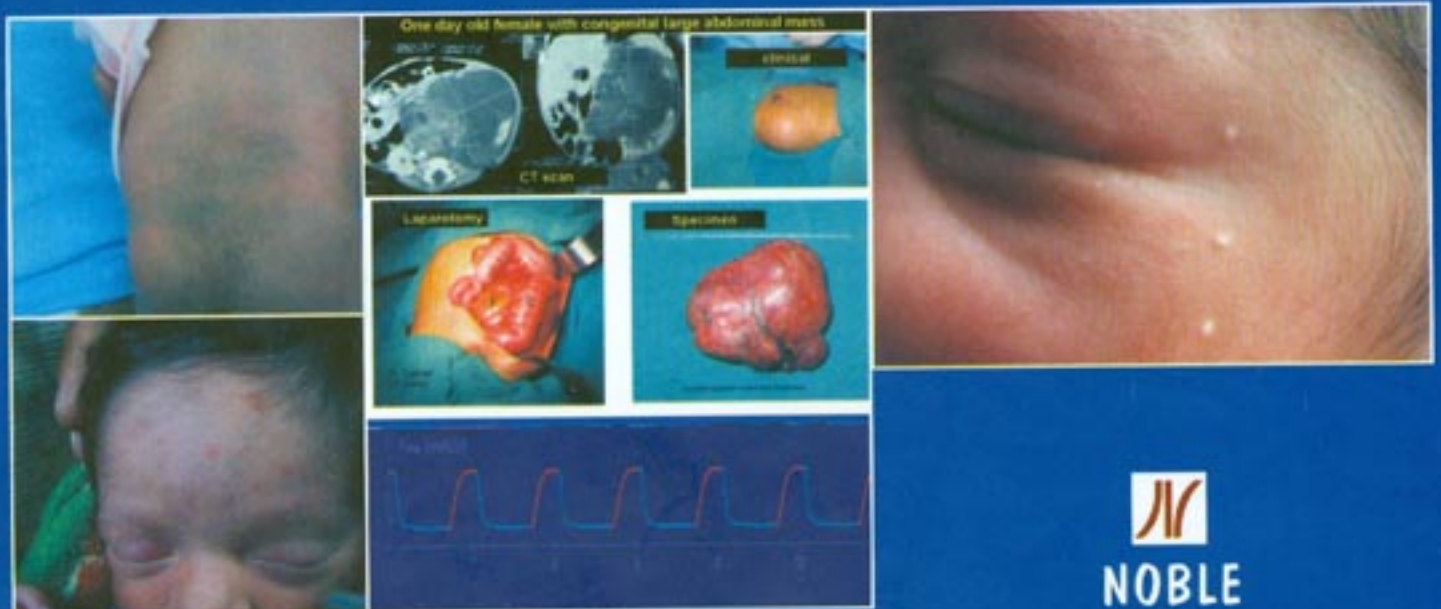




Mathur's

# ESSENTIAL NEONATOLOGY

N. B. Mathur



  
NOBLE

# Oxygen Therapy in Neonates

*KK Diwakar*

### Introduction

The role of oxygen as a mandatory requirement to sustain life has been recognized from historical times. Better understanding of cellular chemistry has revealed that concomitant with the benefits of aerobic respiration, oxygen radicals have inherent properties that could be detrimental to the cellular well being. A complex mechanism of enzymes and free radical scavengers maintains a fine balance between the beneficial and detrimental effects of oxygen. Augmentation of oxygenation is required in disease states or where "hyperoxia" is considered as a therapeutic intervention.

Baseline oxygen consumption in a term fetus ranges from 6.6 - 8.5 ml/kg/min (1) and may increase by 100 - 150 times with activity (2)

Oxygen is utilized by tissues based on the functional and physiological characteristics of the specific organ system, e.g. the oxygen utilization in intestinal cells would not be the same as in skeletal muscles. Under normal circumstances, a physiologically controlled and finely regulated system of extraction ensures that the available oxygen is optimally distributed to tissues. As oxygen requirement of a specific tissue increases, the capillary beds open up making oxygen available at closer proximity for cellular metabolism. As oxygen gets utilized, the partial pressure of oxygen (PO<sub>2</sub>) in the vascular compartment drops. Critical PO<sub>2</sub> is the lowest level at which cellular oxygenation is possible and is tissue specific. The critical PO<sub>2</sub> for brain appears to be 20mm Hg in cerebral circulation. (2), while in skeletal muscles oxygenation is possible at PO<sub>2</sub> as low as 2-3 mm Hg. Presence of myoglobin may be contributing to extract oxygen even at a very low PO<sub>2</sub> (3). This observed difference in critical PO<sub>2</sub>, would help understand to some extent, the selective tissue injury in hypoxemia.

Inadequate supply of Oxygen to tissues is called Hypoxia. It could be due to

1. Low PO<sub>2</sub> in arterial oxygen (hypoxemia) due to pulmonary disease called: Hypoxic Hypoxia.
2. Inability of blood to carry oxygen as in anemia or carbon monoxide poisoning: Anemic Hypoxia.
3. Reduction in tissue blood flow: shock and local obstruction: Circulatory Hypoxia.
4. Inability of tissues to utilize available oxygen: Histotoxic Hypoxia eg. Cyanide poisoning preventing the use of oxygen by cytochrome oxidase



Oxygen therapy can be best discussed by understanding the steps in normal oxygen delivery to the tissues. 1. Availability of oxygen, 2. Passage of oxygen to vascular beds 3. Transportation of oxygen to tissues and 4. Oxygen utilization at tissue level. The aim of therapy is to ensure that optimal oxygen is available to the cell for its oxygen dependent metabolic functions without causing hyperoxic injury.

### Availability

The Partial Pressure of Inspired Oxygen ( $PIO_2$ ) in an infant spontaneously breathing room air can be calculated as Fractional inspired oxygen ( $FiO_2$ ) X (Barometric pressure - water vapour pressure). Viz.  $0.21 \times (760 - 47) =$  approximately 149 mm Hg. (where 760 mm Hg is Barometric Pressure at Sea level, and 47 mm Hg is the water vapour pressure in the moistened air at upper airway). In a hypothetical situation, when this air reaches the alveolus without any physical alteration, the gas equilibrium is influenced by another component viz. the alveolar Carbon dioxide ( $PACO_2$ ). Thus the partial pressure of the oxygen available at the alveolar level ie  $PAO_2$  would be  $[PIO_2] - [PACO_2]$ . The characteristics of easy diffusibility permit us to consider alveolar  $PCO_2$  as equal to arterial  $PCO_2$ .) Therefore if  $PCO_2$  is considered to be 40 mm Hg, the  $PAO_2 = [149] - [40] = 109$  mmHg.

### Passage of Oxygen in to vascular beds

The movement of oxygen and carbon dioxide between alveoli and blood follow the physical principles of **Oxygen Therapy in Neonates** gases and Fick's laws of diffusions. viz the diffusion across membranes is (i) inversely proportional to the thickness of the membrane, (ii) directly proportional to the surface area available for exchange and (iii) directly proportional to the difference in partial pressures across the membrane. It would therefore be easy to understand how interstitial inflammation or edema of the alveoli would adversely affect the movement of oxygen from the alveoli into the vascular bed. A reduction in the surface area for gas exchange occurs when there is exudative lesion of the alveoli as seen in pneumonia, or when large numbers of alveoli are collapsed or partially collapsed as seen in Respiratory Distress Syndrome. Under basal conditions, lung uploads about 4ml/min/kg of body weight of oxygen on to Hemoglobin. This can increase up to 15 times depending on the stimuli received from receptors situated in the carotid and aortic bodies. (2)

A higher partial pressure of oxygen in alveoli ( $PAO_2$ ) accentuates the movement of oxygen across the alveolar membrane into the pulmonary capillary beds. As the partial pressure of the oxygen in the alveoli is more than the  $PO_2$  in the pulmonary artery, oxygen diffuses across the alveolar membrane in to the capillaries. This ensures maximal  $PO_2$  in the pulmonary veins and consequently in the left atrium.

If diffusion of oxygen across the alveolar membrane is achieved, the gas dissolved in the blood would be proportional to its partial pressure (Henry's laws). Oxygen is



poorly soluble in blood. For each mm of Hg, 0.003 ml of O<sub>2</sub> is dissolved in 100 ml of blood hence, for a PO<sub>2</sub> of 100 mm Hg, 0.3 ml of oxygen is dissolved in the 100 ml of blood. The poor solubility of oxygen in the blood would ensure that the partial pressure of oxygen would soon rise and the gradient for oxygen across the alveolar endothelial membrane would diminish as the partial pressure of the undissolved oxygen starts rising within the capillaries. The only mechanism therefore to ensure movement of oxygen into the capillaries would be to have a "capacitance building entity" within the blood. In other words, some mechanism that would quickly 'mop up' oxygen as soon as it crosses the capillaries thus ensuring a gradient between the 'alveolar oxygen' and the 'vascular oxygen' (Figure 1).

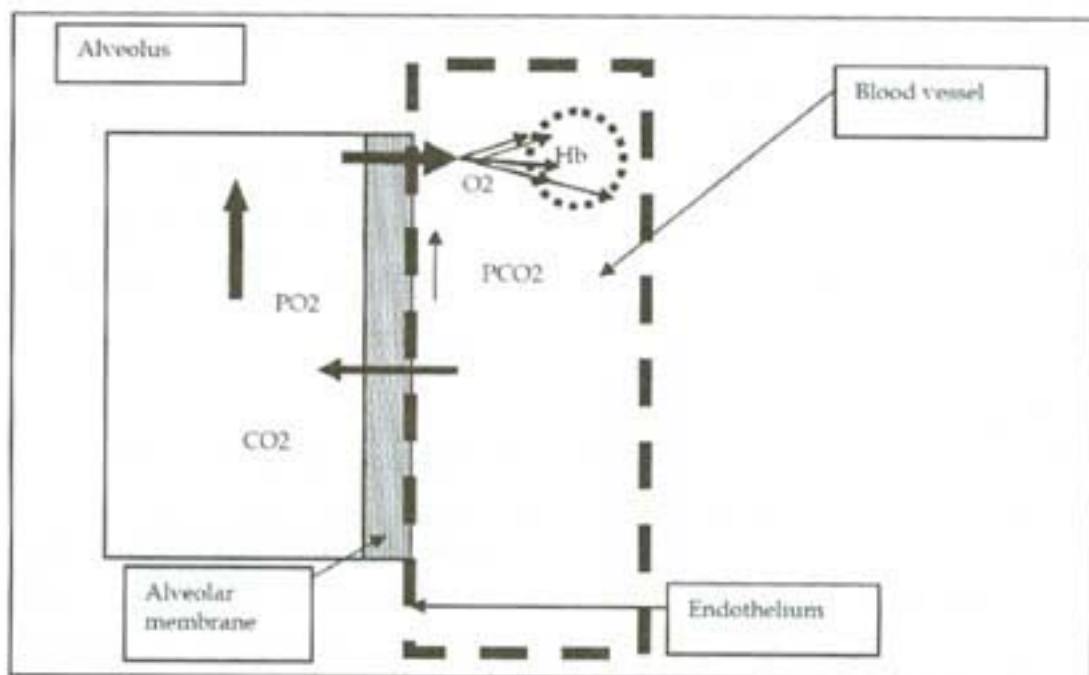


Fig 1: Movement of gas across alveolar membrane in to pulmonary vessels

This capacitance building entity is **Hemoglobin**. One molecule of Hb can carry 4 molecules of oxygen. Therefore 100 molecules of Hb would be able to carry 400 molecules of Oxygen. If there are 388 molecules of oxygen in the presence of 100 molecules of Hb, we could say that that Hb was 97% saturated with oxygen. This process of incorporating oxygen into its own structure would continue till the hemoglobin is saturated beyond which it is no longer able to mop up the oxygen from the blood. If more oxygen molecules are pushed into the blood stream beyond the saturation capacity of the Hb, the insoluble oxygen molecules would accumulate leading to higher partial pressure of oxygen (PO<sub>2</sub>). Fetal Hb is saturated to over 97% at PO<sub>2</sub> of 65 to 70 mm Hg. Further movement of oxygen into the vascular compartment (by enhancing the PAO<sub>2</sub>) results in a concomitant increase in the PaO<sub>2</sub> (partial pressure of arterial oxygen), with Hb continuing to remain maximally saturated. Thus molecular oxygen would now be freely available at the tissues - the quantum of diffusion being proportional to the partial pressure of oxygen (PO<sub>2</sub>), as governed by Fick's laws of diffusion of gases.



### Transportation of Oxygen to the tissues

1.39 ml of Oxygen combines with 1 g of Hb. Therefore a Hb of 15 g /dl would have an Oxygen capacity of  $1.39 \times 15 / \text{dl of blood} = 20.9 \text{ ml/dl}$  (Fig. 2).

Oxygen Saturation:  $\text{SaO}_2 = [(\text{oxygen combined with Hb}) / (\text{oxygen capacity})] \times 100$

At a  $\text{PO}_2$  of 100 mm Hg approximately 97% of adult Hb is saturated, while a similar saturation is attained in Fetal Hb at lesser  $\text{PO}_2$  of 65 – 70 mm Hg.

If Hb is 10g /dl, then the  $\text{O}_2$  capacity of 100 ml of blood would be 13.9 ml. Even if saturation is 97 %, the total oxygen content would be significantly lower (Fig. 2).

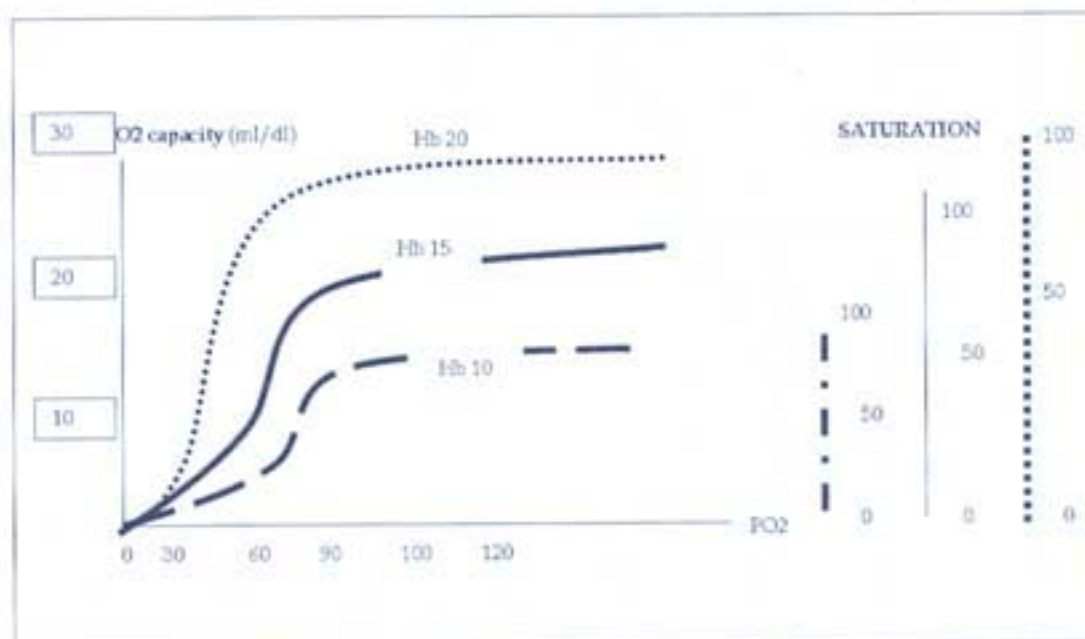


Fig. 2: Adapted from, *Respiratory Physiology: The Essentials*, Ed: West JB, 8th Edition, Lippincott Williams & Wilkins, 2008

Diffusion of oxygen into the tissue follows the physical laws of gas diffusion, and is dependent on the difference in partial pressure of oxygen. The available oxygen molecules in blood get absorbed into the cells, and the partial pressure of oxygen in the capillary blood gradually decreases as it circulates more distally. As the  $\text{PO}_2$  drops, the Oxygen dissociates from the Oxy-Hb. This ensures a "molecular oxygen gas flow gradient" from the blood into tissues. The oxygenation of the tissue is based on the  $\text{PO}_2$  of the capillary blood and the distance between adjacent capillaries viz. inter-capillary distance. As the fall in the  $\text{PO}_2$  is maximal in areas closest to the capillaries, in severely under-perfused tissues the  $\text{PO}_2$  levels would be approaching '0' in parts of the tissue that are far from the perfused capillary (3). Thus in presence of shock, tissue could continue to be hypoxic, despite a higher  $\text{PO}_2$  in the arterial blood gases.

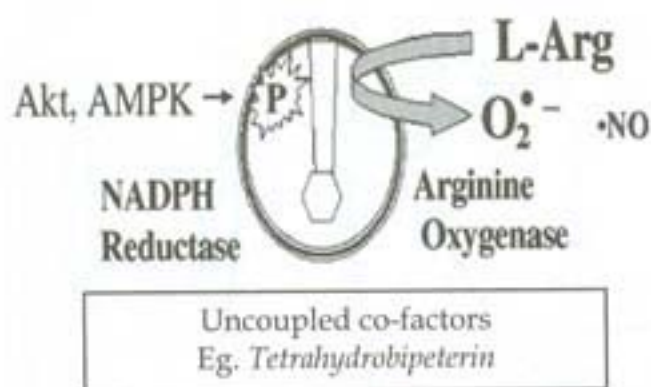
The shift-to-the left of the Fetal Oxygen dissociation curve (*Figure 3*) shows that the Oxygen continues to be bound to hemoglobin, even when the  $\text{PO}_2$  is at very low level ( $\text{P}_{50}$  being 17 mmHg). This ensures that oxygen does not get rapidly dissociated from Hb even when the  $\text{PO}_2$  at the tissue levels are quite low. This



Oxygen has also been found to facilitate the 'liquid absorption phase' in the neonatal lung. While post natal  $O_2$  induced sodium and liquid transport probably functions by influencing the endothelial sodium absorption channels (ENaC), other studies have demonstrated that hypoxia could decrease alveolar liquid clearance by an effect that is independent of ENaC and  $Na^+K^+$  ATPase expression (5).

While projecting the advantages of the oxygen molecule at the level of cellular chemistry, it must be recognized that the generation of reactive oxygen species like super oxides would result in irreversible cellular injury. In vitro studies have shown that uncoupling of co factors like tetrahydrobipeterin, could skew the generation of NO and instead result in generating superoxides (Figure 4) (4). Free oxygen radicals production is being continuously prevented by the activities of enzymes like superoxide dismutase and catalases that ensure that these highly reactive moieties are mopped as  $H_2O_2$  and converted to  $\rightarrow H_2O$  and  $O_2$  It is therefore easy to understand that tissues vulnerable to hyperoxic injury would either have a deficit of these enzyme functions, or be subjected to oxygen load that would far exceed the available 'mopping up' capacity of such enzymes. As the fetus survives in an environment having relatively low oxygen, it would be ill equipped to handle the sudden surge of oxygen exposure that a neonate is subjected.

In humans the Super Oxide Dismutase (SOD) activity in lung increases with age with highest values seen in adults. Therefore more preterm the infant greater is the risk to hyperoxia induced free radical injury. Interestingly, an expected hyperoxic increase in SOD activity was seen in those premature infants without RDS, while no such increase in SOD activity was seen in the premature infants who developed RDS -- suggesting that antioxidant deficiency may be a contributory factor in neonatal lung disease (6).



**Fig. 4: Generation of superoxides  $O_2^{\bullet -}$**

*adapted from G. Ganesh Konduri / Clin Perinatol 31 (2004) 591-611,*

### Oxygen Therapy

The indication for oxygen therapy is most often based on the immediate clinical assessment of the infant. Presence of respiratory distress, low oxygen saturation and cyanosis are indications for oxygen therapy. While the etiology of the presentation

could be varied, (7) the aim of initial therapeutic intervention is always the same viz ensuring adequacy of oxygenation. Monitoring is essential to ensure that oxygen level in the infant does not exceed safe limits - especially in premature infants.

Term infants are at a lower risk for oxygen toxicity. Therefore the effects of high  $PAO_2$  can be used for its therapeutic benefits. Pulmonary interstitial emphysema (PIE) and pneumothorax (PTX) can be treated based on the physical laws of diffusion of gases. (Fick's Law). The 'leaked air' has a higher percentage of nitrogen than oxygen. (Figure 5). If the  $FiO_2$  is 1 then the partial pressure of Nitrogen in inspired gas would be zero. Thus as per laws of diffusion of gases, the nitrogen would move out of the pleural space into the alveoli to be exhaled via the tracheo-bronchial tree.

Pulmonary vasodilatation can be facilitated to some extent by oxygen exposure which increases the activity of cyclo-oxygenase and NOS enzymes (4) in the endothelium (Figure 5). This is one of the principles for providing oxygen in perinatal asphyxia and meconium aspiration syndrome. A higher alveolar oxygen could also ensure lesser fluctuation of  $PaO_2$ , in infants with pulmonary vascular lability - thereby preventing progressive pulmonary vasoconstriction and resultant persistent pulmonary hypertension (PPHN). The benefits of preventing PPHN encourages many to use oxygen generously till respiratory distress settles, in infants at-risk for PPHN, even if hypoxia is not a dominant factor (8). Despite term infants being more tolerant to higher levels of oxygen, hyperoxia is best avoided in them also.

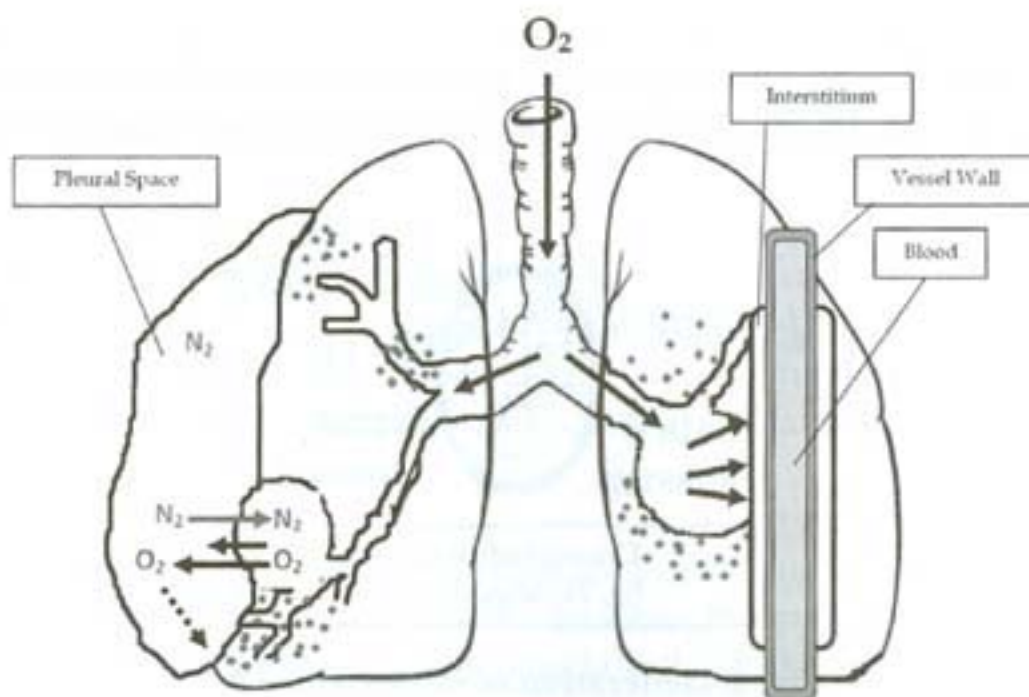


Fig. 5: Effects of higher alveolar oxygen in pneumothorax

In a hypoxemic infant with congenital heart disease elevation of  $PO_2$  may be less desirable in a ductal dependent lesion. At the same time, targeting a higher  $PO_2$  is almost the rule when one is dealing with conditions at-risk to develop PPHN.



It is therefore easy to understand that oxygen therapy, a panacea available for hypoxia of varied etiology, has to be used judiciously. Therapeutic intervention could therefore be by the following methods.

1. Oxygen therapy at pulmonary level
  - a. Increasing the  $F_{iO_2}$
  - b. Opening of more alveoli for larger capillary - alveolar interface. May be achieved by increasing the tidal volume.
  - c. Increasing partial pressure of oxygen by raising the inspiratory pressure of inhaled 'air'.
  - d. Maximize the surface area for gas exchange (Fick's laws of gas exchange) eg. Enhanced alveolar distension and Functional residual capacity.
2. Enhancing the ability of the blood to carry more oxygen by ensuring satisfactory hemoglobin levels.
3. Establish satisfactory tissue perfusion and ensure opening up of more capillary channels to facilitate better oxygenation at tissue level.

While comprehensive treatment of hypoxia involves all or most of the above mentioned interventions, the current chapter would restrict itself to the use of oxygen as a therapeutic tool. It must be recognized that in an inadequately expanded lung adequate distension alone would suffice to ensure satisfactory oxygenation. Undue increase in the  $F_{iO_2}$  in such a situation could result in uncontrolled enhancement of oxygenation with the deleterious effects of hyperoxia. This is most highlighted in neonatal resuscitation (9).

### Delivering Oxygen

Oxygen therapy should encompass the principles of delivering oxygen that is: (i) blended to desired concentration, (ii) suitably humidified and at (iii) physiologically acceptable temperature

Blending oxygen to the appropriate percentage is a primary requisite for optimal oxygen therapy. It is a common practice, more so under resource restricted situation, to quantify oxygen delivery merely as litre/ min of 100% oxygen. eg while a sick infant would be provided about 3-5 litres a clinically more stable infant may be given 1-2 litres of oxygen. It must be realized that the flow of the gas does not alter the percentage of oxygen delivered in any predictable manner. The inadvertent mixing of the oxygen with the atmospheric air is the only cause for reduction of the percentage of oxygen at reduced rates of delivery. It must be recognized that oxygen delivered at 0.5 L/ min, or lower by nasal cannula could also be delivering nearly 100% oxygen to the infant, as neonates are obligate nasal breather. So commenting on the oxygen requirement of an infant based merely on the flow of oxygen is fraught with misinterpretation. Therefore blended oxygen to deliver the pre-designated percentage of oxygen in the gas mixture is mandatory for appropriate oxygen



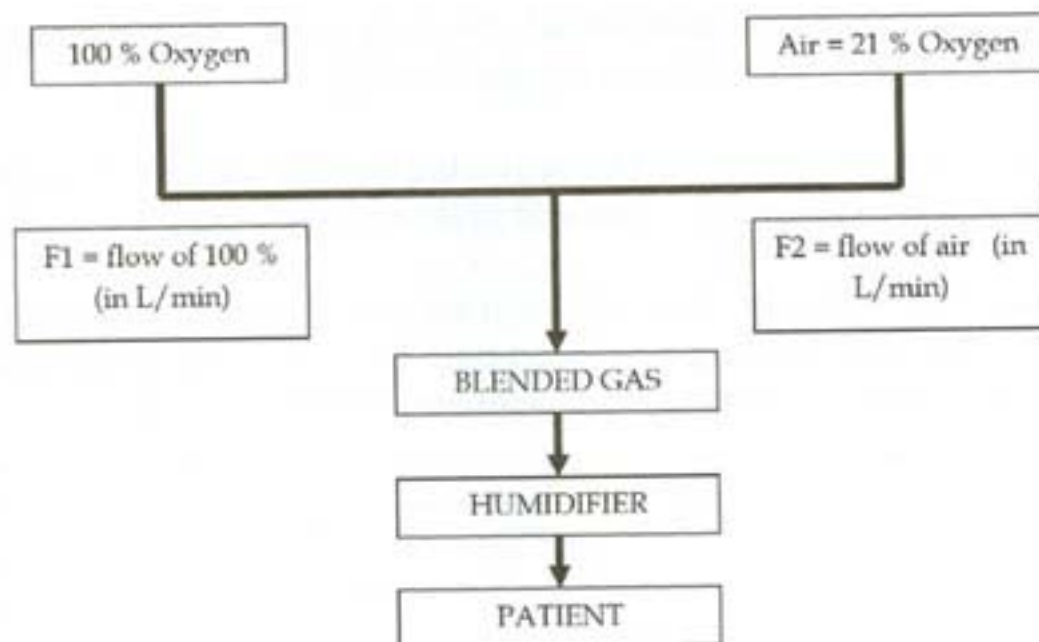


Fig. 6: Blending; % of O<sub>2</sub> = [(F1 X 21%) + (F2 X 100%)] / (F1 + F2)

**Mode of delivery of Oxygen:** Where oxygen requirement is less than 25%, oxygen could be directly delivered into the incubator. More often, oxygen is delivered through nasal cannula, nasal prongs, mask or through oxy-hood. Each of these modes has their advantages and disadvantages.

**Nasal catheter:** Catheters of 5F or 6F size are used for this. The catheter is inserted through any one of the nostrils. A flow rate of 0.5 to 1 litre is reasonable to provide the necessary amount of inspiratory gas mixture. Higher flow rates could have the effect of increasing the resistance to exhalation. The patency of the other nostril, however prevents the flow of gases from inadvertently generating continuous distending pressure. It is easy to apply and does not interfere with the routine nursing care of the infant. Free exhalation, through the other nostril prevents CO<sub>2</sub> retention. Secretions could block the catheter tip. The catheter could get displaced and move more into the oropharynx, leading to a greater delivery of the gas into the esophagus than the trachea.

**Nasal prongs:** This is a very popular mode for delivering oxygen. It has all the advantages of the nasal cannula. As oxygen is inhaled through both nostrils, the percentage of delivered oxygen is more accurate. The shorter size of the prongs decreases the chance of secretions blocking the tip. Appropriate prong sizes are recommended based on the birth weight of the infant. If flow is increased there is a higher chance of inadvertently developing continuous distending pressures. If prongs are ill fitting, they could traumatize the nostrils.

**Mask:** The mask is used more often for short term delivery of oxygen eg at resuscitation or for transport. As it restricts access to the mouth, nursing care for clearing oropharyngeal secretions becomes difficult. The mask could be displaced by



the normal movement of the infant's head, resulting in variation in oxygen delivery. This makes it unsuitable for long term oxygen therapy.

*OxyHood:* This is a common method of delivering oxygen. Despite its popularity, the hood restricts access to the infant's face and oral cavity, hampering nursing care.

Different designs of oxyhoods are available. This could range from a plain hood with an opening for the head and single gas-inlet port, to more complex designs, with side portal, port for oxygen analyzer, thermometer and outlet ports (Fig. 7).

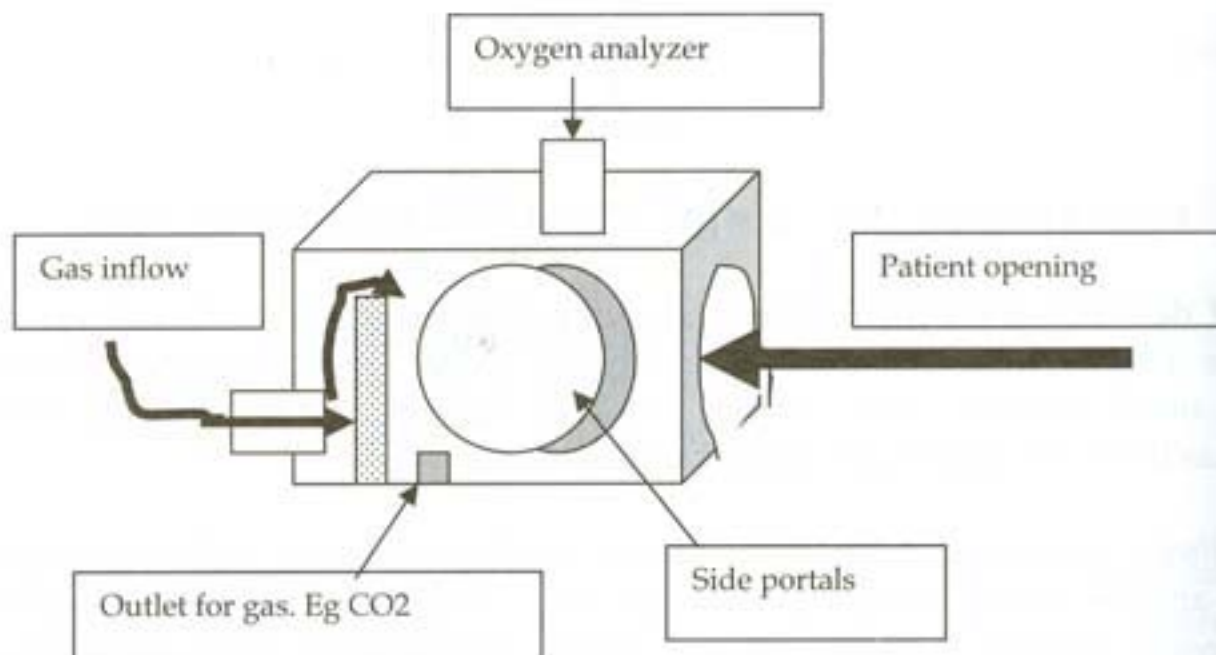


Fig. 7: Schematic diagram of Oxyhood

Ensuring the required  $FiO_2$  could be quite challenging, due to chances of significant leaking through the large portals of the hood. An oxygen analyzer therefore is a mandatory accessory for delivering oxygen through this route.

$CO_2$  being heavier than oxygen, tends to gravitate downwards. Therefore chances of re-breathing  $CO_2$  is higher when the infant is nursed prone under the oxyhood. Hoods should therefore be designed with small outlets at the base to provide an escape portal for the heavier  $CO_2$  molecules (Fig. 7).

**Monitoring of oxygenation** is a mandatory part of all respiratory care. The aim of oxygen therapy is to ensure adequate oxygenation of the blood and ensure appropriate oxygen delivery to the tissues. Clinical examination pays rich dividends in recognizing etiology, response to therapy and general well being of the infants. Various respiratory distress scores like the Downe Score (10) could be useful in monitoring the status of respiratory distress. Capillary fill time (CFT), heart rate and



blood pressure assessment are baseline clinical parameters to ensure adequacy of perfusion, a necessity for satisfactory tissue oxygenation.

While the clinical signs do facilitate evaluation to some extent, monitoring the adequacy of oxygenation require better surrogates viz. arterial blood gases, capillary blood gases, transcutaneous  $PO_2$  and pulse oximetry are all methods that are used. While arterial blood gases would be the gold standard for deciding various interventional strategies, it is the ubiquitous pulse oximeter that is relied upon by most clinicians for the routine assessment of infants requiring supplemental oxygen. The limitations of pulse oximetry ( $SPO_2$ ) should be well understood while monitoring infants. In addition to the equipment dependent variability of  $SPO_2$ , pulse oximetry would be unreliable in a poorly perfused infant. Target levels for saturations vary with the gestation of the infant and the clinical situation. It is not possible to recommend any absolute values for desired oxygen saturation. However there is broad consensus that oxygen saturations of 85 % - 94 % should be targeted in the premature infants. The lower range of 85% - 89% being considered for the more premature infants (<28 wks of gestation). The primary aim is to provide optimal oxygenation while concomitantly avoiding hyperoxia. Higher saturations are often acceptable in term infants. While pulse oximetry could be a broad indicator for oxygen levels in the blood, it would be incorrect to use it as an absolute surrogate for  $PaO_2$  levels. The range of  $SPO_2$  have been found to be quite narrow for rather wide range of change of  $PaO_2$  eg  $PaO_2$  of 50 - 75 mm Hg, have been observed to have  $SPO_2$  of 95% - 97% (11).

Increasing  $FiO_2$  requirements, to maintain acceptable  $PaO_2$  levels would be an indicator for initiating more intensive modalities of respiratory care viz. ventilator support. The threshold for intervention would be lower in smaller and more critically ill infants, than in active term infants. It is our practice to initiate ventilator support if  $FiO_2$  level of 0.6 is unable to sustain a  $PO_2$  of 50 mm Hg. (12). The intervention could be as CPAP or mandatory ventilation, depending on the clinical circumstances. Episodic elevation of  $SPO_2$  to high levels, should not be considered an indicator for reducing the ambient oxygen. A term infant at rest, having  $SPO_2$  values fluctuating between low normal and high values, while receiving a high  $FiO_2$ , should raise the suspicion of the infant having persistent pulmonary hyper tension of the newborn.

### Weaning from oxygen

Commencing oxygen therapy is a fairly straight forward decision. However weaning oxygen is often a combination of clinical art and science. Needless to say an improvement in the clinical signs is a primary requisite for weaning oxygen. An improvement in the respiratory status is reflected in the gradually increasing  $PO_2$  levels and oxygen saturation. Once the saturation is elevated and sustained at a steady level, 1% - 2% of oxygen is gradually weaned hourly, in a step-wise manner.



While weaning the oxygen it would be worth having arterial blood gases in the initial stages, and subsequently rely on the pulse oximetry. Should unpredictable reductions in  $SPO_2$  occur, the weaning is stopped till the saturation rises to the "pre-weaning" levels. Unpredictable drop of saturation to 'hypoxic' levels should be avoided at all circumstances. A very gradual reduction of  $FiO_2$  (not more than 0.05 / hour) is the best way to avoid any precipitous reduction in  $SPO_2$ . It must be remembered that should the  $SPO_2$  drop to hypoxic levels,  $FiO_2$  should be increased significantly till the  $SPO_2$  is raised to normal values. Often elevating  $FiO_2$  to the immediate pre-weaning level does NOT correspondingly revert the  $PO_2$  to the initial levels. Therefore a flip-flop phenomenon of weaning must always be avoided. Rapid and erratic weaning of oxygen is a sure recipe for disaster in the labile neonate.



Fig. 8: Blending with flow meters and humidified gas delivery

### Conclusion

Oxygen therapy is the commonest respiratory support provided to the newborn. While recognizing the invaluable benefits of oxygenation, one should always remember the bane of hyperoxia induced cellular injury. It must therefore be concluded that judicious supplementation of oxygen, as an appropriately blended and thermo-regulated gas mixture, under well indicated circumstances would be the best way to utilize oxygen in neonatal care.

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