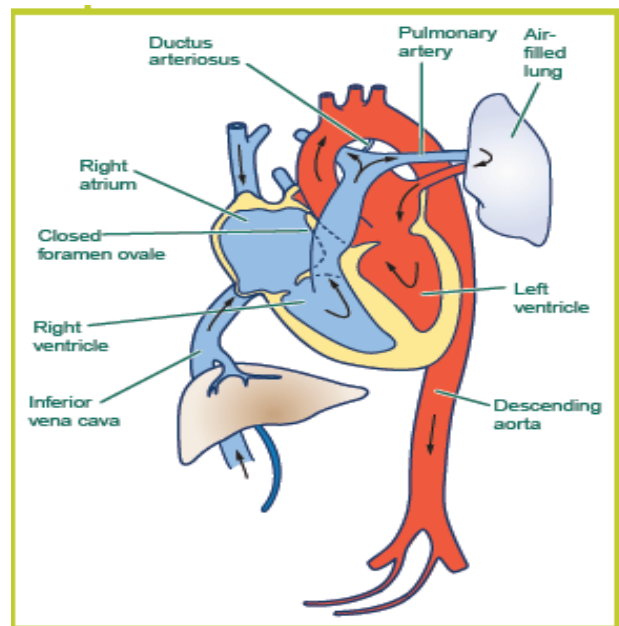
1.1.4: TRANSITION TO NEONATAL LIFE.

Transition is the period taken for a newborn to adapt to extra-uterine life and starts from moment of birth until physiological stability and generally takes 12 to 24 hours (20,21). Two major events that happen after the neonate is born is the clamping of umbilical cord and lungs taking over as the organs for ventilation.

Cardiovascular changes: Clamping the umbilical cord results in the separation of the low-pressure circulatory system from the placenta resulting in sudden increase of the systemic vascular resistance (SVR) (figure 3) (18-21). The increase in SVR results in reversal of shunts through the FO and DA. Increased pulmonary blood flow through the functioning lungs causes more blood

Figure 3: Transition to Neonatal circulation (reprinted with permission)

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to return from the pulmonary veins to the left atrium. This results in increased pressure of LA than RA thus closing the flap like foramen ovale. The muscular lumen of the DA constricts due to increased oxygenation and lack of prostaglandins from separation of the placenta. This results in physiologic closure of the DA by 24 hrs. of life. Final physical closure occurs in approximately 2 weeks when the DA becomes the ligamentum arteriosum (19). The pulmonary blood flow causes stress on the vessels and releases the nitric oxide which causes further dilatation and decreasing pulmonary pressures. The right sided pressure becomes half systemic within the first 24 hours of life and reaches the adult levels by two weeks. Lack of blood flowing through the DV results in its obliteration and is replaced by the ligamentum venosum. The umbilical vein is completely obliterated and is replaced by a fibrous cord called the ligamentum teres within a week of birth of the neonate. The proximal portions of the umbilical arteries become the internal iliac and superior vesical arteries, while the distal portions are obliterated and form the medial umbilical ligaments.

Lung Changes: Fetal lung fluid clearance starts even before the onset of labour and birth (figure 4). It happens in three stages (17, 22-25). Roughly a third of the fluid is cleared a couple of days before the onset of labour.

Fluid secretion from the lungs is decreased. The active secretion of chloride is decreased. There is activation of the Na/K ATPase which result in the sodium going out of the cell which

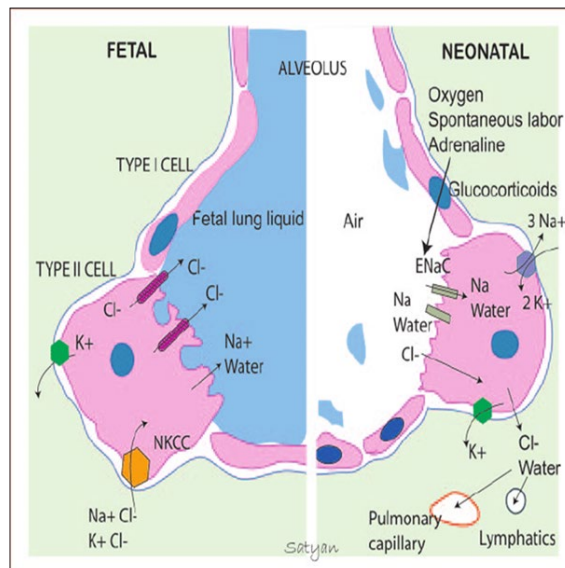


Figure 4 (26): Fetal/Neonatal Alveolar Changes (Reprinted with permission)

Guglani et al (2008). Transient Tachypnea of the Newborn. Pediatrics in review / AAP. 29. e59-65. 10.1542/pir.29-11-e59.

creates a gradient and sodium from the airspace pass it into the cell and chloride and the water follows. Increased secretion of cortisol and thyroid hormones also helps in sodium movement and absorption. Also, there is movement of the fluid from alveoli to the pulmonary lymphatics. With the onset of labour another one third of the fluid gets removed due to the mechanical compression of the vagina on the chest wall. Post delivery roughly a third of the fluid is removed (Figure 5). With the initiation of the first breath and expansion of the alveoli, fluid is pushed into the interstitium. Some of the fluid is taken up by the lymphatics. More surfactant is released thereby decreasing the surface tension in the alveoli and thus keeping the lung open and low pressures.

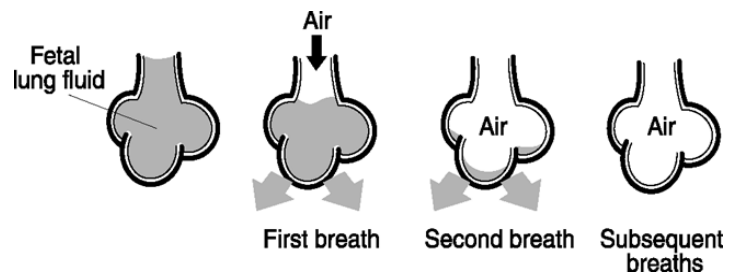


Figure 5: Air replaces fluid in alveoli.

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1.2: RESPIRATORY DISTRESS SYNDROME (RDS) IN THE PRETERMS

1.2.1: Introduction:

A critical factor in the development of BPD in preterm infants is the fact that the lungs at this stage of development are not quite ready for maintaining adequate ventilation and breathing. In addition to underdeveloped alveoli, they lack a key airway product called surfactant (described below), which prevents an infant from breathing normally. The clinical presentation is called respiratory distress syndrome (RDS), also known as hyaline membrane disease. Worldwide RDS is the major cause of mortality and morbidity in preterm infants (3). The incidence is inversely related to the birth weight and gestational age. The NICHD Neonatal Research Network reported that 44% of infants between 501 and 1500 g were noted to have RDS, including 71% between 501 and 750 g, 55% between 751 and 1000 g, 37% between 1001 and 1250 g, and 23% between 1251 and 1500 g (3). Other risk factors include maternal diabetes, hypoxia-ischemia, and male sex. These are the predominant underlying causes of RDS in infants with higher birth weight and gestational age (1,2).

1.2.2: Physiology of RDS:

The primary abnormality in the development of neonatal RDS is the lack of mature type 2 pneumocytes, which produce surfactant (6). According to the law of La Place's, the pressure (P) needed to keep the alveolus open is directly related to the surface tension (T) and inversely related to the radius (R) as shown by the formula:

$$P = 2T/R$$

To counteract this collapsing force (T), surfactant is needed. Surfactant is present in lungs of all mammalian species. Its main function is to lower surface tension (T) at the air-liquid interface and thus prevent alveolar collapse at end-expiration.

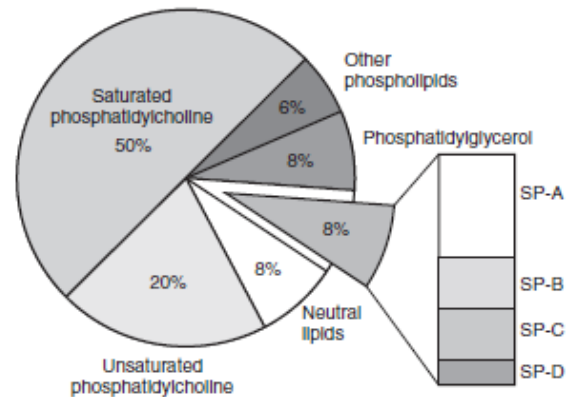
1.2.3: Understanding Surfactant in RDS (4-6):

Composition of Surfactant:

Healthy term infant surfactant contains 70% to 80% phospholipids, about 10% proteins, and about 10% neutral lipids, primarily cholesterol (figure 6).

Figure 6: Composition of Surfactant:
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Surfactant in preterm infants: Preterm

infants lack not only the amount of

surfactant, but also some features in composition. Phospholipids present in surfactants in preterm infants contain relatively large amounts of phosphatidylinositol (10% vs 2%), as compared to phosphatidylglycerol (PG). The PG content increases after 35 weeks' gestation and is considered a marker for lung maturity. The protein content of surfactant from preterm lungs is also low. The expression of the four surfactant proteins varies with gestational age.

Additional factors affecting surfactant production: The following antenatal conditions are associated with decreased surfactant production, delayed lung maturation and RDS.

- Maternal Diabetes.
- Rh isoimmunisation

- Male sex/Androgens
- Caesarian section
- Insulin

1.2.4: Ventilator trauma and inflammation in RDS:

Most extreme (< 28-week gestation at birth) and very preterm (< 32 week gestation at birth) infants require some mechanical ventilation with peak inspiratory pressure (PIP), volume guarantee (VG) and peak end expiratory pressure (PEEP) to open and maintain alveolar opening in the context of decreased surfactant function. This is not normal, and is a stress on the developing lung (2,6,11–13). Mechanical ventilation can cause barotrauma (pressure damage), atelect-trauma (trauma due to collapsing and opening alveoli) and volutrauma (volume stretching damage). This damages the alveolar epithelial lining further, which causes additional reduction in surfactant formation and secretion, aggravating RDS (13). In addition, the damage triggers the release of pro-inflammatory cytokines and chemokines. In addition to the physical stress of MV, these infants will require some supplemental oxygen in the early stages of treatment to avoid hypoxic injury to the body's organs (i.e., brain, kidneys). Oxygen delivery leads to risk of oxygen free radical or reactive oxygen species (ROS) production, which is discussed late in section 1.4(6).

1.2.5: Pulmonary edema and RDS:

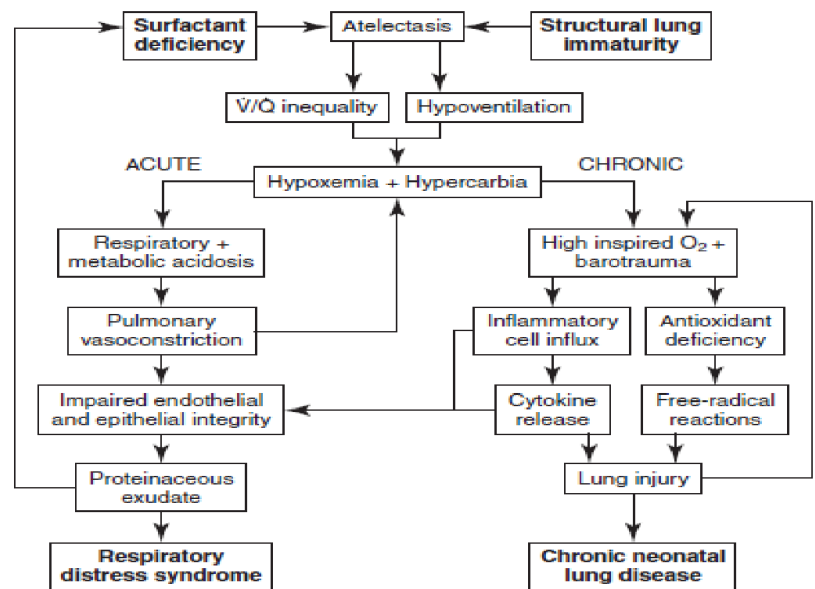
Preterm infants are also at increased risk of pulmonary edema (7–10). In the preterm infants the ENaC channels are not fully developed, which impairs fluid resorption from the alveoli. If a preterm infant is delivered by C-section delivery, this deprives them of the mechanical compression of the fluid out of the lungs and alveolar collapse also reduces the absorption of fluid by lymphatics. Finally, the reduced urine output can occur in the first few days in the

preterm infants due to the immature kidneys results in fluid retention and further aggravates the risk of pulmonary edema. Infants recovering from RDS typically have a spontaneous diuresis on the second to fourth day, followed by improved pulmonary function.

1.2.6: Pathophysiology and clinical course of RDS:

The atelectatic portion of the lungs does not take part in the gas exchange and this results in ventilation perfusion mismatch resulting in hypoxemia and hypercarbia (1,3,4,6,12). In those with the need to use mechanical ventilation, especially at higher pressure with high oxygen levels, a cascade of events progressively increases the severity of disease over several days (figure 7).

Figure 7: Pathophysiology of RDS
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The natural course of the disease if left untreated is progressive worsening over the ensuing few days, with development of hypoxia, lactic acidosis, hypercarbia, respiratory acidosis, and ultimately respiratory failure. Combined respiratory and metabolic acidosis complicates the picture causing cardiac dysfunction, hypotension, and worsening acidosis due to poor perfusion of the tissues. If condition is not treated and reversed, death can occur. In milder

forms spontaneous improvement may occur in 2-3 days owing to the diuresis and release of edema fluid.

1.2.7: Clinical Manifestations of RDS:

Overall, the surface tension in the alveolus remains high in these infants and the alveolar volume remains small (i.e., the radius is low). It is hard for an infant to open these alveoli at end expiration (1,6,12). If this increased pressure cannot be generated, the alveolus collapses, which is called atelectasis. In RDS, the lack of open alveoli causes low lung volumes (called tidal volumes TV) and an inability to move air. Ventilation (V_{min}) is required to inhale oxygen while removing carbon dioxide.

$$V_{\text{min}} = TV * RR.$$

Tachypnea: To compensate for low TV, preterm infants with RDS must develop tachypnea (RR) to maintain their minute ventilation (V_{min}).

Expiratory Grunting: To increase pressure and reopen these alveoli, infants exhale through a partially closed glottis, causing noisy expiration called grunting. Grunting helps prevent atelectasis by maintaining the peak end expiratory pressure (PEEP) and prevent open alveoli from collapsing.

Nasal flaring: Poiseuille's law states that airway resistance is inverse to the radius⁴. Infants try to increase the radius of the nose with nasal flaring to reduce the resistance and increase flow to the lower airways.

Intercostal, subxiphoid, and subcostal retractions: Newborn infants are born with softer bone and highly compliant rib cage. In these infants trying to inhale strongly, the rib cage cannot resist the negative pressures, and is drawn in during inspiration thus causing the appearance of retractions.

Cyanosis: Lack of airflow and oxygen in the alveoli result in the infant appearing blue in color (cyanosis). In addition to the lungs, circulation issues of right to left shunting (discussed in chapter 1.2) can occur (i.e., patent ductus arteriosus), which will exacerbate cyanosis and work of breathing.

1.2.8: Diagnosis and differential diagnosis of RDS:

The diagnosis of RDS is mainly clinical, aided by typical chest X-ray or Lung Ultrasound (16,17). The distinct features of a chest XR in RDS include small lung volumes and air bronchograms (visible black air-filled airways amidst white fluid filled alveoli) (figure 8). If all the lung alveoli are fluid filled a diffuse granular-looking area develops throughout the lung. In severe cases, the lungs may appear as a totally white out with prominent air bronchograms, obscuring the cardiac silhouette on the XR.

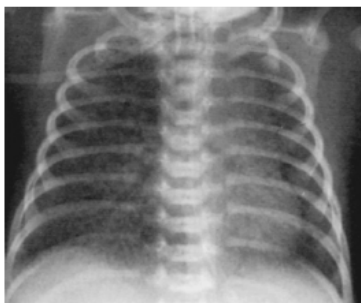


Figure 8-A: Mild RDS



Figure 8-B: Severe RDS with ground glass opacities

Figure 8: X-Rays of different stages of RDS (Reprinted with permission)

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Arterial blood gases show hypoxemia and initially low to normal pCO₂. Later higher pCO₂ develops as the disease worsens. pH usually is low owing to mixed metabolic and respiratory acidosis (18). Lactate increases with the worsening disease and bicarbonate levels are low due to increased losses by the immature kidneys. Serum sodium initially is low due to dilutional effect as the urine output is reduced in the first few days. Meticulous attention to the fluid balance corrects the problem. The sodium normally corrects itself once the baby starts to pass urine.

Differential Diagnosis:

There is other potential cause of increased work of breathing like RDS which doctors consider. These include:

- Transitory tachypnea of newborn. Normally seen in more mature infants and with C-section babies. Milder distress with rapid improvement.
- Bacterial pneumonia: especially Group B streptococcus is often difficult to differentiate from RDS as the radiographic features are similar in both the diseases. This is the reason antibiotics are commonly prescribed in preterm neonates with RDS.
- Persistent Pulmonary hypertension. A common cause of cyanosis in the neonates. Echocardiogram reveals elevated right sided pressures.
- Congenital cyanotic heart disease: Echocardiography confirms the diagnosis.

1.2.9: Prevention and Treatment of RDS:

Specific interventions are available to prevent or decrease the severity of RDS (18). These include.

- Antenatal corticosteroids
- Provision of exogenous surfactant
- Mechanical Ventilation
- Meticulous attention to fluid, electrolyte, and acid base balance.

Antenatal Steroids: There is ample evidence that antenatal corticosteroids increase the maturation of the fetal lungs by hastening the development of type 1 and type 2 pneumocytes. Increased maturity of type 2 pneumocytes results in increased production of surfactant proteins and phospholipids (19–23). Other noteworthy effects include upregulation of ENaC receptors helping in fluid resorption and decreasing pulmonary edema

and induction of pulmonary beta receptors which also help in surfactant synthesis and fluid absorption. Antenatal steroids should be given to all pregnant women after 23-24 weeks of gestation who are at risk of delivering a preterm baby within the next 7 days. The Cochrane meta-analysis (42) for the use of antenatal steroids revealed that it not only decreases the incidence of RDS but also decreases the incidence of necrotising enterocolitis, Intraventricular hemorrhage, neonatal mortality, and early onset sepsis.

Provision of exogenous surfactant: Commercially available surfactant preparation includes both natural and artificial surfactants (35–38). These products are instilled into the infant airway shortly after birth. Natural surfactants are shown to be superior in efficacy compared to artificial surfactants that do not contain Protein B and Protein C. However, both animal-derived and newer synthetic surfactants with SP-B– like activity are efficacious in reducing the morbidity and mortality in preterm infants with RDS. The three commercially available products are: Poractant alfa (Porcine lung minced extract), Calfactant (Bovine lung lavage extract) and Beractant (Bovine lung minced extract).

Ventilation Strategies: Despite early use of surfactant therapy, mechanical ventilation with positive end expiratory pressure (PEEP) is needed to recruit and maintain the alveoli volumes (13,24–27). Such continuous positive airway pressure (CPAP) is acquired by placing a tube in the airway or by using a plastic cannula in the nose. Detailed explanation of these is beyond the scope of this paper.

Other Supportive Care: Optimal metabolic needs, cardiovascular status and nutritional requirement of the infant should also be taken care of beside the specific lung therapies (7,11,28,29). Care should be taken for:

- Thermoregulation: Preterm infants have immature skin, large surface area and inability to produce heat due to lack of Brown fat so they can develop rapid hypothermia which increases the mortality and morbidity.
- Fluid management: Provision of adequate fluid and electrolytes is complex in the preterm infants owing to immature kidneys. Frequent blood gas and electrolyte measurements may be needed to provide adequate replacement of different electrolytes.
- Acid Base status: RDS causes both metabolic and respiratory acidosis. Maintenance of normal acid base balance is critical in management of RDS.
- Hemodynamics: Hypotension can occur early during RDS which can be treated with the use of inotropes.
- PDA: Large, left to right, symptomatic and hemodynamically significant PDA can complicate the picture and should be treated with either ibuprofen or indomethacin.
- Nutrition: The provision of early nutrition is important in the overall care of preterm infants to cover for the caloric requirement for growth, thermoregulation and resting metabolic rate. Starting total parenteral nutrition to extreme low birth weight (<1500 grams) infants is pivotal to prevent the catabolic state in the first days of postnatal life.

1.2.10: Outcome:

With advances in healthcare, survival rates of preterm infants have improved, but long-term morbidities such as bronchopulmonary dysplasia, retinopathy of prematurity, and neurodevelopmental issues remain a major concern (39–41). Early detection and management of these chronic problems can result in better neurodevelopment outcomes.

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1.3: OXYGEN USE AND ITS POTENTIAL SIDE EFFECTS IN PRETERM INFANTS

An ability to maintain oxygen homeostasis is necessary to meet cellular energy requirements, and to avoid adverse short- and long-term outcomes. As such, supplemental oxygen is one of the most widely used therapies in the NICU. Adequate oxygen should be delivered in order to prevent cellular and organ dysfunction (1). However, it is important to recognize that both hypoxemia especially intermittent hypoxic episodes and hyperoxemia can be detrimental in the preterm population and its role in the neonatal mortality and morbidity is well recognized (1-2).

1.3.1: Hyperoxemia and its impact on preterm infants:

As discussed in early chapters, the fetus has unique circulatory and hematologic adaptations, which helps it to survive in a physiologic hypoxemic environment. Unfortunately, preterm birth and associated lung dysfunction results in the need for exposure to higher levels of oxygen (FiO_2) leading to oxidative stress. Unlike term infants, preterm infants lack the appropriate antioxidant protective mechanism at birth. For example, levels of superoxide dismutase are lower (3). This renders the infant susceptible to free oxygen radicals toxicity produced by the high oxygen delivery even for a short period (3-4).

Hyperoxemia in the preterm population with its complications has become an area of concern for decades. Increased oxygen in the blood is implicated in the pathogenesis of many complications associated within the preterm population including bronchopulmonary dysplasia (BPD) (11-12), poor neurodevelopmental outcomes (from intraventricular hemorrhage or periventricular leukomalacia), retinopathy of prematurity, and necrotizing enterocolitis (1,3). BPD will be discussed later in a separate section 1.4.

1.3.2: Hyperoxemia and Retinopathy of Prematurity (ROP):

ROP was first seen in preterm infants in the 1940s. It was called retrolental fibroplasia and was thought to be because of high oxygen given to preterm infants which helped to improve survival but caused blindness (5). ROP is characterized by neovascularization and in advanced stage by retinal detachment and visual loss. However, ROP usually resolves in most infants (80%). ROP is a 2-phase disease. In the first phase due to hyperoxia retinal growth factors are suppressed and there is arrested maturation of the retina. Later as the gestation advances the relative avascular retina causes hypoxemia and release of growth factors like VEGF (Vascular endothelial growth factor). The surge of VEGF results in formation of abnormal blood vessels (neovascularization). These blood vessels can result in retinal detachment and blindness. Retinal ablation with cryotherapy or LASER therapy is the standard of management in advanced cases (5-10).

In a study by Sears et al and Vander Veen et al low saturation targets of 85-92% showed a significant reduction in ROP in infants < 34 weeks gestation. However, the STOP ROP multicenter trial did not show any reduction in progression of severe disease by giving supplemental oxygen in infants with ROP (8-10). This is now the standard of care.

1.3.3: Hyperoxemia and Immature Brain:

The development of the human brain involves various stages of neuronal migration and proliferation (14-15). While many inciting agents like drug exposure, maternal stress, and use of steroids can cause injury to the developing brain, there is evidence from clinical and animal studies that oxidative stress and hyperoxemia can lead to malformed neuronal circuits and poor neurodevelopmental outcomes in preterm infants. With increased survival,

clinical efforts are focused on improved long term neurodevelopmental outcomes. However, a substantial number of infants have cortical grey matter loss and diffuse white matter injury with motor and cognitive delays. Giving supplemental oxygen to preterm after birth and lack of proper antioxidant protective mechanisms compounds the hyperoxemic insult. Exposure to these high oxygen levels can result in cystic or diffuse periventricular leukomalacia (PVL) (1,14).

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1.4: UNDERSTANDING BRONCHOPULMONARY DYSPLASIA

Preterm infants with RDS may have lung injury and repair after birth due to factors underlined in 1.2-1.3. This can result in a chronic lung disease called Bronchopulmonary dysplasia (BPD) (1–4). There is no unified definition of BPD. Different authors have used different definitions in the literature. The first description was by Northway and colleagues nearly 55 years ago in 1967 (1). It was based on radiological features. Shennan et al used requirement of oxygen at 36 weeks corrected age instead of 28 days therapy with oxygen as the criterion for BPD (5). In the National Institutes of Health (NIH) working group on BPD proposed a classification of BPD based on severity of illness (Table 1) (6). Walsh et al used

an oxygen reduction test at 36 weeks. They defined

Gestational Age	<32 wk	≥32 wk
Time point of assessment	36 wk PMA or discharge to home, whichever comes first	>28 d but <56 d postnatal age or discharge to home, whichever comes first
	Treatment with oxygen > 21% for at least 28 d plus	
Mild BPD	Breathing room air at 36 wk PMA or discharge, whichever comes first	Breathing room air by 56 d postnatal age or discharge, whichever comes first
Moderate BPD	Need * for <30% oxygen at 36 wk PMA or discharge, whichever comes first	Need * for <30% oxygen at 56 d postnatal age or discharge, whichever comes first
Severe BPD	Need * for ≥30% oxygen and/or positive pressure, (PPV or NCPAP) at 36 wk PMA or discharge, whichever comes first	Need * for ≥30% oxygen and/or positive pressure (PPV or NCPAP) at 56 d postnatal age or discharge, whichever comes first

BPD as infants who failed to maintain O₂ Saturation > 88% in room air (8). There is a need for the unified definition of BPD to get an exact idea of the burden of disease. However, for our study and project we have used NIH classification of BPD.

1.4.1: Incidence of BPD: The risk of BPD is inversely proportional to the gestational age. The incidence of BPD is 40%-60% of extreme preterm (< 28 week gestation at birth) and very preterm (< 32 week gestation at birth) and has remained relatively constant over the

years (1,6,9) due to advances in the medical management with regards to ventilation and lung protective strategies and increased survival rate of extreme/very preterm infants.

1.4.2: Pathogenesis of BPD: BPD had a multifactorial and complex pathogenesis. Many antenatal, natal, and postnatal insults to the preterm lungs along with some genetic influence causes arrest of maturation of the lungs as shown (figure 10)

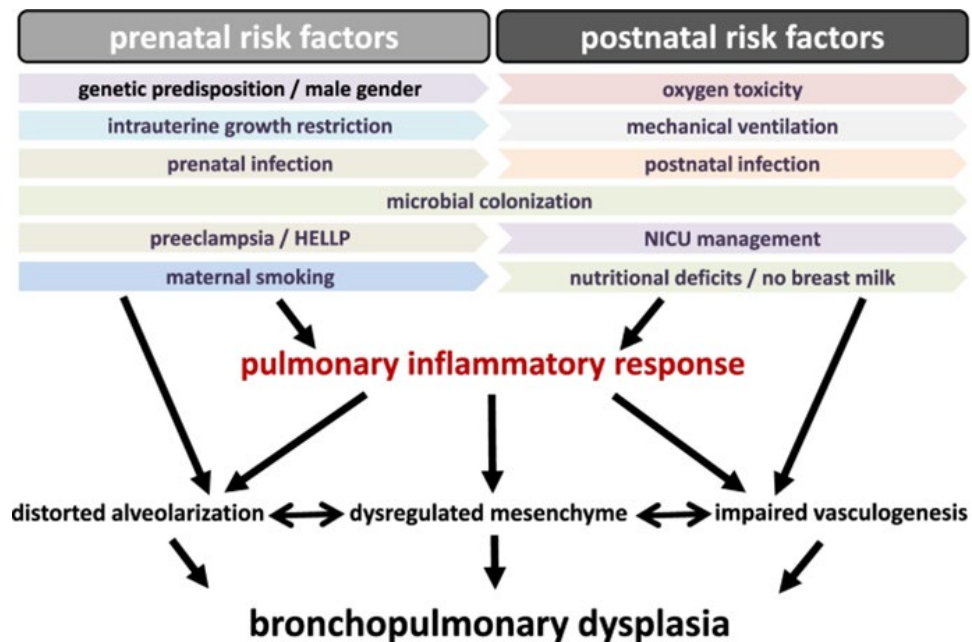


Figure 09: Pathogenesis of bronchopulmonary dysplasia (55)

Holzfurtner L et al. When inflammation meets lung development-an update on the pathogenesis of bronchopulmonary dysplasia. Mol Cell Pediatr. 2022 Apr 20;9(1):7. doi: 10.1186/s40348-022-00137-z.

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1.4.3: Risk Factors for BPD:

There include but are not limited to:

Prematurity and Low Birth weight: Prematurity and birth weight are inversely related to incidence of BPD. Lower the GA higher the incidence. According to data by Stoll et al there is 78 % chance of an infant to have BPD if born at 23/40 compared to 23% if the infant is

born at 28 weeks gestation (12). Similarly the lower the Birth weight the higher the chance to have BPD (7).

Genetic susceptibilities: Twin studies have revealed that genetic susceptibility may be a factor in developing moderate to severe BPD. Identical twins have more severe disease than non-identical twins. Several genes have been identified in the genome study that can be associated with BPD (13,14).

Chorioamnionitis: The role of chorioamnionitis in the evolution of BPD is still controversial. A meta-analysis by Watterberg et al showed some association between chorioamnionitis and BPD. Chorioamnionitis increases the likelihood of early onset sepsis in the newborn, which is a risk factor for development of BPD (15–17) .

Intrauterine growth restriction (IUGR): Studies by Reiss et al, Bose et al, and Erikson et al show that preterm infants who are small for gestational age and have intrauterine growth restriction have double the risk of developing BPD and neonatal mortality (18-20). (28% vs. 14%), (23% vs. 11%). This is due to the poor lung development due to lack of insulin like growth factor, vascular endothelial growth factor (VEGF) and VEGF receptor as seen in IUGR (1,18–20). Moreover, extreme preterm infants are more prone to postnatal growth restriction owing to the poor nutrition esp. in the first week of life. More enteral nutrition esp. breast milk rather than parenteral nutrition helps in preventing BPD (1).

Maternal Smoking: Population based, and animal studies have shown that mothers who smoke during pregnancy have a high rate of preterm delivery and increased risk of BPD in the infants. Exposure to pregnant rodents with nicotine or cigarette smoke results in changes in the lungs of their newborn like those seen in BPD in human infants (21–23). Cigarette smoke causes impaired fetal breathing and abnormal lung development. It causes placental

dysfunction. Altered metabolism of type 2 alveolar cells and epigenetic changes are also reported (22).

Male sex: Male gender is associated with increased incidence of BPD and death (24). It is suspected to be the result of smaller airway development of males versus females.

Quality and quantity of Mechanical Ventilation: Mechanical ventilation in the extreme preterm (< 28-week gestation at birth) and very preterm (< 32 week gestation at birth) after birth can result in ventilator induced lung injury (VILI). VILI can result from barotrauma, volutrauma, atelectrauma and biotrauma due to mechanical ventilation. Barotrauma is caused by increased airway pressure, volutrauma is caused by increased lung expansion, atelectrauma is due to the collapsing of the alveoli at end inspiration because of lack of adequate PEEP and biotrauma is the inflammatory response of the lungs due to barotrauma, volutrauma and atelectrauma (1,6,11). Details regarding VILI are beyond the scope of this paper.

Hyperoxemia: While the pathogenesis of BPD is multifactorial, hyperoxemia does damage the lungs causing bronchopulmonary dysplasia (BPD). The high oxygen is one of the principal factors causing formation of reactive oxygen species (ROS) which can directly harm the lung by inactivation of surfactant, damage to pulmonary epithelium, pulmonary edema, and later fibrosis (29-32). The recruitment of inflammatory cells in response to the ROS further adds insult to injury. In animal studies it is shown that giving high oxygen for a period result in recruitment of inflammatory cells like mast cells and eosinophils resulting in septal thickening of alveoli and reduced surface area, resulting in a picture like BPD seen in the preterm infants (56).

Infections: Postnatal infection/Sepsis increase the incidence of BPD by causing inflammation resulting in free radical induced endothelial injury (1,6,11,32).

Patent ductus arteriosus: Whether PDA is directly associated with increased incidence of BPD is still not clear as many studies have shown that closing the PDA medically or surgically does not decrease the incidence of BPD (34–36).

1.4.4: Prevention of BPD:

Varied approaches have been adopted to address the multifactorial pathogenesis of BPD. These include both medical and ventilation strategies and better nutritional resuscitation of the preterm infants.

Changes in approach of ventilation: Avoidance of intubation using non-invasive ventilation (NIV) with using nasal cannula to deliver CPAP have shown to reduce BPD (37–40). In addition, the least invasive surfactant administration techniques are also helpful as it prevents intubation. In some infants, NIV fails, and intubation is required. To reduce the incidence of barotrauma and volume trauma gentle ventilation strategy has been successfully initiated. Volume targeted ventilation has been seen as a successful ventilation approach reducing the incidence of BPD (43,44). High frequency jet and oscillation ventilation can reduce the incidence of BPD. However, the Cochrane meta-analysis shows a very minimal reduction in the incidence and does not recommend high frequency ventilation as a prophylactic management off RDS (41,42). Permissive hypercapnia is an approach which accepts higher CO₂ levels while still avoiding acidosis. This approach reduces the ventilator pressures required to keep the lungs open. The newer ventilation techniques

applying neurally adjusted ventilator assist device (NAVA) are showing promising results as it improves the patient ventilator synchrony (37).

Post Natal Steroids: Use of systemic glucocorticoids will reduce the incidence of BPD as it is suspected to decrease inflammation in the lungs and improves lung maturation (45–49). New data has shown prophylactic use of hydrocortisone in extreme preterm (<28 weeks GA) babies can reduce the incidence of BPD (48). However, glucocorticoids cause concern for long-term poor neuro developmental outcome. Currently, steroids are being used in a select group of patients to achieve early extubation and decreasing the respiratory support.

Caffeine: Use of caffeine reduces the incidence of BPD (50–52). This has been shown by a recently conducted randomized multicenter Caffeine for Apnea of Prematurity (CAP) trial (51). The exact mechanism by which caffeine reduces the BPD is not clear. Early extubation and reduced lung injury by minimising invasive ventilation may be the proposed mechanism.

Vitamin A: Mega doses of vitamin A help in reducing the incidence of BPD (53). Vitamin A helps in maintaining the integrity of respiratory epithelium and promotes Lung growth. To achieve effect Vitamin A must be given as intramuscular injection. A large trial is currently underway to see the effects of oral vitamin A.

Nutrition: Several observational studies have shown BPD infants have poor growth as compared to non-BPD preterm infants (54). Improving growth by providing adequate proteins and calories helps in promoting lung growth. Adequate nutrition should be provided not only in NICU but also after discharge of the infant from NICU.

1.4.5: Summary:

BPD is a chronic lung disease seen in the preterm infants due to different inciting events causing injury and repair cascade to the preterm lungs. There is a need of unified definition of BPD to understand its burden. Due to the advances in medical sciences more extreme preterm infants are surviving to discharge from NICU thus keeping the incidence of BPD constant. The pathogenesis of BPD is multifactorial and can be prevented by improving ventilation strategies, better nutrition, early extubation, use of NIV/CPAP, use of steroids and caffeine.

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1.5: IMPAIRED CONTROL OF BREATHING AND EFFECTS OF INTERMITTENT HYPOXEMIA IN PRETERM INFANTS.

In addition to the effects of premature lung disease, preterm infants have additional risk for low oxygen and higher CO₂ levels due to impaired control of breathing (i.e., apneas) and increased vagal nerve activity with low heart rate (i.e. bradycardias) (8-9). Apnea is a cessation of airflow. Impaired neurologic drive to breath is called a central apnea (i.e., ≥15 seconds in duration). Impaired airflow from obstruction is called an obstructive apnea. These preterm infants are also at increased risk of both apneas with resultant oxygen desaturation. The pause of breathing may also be associated with bradycardia (<100 beats per minute), cyanosis, or pallor. These apneas can lead to intermittent hypoxic events (IHE). Data from animal models showing that that intermittent hypoxic episodes (IHE) during early life can lead to autonomic dysfunction resulting in hypertension. In rats, IHE in the neonatal period resulted in increased responses from the carotid body and augmented blood levels of catecholamine (5).

Randomized controlled trials and meta-analysis of trials in human preterm infants demonstrated increased mortality among infants assigned to lower oxygen saturations (SpO₂) range (3-4). The post hoc analysis of the participants in the COT (Canadian Oxygen Trial) trial performed by Poets et al reviewed the relationship between intermittent hypoxic events or bradycardia on late death or disability at a corrected age of 18 months. The risk of mortality, severe retinopathy of prematurity, neurodevelopmental delay, language delay and poor cognitive outcome was increased (6). Tatiana et al (7) in a recent review article discussed the harmful effects of intermittent hypoxia in infancy and childhood. These include.

- Sleep-disordered breathing with activation of sympathetic nervous system and inflammatory cascade resulting in augmented risk of end organ damage and dysfunction e.g., augmented endothelial dysfunction and atherogenesis (7,8,9).
- Severe retinopathy of prematurity.
- Changes in sympathetic-vagal balance of cardiovascular regulation resulting in lack of physiologic response to stress such as increasing heart rate and blood pressure.
- Impaired neurodevelopment outcome and poor weight gain as shown in animal models.
- Possible bronchopulmonary dysplasia.

1.5.1: Intermittent Hypoxemia and Epigenetics:

Experimental studies in rats have revealed that adult rats that were exposed to intermittent hypoxia as neonates showed increased responses from the carotid body and augmented levels of catecholamines in their blood. This effect was attributed to the epigenetic mechanism of DNA methylation. One of the results of DNA methylation is decreased release of superoxide dismutase, an antioxidant enzyme due to the decrease in expression of *Sod2* gene(10). Antioxidant enzymes like superoxide dismutase are important scavengers for the reactive oxygen species (11).

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1.6: MONITORING OXYGENATION IN PRETERM INFANTS

1.6.1 PULSE OXIMETRY (POX):

Based on our understanding of hypoxia and hyperoxia in neonatal mortality and morbidity, there is a widespread use of pulse oximetry in the delivery room settings and the Neonatal Intensive Care Units (NICU) with the aim of regulating the use of oxygen (1). Measuring Oxygen saturation has become one of the vital signs in the management of neonates in the Neonatal Intensive Care Units.

Principle of Pulse Oximetry:

Pulse oximetry is based on the principle of the Beer Lambert Law. This law states that “The quantity of light adsorbed by a substance dissolved in a non-absorbing solvent is directly proportional to the concentration of the substance and the path length of the light through the solution”. This principle is being utilized in co-oximeters for blood gas analysis (1, 2).

Pulse oximeters make use of complex microprocessors to analyze ratios of different wavelengths of light adsorbed by the oxygenated and deoxygenated blood (figure 10). The oxygenated blood absorbs light in the

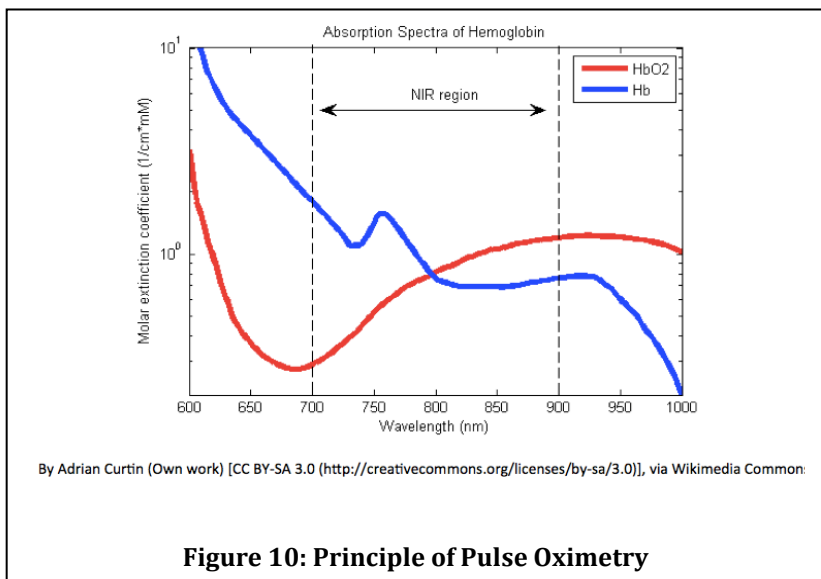


Figure 10: Principle of Pulse Oximetry

wavelength of 660nm (red spectrum) and de-oxygenated blood absorbs light at 910-940 nm (infra-red spectrum). The Light emitting diodes in the pulse oximeter send 2 light signals in the red and infra-red spectra. These lights pass through the tissues and are collected by the

photodetector placed opposite to the LED. The different assimilation of the light wavelengths is used by the pulse oximeters to compute the relative concentrations of oxy and de-oxy hemoglobin and compare it with the reference values (1–6). The technology of pulse oximetry has advanced a lot since the first pulse oximeter designed by Karl Mathes in 1935 (3, 7). The newer generation pulse oximeter can detect the pulsatility of the blood flow and can give readings which are very close to arterial oxygen saturation. Arterial saturation is called SaO₂, and saturation measured by the pulse ox is called SpO₂. Apart from SpO₂ the newer models can also reliably detect the heart rate which is of particular importance in the delivery room settings (3, 8–10).

The pulse oximetry for our study will be done by using a monitor manufactured by Circadiance. It has a 2 channel pneumographic capability and using the Synergy-E event software gives detailed information with regards to infant’s heart rate, respiration, oxygen saturations and graphical displays helping to identify apneas or bradycardias and accurately record potential life-threatening events (Fig 11) . It is integrated with Massimo technology for accurate oxygen saturation monitoring with an averaging time of as low as 3 sec.



Figure 11: Synergy-E Software screenshot

Limitations of Pulse oximetry: It is a very safe monitoring tool and has no contraindication to its use. However, there are some limitations to its use, and one should be familiar with those.

1. The Pulse Ox probe should be placed on the right upper limb in newborn infants as the ductus arteriosus is still patent and mixing of blood in the post ductal areas can give low saturation readings (1).
2. The probe should be placed in a way that the LED and the photodetector are opposite to each other to capture maximum light coming out of the tissues (6, 11).
3. Continuous movement and shivering can give erroneous readings. Always look at a stable waveform to see whether the reading is reliable or not (9).
4. Bright light can affect the readings. It is a common practice to cover the neonates' probe to have least interference from the light in the room (2, 8, 12).
5. Presence of carboxy-hemoglobin (can give high saturation readings and false sense of security even if there is hypoxemia) and Met-hemoglobin (can give high or low saturation readings) can affect the readings. Some of the newer generation pulse oximeters can detect the concentration of these hemoglobin (2).
6. Fetal hemoglobin has increased affinity for oxygen and shifts the oxygen dissociation curve to the left. Fetal hemoglobin is the predominant hemoglobin at birth in neonates. However, its impact on the readings of pulse oximetry is still obscure.
7. Long term use in the same site can give rise to areas of local necrosis and burns in extreme preterm neonates (2, 8, 9, 12).

1.6.2: NEAR INFRARED SPECTROSCOPY (NIRS):

As discussed, hyperoxia, hypoxia, and fluctuations in cerebral oxygenation adversely affect brain development. Blood Pressure (BP), Heart Rate (HR) and Oxygen Saturation (SpO₂) are important to assess the condition of the neonate but do not directly assess brain oxygenation as cerebral oxygenation is not always reflected by systemic arterial oxygenation (13,14).

Currently there are no monitoring strategies employed to assess regional blood oxygenation especially to the brain. Such monitoring is largely dependent on inferring measurements from systemic arterial oxygenation and mean arterial blood pressure (MABP).

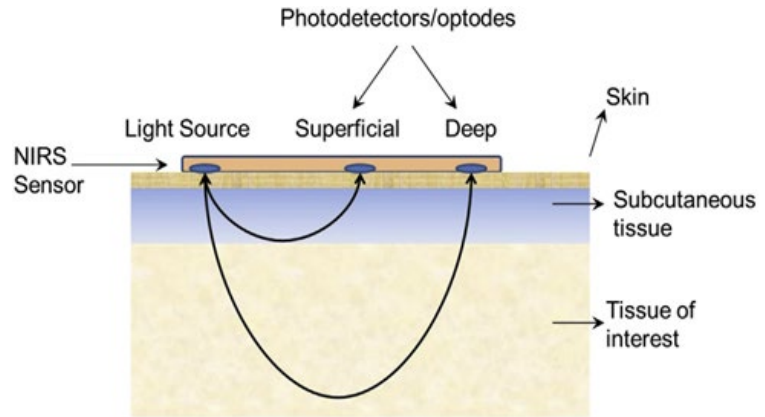
The potential for NIRS in preterm infants:

Near-infrared spectroscopy (NIRS) is a possible method to indirectly measure brain perfusion and oxygenation, as the presence of thin layers of skin and skull allow good penetration of NIR light to the neonatal brain tissue. Cerebral NIRS can be employed for the continuous measurement of cerebral oxygenation. Cerebral oxygenation is used as a substitute for cerebral blood flow, thus NIRS can potentially assess the integrity of cerebral circulation. (13,14, 15, 16). Continuous monitoring of brain oxygenation and cerebral blood flow can help in reducing cerebral injury and improving the neurodevelopmental outcome in preterm infants (17).

How Does NIRS Work.

NIRS probe has a light emitting diode (LED) which gives off NIR light of two wavelengths (730 and 810 nm), in a semi curvilinear shape. It has 2 detectors. The detector close to the LED receives a signal from the peripheral tissue and the detector away from the LED receives a signal from both the peripheral and deep tissues (figure 13).

Differences in NIR light adsorption are used to calculate the concentrations of Oxy (O₂Hb) and de-oxy (HHb) hemoglobin concentration using the modified law of Lambert–Beer. The ratio between O₂Hb and HHb is expressed as the RcSO₂. As the



**Figure 12: Principle of NIRS
(Reprinted with permission)**

Sood BG et al, Near-infrared spectroscopy: applications in neonates. *Semin Fetal Neonatal Med.* 2015 Jun;20(3):164-72. Epub 2015 Apr 29. PMID: 2593411

tissue microcirculation contains arterial, venous, and capillary components, RcSO₂ is an average value with approximately 75-85% of the signal originating from venules. Thus, NIRS reflects mainly cerebral venous oxygen saturation (13, 18).

Quantity of Oxygen used by the brain tissue can then be calculated from regional (cerebral) oxygen saturation (RcSO₂) and arterial oxygen saturation (SO₂) by using the formula:

$$[FTOE = (SO_2 - RcSO_2) / SO_2].$$

Where FTOE stands for fractional tissue oxygen extraction.

FTOE is a measure for the quantity of oxygen removed by the tissue and emulates the equilibrium between oxygen supply and oxygen demand/utilization. (19–21)

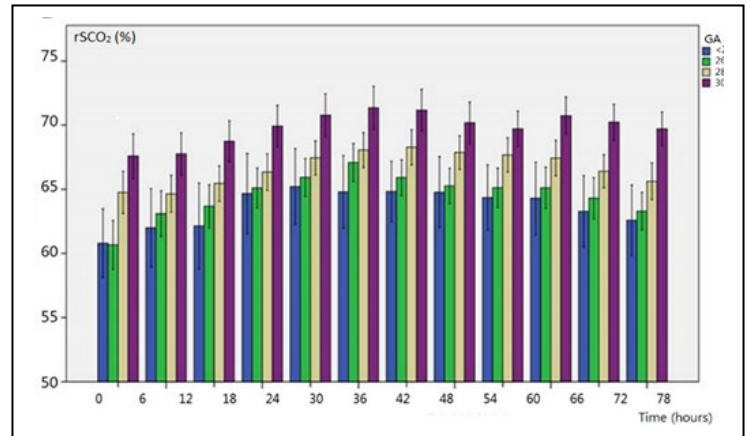
Reference Values in Neonates: RcSO₂ is between approximately 40% and 56% directly after birth (irrespective of delivery mode) and increases up to 78% in the first 2 days after birth and then slowly stabilizes during 3–6 weeks after birth with values between 55% and 85%

(21-23). A recent study by Alderliesten et al. provides reference values based on a large study cohort during the first 72 hours of life in preterm infants. [<32 weeks gestational age (GA); $n = 999$]. The data is converted into reference curves stratified for different GAs which can be used for bed side interpretation (22, 23).

Figure 13:
Reference NIRS values in Neonates. (29)

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Benefits of NIRS:

- NIRS is a non-invasive way to monitor brain oxygenation (16, 18, 24–27).
 - R_cSO₂ monitoring can be used at bedside for extended periods of time (up to several days) without side effects.
 - Other Modalities like cranial ultrasound or MRI do not allow for continuous monitoring.
 - NIRS can be used even in the sickest infants.
 - The device can be used at bedside in the NICU as well as during surgery or transportation.
 - NIRS can easily be combined with monitoring of cerebral electrical activity by a-EEG.

Potential Uses of NIRS in Preterm Infants:

PDA and NIRS:

The management of hemodynamically significant PDA remains a controversial topic to-date. Ductal steal causes shunting of the blood through the ductus away from the brain and other tissues to lungs resulting in decreased regional oxygen saturation (13, 16, 28). This effect is

independent from SaO_2 , which remains within normal limits during a PDA. It has been proposed that monitoring of $RcSO_2$ may prompt early diagnosis and treatment of HsPDA, potentially reducing damage to the vulnerable preterm brain (28).

NIRS for the management of ventilation:

Cerebral Blood Flow is significantly correlated with the type of respiratory support and CO_2 concentration in the blood (13, 15, 16, 26). Hypercapnia induces cerebral vasodilatation while hypocapnia induces cerebral vasoconstriction. The pCO_2 - induced changes in cerebral

perfusion and oxygenation can be monitored by NIRS (figure 14). For example, despite no change in POX or MABP (blue line and red line), hypocapnia which is measured by $etCO_2$ (purple line) induces vasoconstriction and low oxygenation in brain, which is shown by the NIRS data (green

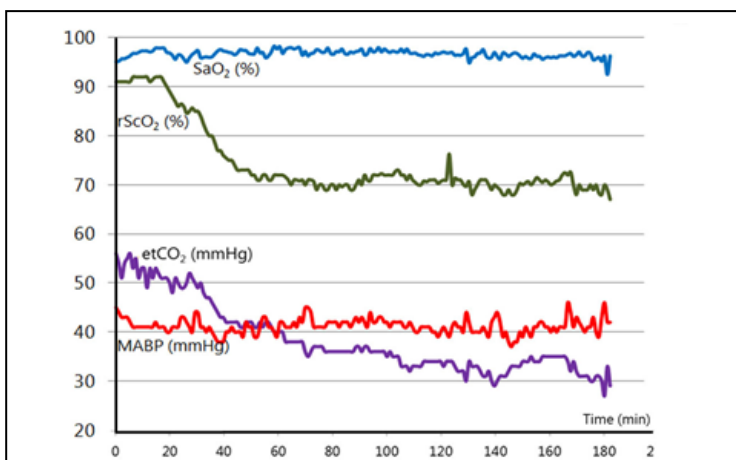


Figure 14: End-tidal CO_2 ($etCO_2$) and SaO_2 vs NIRS. (29)
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line). This can alert the team that the preterm infant is over-ventilated and the settings on the ventilator need to be weaned. Thus, NIRS monitoring can help in improving ventilator management.

NIRS and Blood Pressure in Neonates:

Current definitions of *hypotension of prematurity* do not always reflect true hypotension. Use of inotropes to treat possible hypotension have been linked to increased incidence of intraventricular hemorrhage. As such, permissive hypotension is becoming increasingly

accepted unless there are signs of hypoperfusion like low urine output and increasing lactate in the blood (13, 16, 24, 29). Cerebral oxygenation along with blood gasses, urine production, and capillary refill can help making decisions about treatment for hypotension. Identifying small reductions in blood pressure that do not affect cerebral oxygenation, and systemic perfusion might prevent unnecessary treatment with inotropes in neonates (30). NIRS could monitor cerebral oxygenation.

NIRS and Cerebral Autoregulation:

Cerebral Autoregulation is the ability of the brain to maintain perfusion and oxygenation in response to different stresses impaired autoregulation has been associated with poor neurodevelopmental outcomes. Preterm infants have impaired cerebral autoregulation due to lack of blood brain barrier. Fluctuations in blood pressure can lead to cerebral hypoxia and brain injury. High dose inotropes use, RDS, and surgery can also result in impaired autoregulation. Arterial BP monitoring with cerebral NIRS can help in monitoring the cerebral autoregulation (13, 26, 29, 30).

NIRS and PRBC transfusion:

Studies have shown that there is a significant increase in cerebral oxygenation after red blood cell transfusions in anemic infants. High cFTOE levels (>0.4) indicate an imbalance between cerebral oxygen supply and demand which indicates the need for red blood cell transfusion. Cerebral oxygenation monitoring by NIRS might be useful as a marker to identify infants who might benefit from blood transfusion. This may prevent neonates from unnecessary exposure to transfusion and its complications (13, 16, 24, 26, 29, 31).

NIRS and Neurodevelopmental outcome: Disturbances in cerebral perfusion and oxygenation increase the risk of impaired neurodevelopmental outcomes. Several studies, in

newborn animals and humans, showed that $RcSO_2$ values consistently below 40% are related to brain damage (13, 16, 26, 29, 32–35). Other clinical studies showed that low cerebral oxygen saturation immediately after birth (<15 min) is associated with Peri/intraventricular hemorrhage (PIVH) (19). Low cerebral oxygenation during the first 48 hours after birth was associated with death or severe PIVH in a study by Cerbo et al. The SafeboosC study (Safeguarding the brains of our smallest children) (32, 33), has investigated whether it is possible to reduce the hypoxic and/or hyperoxic burden on the immature brain with cerebral oxygenation monitoring to prevent neurological damage and to improve outcome. The study has shown that disturbances in cerebral oxygenation could be identified with NIRS. A treatment protocol steps to restore normal brain oxygenation. The burden of hypoxia (and hyperoxia), as expressed by the percentage of time spend outside the normal range of $RcSO_2$ (55–85%), was significantly lower in the group with (visible) NIRS monitoring as compared to the blinded control group (median 36.1% vs. 81.3%). This difference was mainly due to a reduction in hypoxic episodes.

NIRS use in Hypoxic Ischemic Encephalopathy (HIE):

Several studies have shown that NIRS can be used as a prognostic tool in the management of severe HIE babies (36–41). High cerebral oxygenation and low fractional tissue oxygen extraction as measured by NIRS combined with abnormal aEEG findings has been associated with poor neurodevelopmental outcome (39–41).

Limitation of NIRS:

- Hair or dark skin can interfere with the readings.
- Phototherapy and other bright lights can affect the readings.

- Edema or fluid collection under the sensor can affect measurements.
- Shape of the head can affect the placement of the probe.
- A-EEG monitoring can hamper the placement of NIRS probes. (42, 43).

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CHAPTER 2:

DETERMINING OPTIMAL HOME OXYGEN FLOW RATE FOR INFANTS WITH BRONCHOPULMONARY DYSPLASIA (BPD)

2.1: BACKGROUND:

In Canada, nearly 8% of all infants are born preterm; ≤ 37 weeks gestation (1). Preterm are further classified according to gestational age as late preterm (GA 34-37 weeks at birth), moderate preterm (GA 32-34 weeks at birth), very preterm infants (GA 28-32 weeks at birth) and extreme preterm infants (GA ≤ 28 weeks at birth). With advances in neonatal care, survival rates have increased for extreme preterm infants, but with this success come co-morbidities (4). One of the most common co-morbidities is bronchopulmonary dysplasia (BPD). BPD remains one of the most common causes of morbidity with incidence close to 40% in preterm infants ≤ 28 weeks gestation. BPD is a chronic lung disease of very and extreme preterm infants who required oxygen therapy for at least 28 days after birth, and then still require oxygen at the time of discharge or corrected gestational age of 36 weeks (2, 6, 7).

For infants going home on supplemental oxygen, both hypoxia and hyperoxia can be detrimental in the preterm population (8-9). A “normal” oxygen saturation level for the preterm infant can be difficult to define. The post hoc analysis of the participants in the COT trial (Canadian Oxygen Trial) showed that intermittent hypoxic events or bradycardia increased the risk of mortality, neurodevelopmental delay, language delay and poor cognitive outcome at a corrected age of 18 months (10). In contrast, hyperoxemia in the

preterm population leads to free radical productions, which are implicated in the pathogenesis of many complications associated within the preterm population (11-12).

Given the role that hypoxemia and hyperoxemia play in neonatal mortality and morbidity, there is a need for measurement and regulation of oxygen delivery in the NICU (13). Bed side registered nurses are responsible for titrating inhaled oxygen based on the targeted oxygen saturation according to the unit policy. Successful maintenance of targeted oxygen saturation varies widely. There is limited data in the literature, which addresses the question about the percentage of the time that these preterm infants remain within the targeted oxygen saturation limits as set by the unit policy and its impact on neonatal morbidity and long-term outcome. Continuous monitoring of brain oxygenation and cerebral blood flow could help in reducing cerebral injury and improving the neurodevelopmental outcome in preterm infants (17-18). Currently there is no consensus on monitoring strategies to assess regional blood flow especially to the brain. Monitoring is largely dependent on measuring systemic arterial oxygenation and mean arterial blood pressure (MABP).

As discussed in detail earlier, Near-infrared spectroscopy (NIRS) is a possible method to indirectly measure brain perfusion, as the presence of thin layers of skin and skull allow good penetration of NIR light to the neonatal brain tissue. Differences in NIR light absorption are used to calculate the concentrations of Oxy (O_2Hb) and de-oxy (HHb) hemoglobin concentration using the modified law of Lambert–Beer. The ratio between O_2Hb and HHb is expressed as the $RCSO_2$. $RCSO_2$ is an average value with approximately 75-85% of the signal originating from venules. Thus, NIRS reflects mainly cerebral venous oxygen saturation (19-20). Recently published (phase 2) RCT for the use of NIRS in extreme preterm infants (≤ 28

weeks gestation) observed that NIRS can be employed for the continuous measurement of cerebral oxygenation. (22). Cerebral oxygenation is used as a substitute for cerebral blood flow, thus NIRS can potentially assess the integrity of cerebral circulation. The reference range for cerebral oxygenation in preterm population has a wide variation. Pellicer et al during the SafeboosC phase II randomised clinical trial used the range between 55%-85% in their guideline in the preterm infants in first 3 days of life. The value of <50% was associated with poor neurodevelopmental outcomes (23). To the best of our knowledge, there are no normalized data for NIRS values in neonate infants going home without oxygen. In our NICU in JPCH we use < 60% as abnormal low range (hypoxemia), 60-80% as normal and > 80% as high (hyperoxemia) in neonates on oxygen.

The current NICU practice is all ex-preterm infants with moderate BPD who are stable enough to be discharged are started on oxygen via low flow nasal cannula (Low flow nasal cannula in our unit is defined as oxygen flow ≤ 0.5 lpm) to maintain adequate oxygen saturation between 90-96%. The amount of oxygen or the flow rate of oxygen for these infants has not been determined. The BPD rate of preterm infants born in NICU in JPCH/RUH Saskatoon is one of the lowest in the country. While our current practice is to discharge infants with moderate BPD requiring oxygen at a rate of 0.12 lpm, we do not have any data that shows that this flow is adequate, too little, or too high. With the use of NIRS we can estimate the fractional tissue oxygen extraction of the brain and use these values as surrogate for oxygen saturation in the brain. Our aim was to provide adequate oxygen to preterm infants especially to the brain and improve neurodevelopmental outcomes.

Our aim was that combination of NIRS, and pulse oximetry could better identify a safe oxygen flow rate at the time of discharge. We also sought to better understand the normal range for NIRS measurements in these infants. To the best of our knowledge, there is a lack of normalized data for NIRS values in neonate infants going home with or without oxygen. We proposed that with combination of NIRS and pulse oximetry we could better identify a safe oxygen flow rate for babies with BPD. In doing so, we also sought to determine what the normative values of NIRS are in premature infants.

2.2: METHODS:

Study Design/Inclusion/exclusion criteria: This was a prospective cohort study. This study was approved by the Bioethics Board, University of Saskatchewan. After receiving written informed consent, we enrolled preterm ($\leq 37/40$) neonates admitted to NICU of Jim Pattison children hospital, Saskatoon, Canada. To obtain data for normal baseline NIRS and oximetry values, we recruited a control group of non-BPD preterm infants (n=22) who were being discharged home in room air. For the study group, we enrolled preterm infants with gestational age ≤ 32 weeks having moderate BPD and going home on oxygen via low flow nasal cannula (n=10) (Table 2). We chose this gestational age as it represents the most vulnerable preterm population from both mortality and morbidity. We excluded all preterm infants with congenital malformations.

Table 2. DEMOGRAPHICS DATA

Demographic	Control Group	Study Group
Gender	Male: 13 Female: 10	Male: 5 Female: 5
Percentage (Gender)	Male= 56% Female=44%	Male= 50% Female= 50%
Average GA at birth	32.7 weeks	28.8 weeks
Range of GA at birth	26+1/7→36+1/7	26+4/7 → 30+6/7
Average GA at Study	35.6 weeks or 35 weeks and 4.5 days	38.8 weeks or 38 weeks and 5.5 days
Range of GA at Study	32+6→38+2 weeks	36+1 →43.2 weeks

Definitions:

Hypoxia was defined as a pulse oximetry (SpO₂) value <90 % saturation (10, 24, 26); hyperoxia as > 96% saturation and normal between 90-96% for infants on Oxygen (24-26). Moderate BPD was defined by an infant’s need for supplemental oxygen at 36 weeks' postmenstrual age, or discharge (whichever comes first) for babies born < 32 weeks. Based on NICHD criteria as described in the section 1.4. (27). The alarm limits for POX were set according to the NICU policy (low limit of 90% to high limit of 95%) with intention to treat if prolonged hypoxic or hyperoxemic events were observed (10). NIRS values were stratified in 3 groups as adapted from Pellicer A et al SafeboosC trial (22, 23): < 60%, 60-80% and >80%. NIRS values of < 60% have been reported to suggest hypoxemia in infants with associated morbidity (22, 23). NIRS values of > 80% have been reported to suggest hyperoxemia in neonates on oxygen (22, 23).

Equipment used: NIRS measurements were performed using cerebral near infrared spectrometry by INVOS™ 5100C Cerebral/Somatic Oximeter employing INVOS™ Cerebral/Somatic Oximetry Infant-Neonatal sensors. For pulse oximetry data we used the Smart monitor manufactured by Circadiance. It has a 2 channel pneumographic capability and using the Synergy-E event software gives detailed information with regards to infant's heart rate, respiration, oxygen saturations and graphical displays helping to identify apneas or bradycardias and accurately record potential life-threatening events. It is integrated with Massimo technology for accurate oxygen saturation monitoring with an averaging time of as low as 3 sec.

Methods: We performed 8 hours of measurement using POX and NIRS monitoring in both non-BPD and BPD infants. The data for NIRS and POX study was obtained in room air for non-BPD infants and on the flow rates of 0.03 lpm (1/32), 0.06 lpm (1/16), and 0.12 lpm (1/8) for BPD infants going home on oxygen.

2.3: STATISTICAL ANALYSIS:

Sample size was chosen for convenience as approximately 1 patient would fulfil the inclusion criteria every 1-2 months. As such, especially considering this was during the COVID epidemic, it took us almost 3 years to enroll these infants. The acquired data was anonymized, stored, and recorded on hospital provided server.

We employed paired samples t-tests to compare the mean values of two key variables, POX (Pulse Oximetry) and NIRS (Near-Infrared Spectroscopy), across a study group with

different oxygen flow rates (0.03 LPM, 0.06 LPM, and 0.12 LPM). Cohen's correlation coefficient was calculated to assess the strength of the relationship between the two variables Pulse Oximetry and Near-Infrared Spectroscopy. The significance of the correlation was determined using one-sided and two-sided p-tests. Furthermore, we examined the percentage of time spent in various oxygen saturation categories for both POX and NIRS data across different flow rates to provide a comprehensive perspective on the relationship between these variables under varying oxygenation conditions. These statistical methods allowed us to rigorously assess the interplay between POX and NIRS in our study group.

2.4: RESULTS:

Control non-BPD infants on room air: Of the 22 participants in the control group, there were a total of 83058 observations. The time difference between the 2 consecutive observations was calculated. The total time of all the participants were documented and the average time was calculated for the 2 groups to find percentage time an infant remained in saturation group < 90% or >90%. Of the 22 participants in the control group the average time the participants remained with saturation > 90% was 96.5% (Table 3) with standard deviation of 1.661 and Standard error of means 0.006. Participants 4, 11 and 18 were the only infants that showed any significant desaturation (<90%) during the study period. All were brief (<30 seconds). Such brief desaturations are within the range of normal in this age of infant, and were not unexpected, and no intervention was needed.

Table 3: PULSE OXIMETER DATA FOR CONTROL GROUP (Room Air):

Participant Number	Value < 90%	Value >90%.
participant 1	0.6%	99.4%
participant 2	0.5%	99.5%
participant 3	2.8%	97.2%
participant 4	13.0%	87.0%
participant 5	2.6%	97.4%
participant 6	4.8%	95.2%
participant 7	1.7%	98.3%
participant 8	2.1%	97.9%
participant 9	2.4%	97.6%
participant 10	0.3%	99.7%
participant 11	11.0%	89.0%
participant 12	0.5%	99.5%
participant 13	1.0%	99.0%
participant 14	0.5%	99.5%
participant 15	2.9%	97.1%
participant 16	0.4%	99.6%
participant 17	0.3%	99.7%
participant 18	27.2%	72.8%
participant 19	0.9%	99.1%
participant 20	1.1%	98.9%
participant 21	0.3%	99.7%
participant 22	0.2%	99.8%
Average	3.5%	96.5%

The average NIRS values in the control group were 1.4 % in <60, 50.7 % in 60-80 and 47.9% in > 80% (Table 4). With the mean of 78.24, SD of 7.705 and SEM 0.027. As the control group

had no supplemental oxygen given these values of > 80% were considered normal and no action was taken.

Table 4: NIRS DATA FOR CONTROL GROUP (Room Air)

Participant Number	Value < 60%	Value 60%-80%	Value >80%
participant 1	0.0%	3.3%	96.7%
participant 2	0.0%	97.0%	3.0%
participant 3	0.0%	85.9%	14.1%
participant 4	0.0%	16.0%	84.0%
participant 5	0.0%	95.8%	4.2%
participant 6	0.0%	6.2%	93.8%
participant 7	0.6%	93.5%	5.9%
participant 8	0.0%	68.1%	31.9%
participant 9	0.0%	30.8%	69.2%
participant 10	0.0%	3.2%	96.8%
participant 11	0.0%	99.7%	0.3%
participant 12	0.1%	50.6%	49.3%
participant 13	0.0%	99.6%	0.4%
participant 14	0.0%	7.9%	92.1%
participant 15	0.1%	98.7%	1.3%
participant 16	0.1%	6.7%	93.2%
participant 17	0.0%	1.3%	98.7%
participant 18	0.6%	59.5%	39.9%
participant 19	0.0%	16.5%	83.5%
participant 20	29.3%	70.7%	0.0%
participant 21	0.0%	7.8%	92.2%
participant 22	0.0%	96.8%	3.2%
Average	1.4%	50.7%	47.9%

The difference of means between POX and NIRS (POX – NIRS) was 19.557 with the 95% confidence interval of 19.503 to 19.61. This difference of means does correlate with previous studies which suggested that there is an approximate difference of 20 among the POX and NIRS values with POX being higher than NIRS. Cohen's correlation coefficient was 0.02 between the two variables Pulse Oximetry and Near-Infrared Spectroscopy. One-sided and two-sided p-tests values were 0.00. (Table 5)

Table 5: Significance of POX vs NIRS

	Number of observations	Coefficient of Correlation	One sided p test value	Two-sided p test value
POX vs NIRS	83058	0.020	0.000	0.000

Study group BPD infants on supplemental O2: For the study group patients, the results were stratified according to oxygen flow rate and oxygen saturation. The average time an infant remained within the set saturation range in a particular flow rate was calculated. At the oxygen flow of 0.03 lpm, the average time the participants remained <90%, 90-96% and > 96% were 2.35%, 15.52% and 82.13 % of total time respectively. At the oxygen flow of 0.06 lpm, average time <90%, 90-96% and > 96% were 1.43%, 6.08 % and 92.49 % of total time respectively. At the oxygen flow of 0.12 lpm, average time <90%, 90-96% and > 96% were 1.46%, 11.54% and 87.00 % of total time respectively (Table 6).

Table 6: PULSE OX DATA FOR STUDY GROUP:

	FLOW 0.03 LPM			FLOW 0.06 LPM			FLOW 0.12 LPM		
	Percentage time < 90%	Percentage time 90-96%	Percentage time >96%	Percentage time < 90%	Percentage time 90-96%	Percentage time >96%	Percentage time < 90%	Percentage time 90-96%	Percentage time >96%
participant 1				3.04%	9.07%	87.88%	2.56%	4.26%	93.18%
participant 2				0.32%	2.32%	97.36%	0.10%	0.71%	99.19%
participant 3	1.16%	8.76%	90.08%	2.88%	13.31%	83.81%	1.69%	8.66%	89.64%
participant 4	0.26%	5.59%	94.15%	0.33%	1.02%	98.64%	0.80%	1.11%	98.09%
participant 5				0.07%	1.29%	98.65%	0.18%	1.08%	98.74%
participant 6	5.20%	49.59%	45.21%	3.82%	10.14%	86.04%	2.64%	72.06%	25.30%
participant 7	1.72%	9.83%	88.45%	0.13%	7.72%	92.14%	0.00%	5.74%	94.26%
participant 8	4.26%	11.21%	84.53%	1.51%	3.79%	94.69%	1.71%	4.42%	93.88%
participant 9	1.49%	8.14%	90.37%	0.77%	6.05%	93.19%	3.49%	5.83%	90.68%
participant 10				1.52%	38.70%	59.78%	2.73%	17.10%	80.16%
Average	2.35%	15.52%	82.13%	1.43%	6.08%	92.49%	1.46%	11.54%	87.00%

The NIRS values were stratified in 3 groups with oxygen. < 60%, 60-80% and >80%. The average time an infant remained within the set NIRS range with a particular flow rate was calculated. At the oxygen flow of 0.03 lpm, average time the participants remained <60%, 60%-80% and > 80% were 0.01%%, 58.5% and 41.5% of total time respectively. At the oxygen flow of 0.06 lpm, average time the participants remained <60%, 60%-80% and > 80% were 0.6%, 65% and 34.4% of total time respectively. At the oxygen flow of 0.12 lpm, average time the participants remained <60%, 60%-80% and > 80% were 0.2%, 65% and 34.8% of total time respectively. Unfortunately, participants 1, 2, 5 and 10 did not get study done at a flow rate of 0.03lpm as this was not agreed by MRP and clinical team (Table 7).

Table 7: NIRS DATA FOR STUDY GROUP

	FLOW 0.03 LPM			FLOW 0.06 LPM			FLOW 0.12 LPM		
	Percentage time < 60%	Percentage time 60%-80%	Percentage time > 80%	Percentage time < 60%	Percentage time 60%-80%	Percentage time > 80%	Percentage time < 60%	Percentage time 60%-80%	Percentage time > 80%
participant 1				0.00%	45.55%	54.45%	0.38%	42.77%	56.85%
participant 2				5.12%	94.88%	0.00%	1.45%	98.55%	0.00%
participant 3	0.00%	86.99%	13.01%	0.00%	75.69%	24.31%	0.00%	84.24%	15.76%
participant 4	0.00%	43.58%	56.42%	0.00%	73.48%	26.52%	0.00%	99.92%	0.08%
participant 5				0.00%	43.76%	56.24%	0.00%	37.33%	62.67%
participant 6	0.00%	100.00%	0.00%	0.00%	97.76%	2.24%	0.00%	99.96%	0.04%
participant 7	0.00%	2.47%	97.53%	0.00%	19.75%	80.25%	0.00%	0.03%	99.97%
participant 8	0.05%	99.89%	0.06%	0.00%	100.00%	0.00%	0.00%	100.00%	0.00%
participant 9	0.00%	18.14%	81.86%	0.05%	34.39%	65.56%	0.00%	22.44%	77.56%
participant 10				2.17%	97.83%	0.00%	7.02%	92.98%	0.00%
Average	0.01%	58.5%	41.5%	0.6%	65.0%	34.4%	0.2%	65.0%	34.8%

Comparison of POX and NIRS data: The comparison of data between POX and NIRS at different oxygen flow rates was performed (figure 15). The POX of < 90% (hypoxemia) was compared to NIRS values of <60%. The POX of > 96% (hyperoxemia) was compared to NIRS values of > 80% and the target range of 90%-96% was compared to NIRS values of 60%-80%. At a flow rate of 0.03 lpm the average percentage of time infants remained < 90% POX saturation was 2.35% while NIRS < 60% was 0.01% of total time. The average percentage of time the infants remained > 96% POX saturation was 82.13% while the NIRS >80% was 41.5%. Average percentage of time in the goal saturation range of 90%-96% POX was 15.52%, while the NIRS values within 60-80% was 58.5%. At a flow rate of 0.06 lpm the average percentage of time the infant remained < 90% POX saturation was 1.43%, while NIRS values of < 60% was 0.6%. The average percentage of time the infant remained >96% POX saturation was 92.49% while NIRS >80% was 34.4%. Average percentage of time in the POX saturation range of 90%-96% was 6.08% while the NIRS

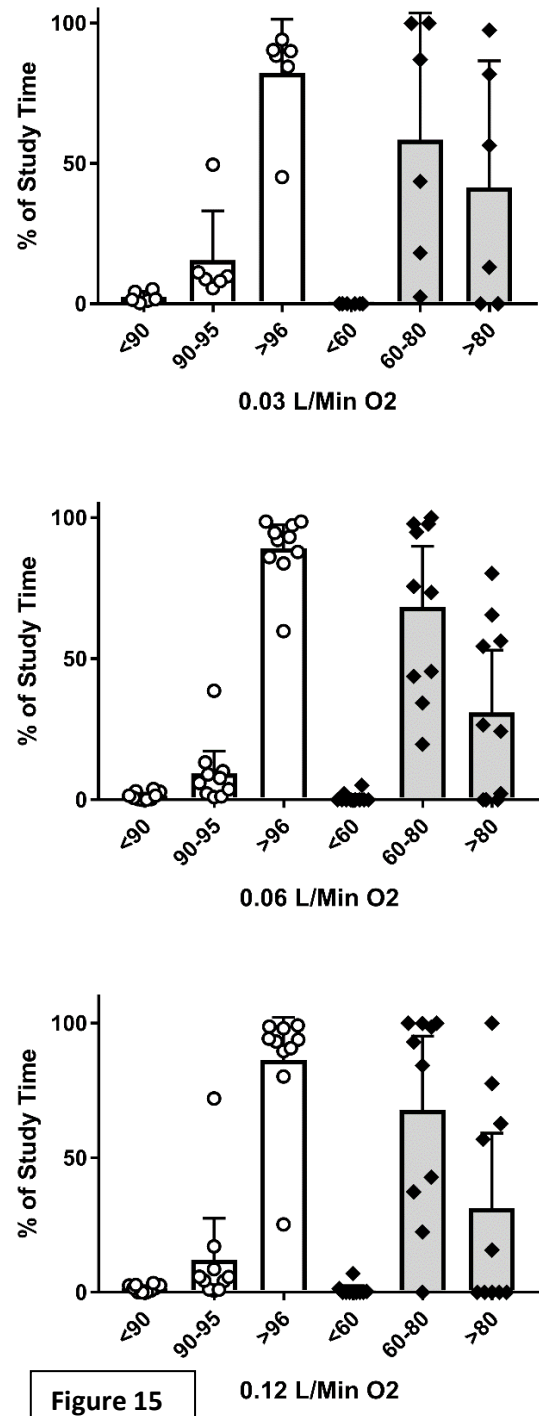


Figure 15

within 60-80% was 65%. At a flow rate of 0.12 lpm the average percentage of time the infant remained < 90% POX saturation was 1.46%, while NIRS < 60% was 0.2%. The average percentage of time the infant remained >96% POX saturation was 87.00%, while NIRS >80% was 34.8%. Average time in the POX saturation range of 90%-96% was 11.54%, while the NIRS within 60-80% was 65%.

Lack of dose response to oxygen: Infants on any amount of oxygen were rarely hypoxemic with an average time of 1.75% (POX < 90%). Similarly, regardless of O2 flow rate, infants were in the hyperoxemia category (POX >96%) most of the time at 87% (figure 16). Infants on any oxygen were in the target saturation range (POX 90-96%) only 11% of the time. We did not find any dose relation with increasing flow rate from 0.03lpm to 0.06lpm to 0.12lpm (82.1% with flow 0.03lpm vs 92.5 % with flow 0.06lpm vs 87% with flow 0.12lpm). While infants did not spend much time in saturations < 60% (0.27% of time), the average time an infant remained within the target NIRS range (60-80%) was better than POX data with an average time of 62.8%. The time with hyperoxia was also better at 37% time with NIRS > 80%. Like POX, we did not find a dose response with increasing flow rate and the time in the hyperoxemic range >80% (41.5% with flow 0.03lpm vs 34.4 % with flow 0.06lpm vs 34.8% with flow 0.12lpm).

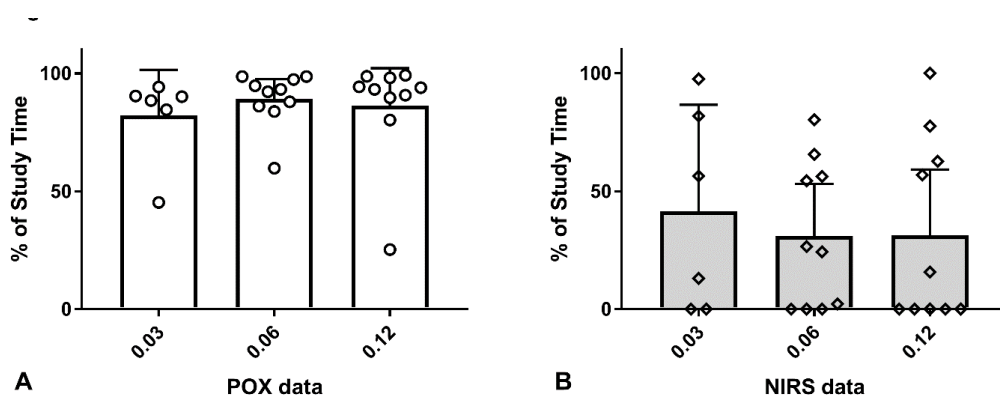


Figure 16

2.5: DISCUSSION

Both hypoxia and hyperoxemia is detrimental in the preterm population and can lead to poor neurodevelopmental outcome. As such, we sought to identify the minimum safe high and low oxygen flow rate for infants with moderate BPD going home on oxygen. In addition, there is little data on the NIRS technology in infants not on O₂ and as such these data are quite novel. We performed POX and NIRS studies on preterm infants going home in room air to determine the normal data for POX and NIRS without oxygen. We were happy to confirm previous data that there is an approximate difference of 20 between the POX and NIRS values with POX being higher than NIRS. Reason for higher POX values is the pulse oximeters detect the pulsatility of the blood flow and give readings which are very close to arterial oxygen saturation. In contrast the NIRS collects data from the tissue microcirculation which contains arterial, venous, and capillary components. $RcSO_2$ is an average value with approximately 75-85% of the signal originating from venules. Thus, NIRS reflects mainly cerebral venous oxygen saturation. We were also intrigued by the data that shows most infants not on supplemental oxygen do have POX data well above 96 % for most of the time. This obviously becomes relevant in the context of potential hyperoxia for the oxygen treated BPD study group.

For the study group our aim was to determine the percentage of time the preterm infant remains within the target saturation range and to find the adequate oxygen flow rate for these infants going home on low flow nasal cannula. For all infants on any oxygen, we did not find any dose relation with increasing flow rate from 0.03lpm to 0.06lpm to 0.12lpm.

Similarly, the average time an infant remained within the set NIRS range was also lower than expected. Again, we did not find any dose relation with increasing flow rate and the time in the hyperoxemic range >80%. (Figure 16)

Based on these POX and NIRS findings it is reasonable to suggest that home oxygen of 0.06 to 0.12lpm is probably adequate to protect against hypoxemia and hyperoxemia. We could not find any correlation between POX and NIRS values. Even though we see that infants spend most of the time with higher POX saturations >96% the NIRS was not the same. It's possible that the brain does not see the higher values due to the cerebral autoregulation. Cerebral Autoregulation is the ability of the brain to maintain perfusion and oxygenation in response to different stresses. Impaired autoregulation has been associated with poor neurodevelopmental outcomes. Although preterm infants have impaired cerebral autoregulation at birth, we hypothesise that the infants close to going home may have developed enough autoregulation capability that it does not see the impact of hypoxia or hyperoxia immediately. However, to test this hypothesis, we would need a separate study.

2.6: SUMMARY.

This is the first report showing the normal NIRS values of relatively healthy preterm infants. We suggest the flow rate of 0.06 lpm probably should be adequate for home O₂ with moderate BPD, however the final decision would lie on the discharging physician and neonatal team.

Also there seem to be no correlation between the cerebral NIRS values and POX values over a short time. Desaturations in POX did not follow the NIRS. This is likely due to the cerebral autoregulation. However, this report was not designed to study the effects of cerebral autoregulation in these infants. NIRS still plays an important adjunct role as a monitoring device which gives us insight into the brain oxygen saturation. We suggest that the NIRS numbers should be considered in the management of preterm infants along with other monitoring tools but not as stand alone.

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CHAPTER 3:

3.1: LIMITATIONS OF STUDY AND FUTURE DIRECTIONS.

As outlined above, there were limitations to this work, which we could have improved if I/we had more time. For example, in the study population we saw that most of the time the preterm infants remained in the hyperoxemic range for POX in all flow rates (82.13% with 0.03 lpm, 92.49 % with 0.06 lpm and 87% with 0.12 lpm). The guidelines suggest that POX greater than 96% is potentially hyperoxemic. However, true hyperoxemia is only known by measuring a blood gas with a $PO_2 > 150$ mmHg. Measuring oxygen free radicals is another experiment to consider confirming hyperoxemia. Obviously, our study could not do this, as these methods are too invasive. An animal model like piglet or sheep model could be done, but that doesn't truly represent the human experience. I/we created the results based on the >96% cut-off, but in hindsight, I should have also created a >99% cut-off. This would have better defined a percent time where the chance of an abnormally high pO_2 could exist. The >96% cut-off is clinically relevant and is still important to see.

The other limitation is that we didn't define a clear dose response to oxygen flow rate. In hindsight, the experiment should have added another higher dose of oxygen (i.e. 0.24 lpm). The reason we didn't was to avoid harm and minimize risk for the infants. The standard of care in our institution and at most centres in North America is 0.03-0.12 lpm. As such this dose would not have been ethically feasible. Again, an animal model could be used to control the flow of oxygen to assess dose response without ethical concerns and see if by increasing the oxygen delivered has an impact on the cerebral NIRS values or not.

The other consideration is that our sample size was too small, and we missed the dose response. The data are statistically strong, and this seems unlikely. However, in future we could design a similar study and enroll more infants to increase the power of the study and be able to make definite suggestions to change the clinical practice.

3.2: STRENGTHS OF STUDY.

Despite the above-mentioned limitations there were couple of strong points that are worth highlighting here. The NIRS data for control group which was collected in room air data close to discharge home is quite novel to us. To the best of our knowledge, all the published NIRS data in preterm is collected either during the transition period (first 3 days of life) or during an event like blood transfusion given to the preterm, HIE patients and cardiac surgery. Looking at NIRS in relatively healthy preterm infants at the time of discharge and comparing with the pulse oximetry is never published before.

Though our sample size was small in both control and study group, we had 83058 data points in the control group and 72806 data points in the study group. This makes our data statistically strong.

We did not observe too much hypoxemia in our study group (average POX < 90% was 1.48% on any oxygen and average NIRS <60% was 0.5% of the time). This observation was reassuring that we are avoiding hypoxemia and its complications (the primary goal of supplemental oxygen) in our study group patients. Another strength of the study was clarity of definitions and parameters to study. These definitions were backed by strong studies done in the past.

3.3: MAJOR OUTCOMES AND RECOMMENDATIONS.

We observed that the preterm infants going home on oxygen spent most of the time in the hyperoxemic range (>96%), but this value is likely not causing harm. We suggest the flow rate of 0.06 lpm probably should be adequate for home O₂ with moderate BPD, however the final decision would lie on the discharging physician or MRP and neonatal team.

Also there seem to be no correlation between the cerebral NIRS values and POX values over a short time. NIRS still plays an important adjunct role as a monitoring device which gives us insight into the brain oxygen saturation. However, we suggest that the NIRS numbers should be considered in the management of preterm infants along with other monitoring tools but not as stand alone.

We also suggest a future study, probably animal study like piglet or sheep model to answer the questions that were ethically not feasible for us to answer as this was a human study.