Principle of oxygen therapy in the newborn

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Oxygen

The most common drugs used in NICU

Goal

to achieve adequate delivery oxygen to tissues without creating oxygen toxicity
Oxygen

The biomedical double-edged sword

- energy source of cellular life
- risk for oxygen toxicity

*There must be an oxygen pressure at which biological activity is optimal*
Physiologic consideration

- External respiration
  - transfer oxygen molecules from the atmosphere to blood
- Blood oxygen transport
  - movement of oxygen from blood to the site of intracellular utilization
- Internal respiration
  - oxygen consumption
External respiration

- definition: transfer oxygen molecules from atmosphere to the blood
- factors influence external respiration
  - fraction of inspired oxygen
  - distribution of ventilation
  - alveolar gas exchange
  - mixed venous-oxygen content
Unloading oxygen capability (Term and Preterm)

Term

Preterm 1000-1500 g.
Blood oxygen transport

- definition: movement of oxygen from the blood to the site of intracellular utilization
- factors influence blood oxygen transport
  - cardiac output
  - hemoglobin concentration
  - hemoglobin oxygen affinity
Factors affected oxygen transport

- amount of oxygen in blood
  - hemoglobin concentration
  - partial pressure of oxygen
  - oxygen-hemoglobin affinity
- delivery of oxygen
  - blood pressure and blood volume
  - cardiac output and distribution of flow
  - viscosity
- abnormalities in cellular metabolism
  - increased oxygen requirement e.g. hyperthermia, hypothermia
Hemoglobin-oxygen dissociation curve

- **Shift to the left**
  - increased oxygen affinity
  - less oxygen delivering to the tissue
  - increased oxygen content

- **Shift to the right**
  - decrease oxygen transport capability
  - enhance movement of oxygen from blood to tissue
  - decrease oxygen supply to tissue
  - decrease oxygen content
Hemoglobin-oxygen dissociation curve
Blood oxygen transport

- oxygen content (OC)
  - amount of hemoglobin
  - hemoglobin-oxygen dissociation curve
- \( OC = \text{oxy hemoglobin} + \text{dissolved oxygen} \)

Side chains:
- Methyl, -CH\(_3\)
- Vinyl, -CH-CH\(_2\)
- Propionic acid, -CH\(_2\)-CH\(_2\)-COOH
Internal respiration

- definition: oxygen consumption
- factors influence internal respiration
  - capillary perfusion
  - diffusion of oxygen to tissue
  - tissue oxygen utilization
Oxygen tension in cord blood and arterial blood at different postnatal age
Method to delivery oxygen

- simple oxygen mask
- oxygen cannula
- oxygen hood
- oxygen box
- oxygen via incubator
- continuous positive airway pressure (CPAP)
Oxygen mask and cannula

- **Simple oxygen mask**
  - apply in an emergency situation
  - provide a concentration of 50-90%
  - recommended flow 3-6 LPM

- **Oxygen cannula**
  - provide a fixed concentration which vary on flow rate
  - require a specific type of flow meter
Oxygen hood

- provide a stable concentration, visibility and access to most of the body
- recommend for acutely ill or unstable infants who require a $\text{FiO}_2 > 0.40$
- a minimum flow rate of 3 LPM is recommended in order to prevent $\text{CO}_2$ retention
Oxygen box

- provide a stable concentration, visibility and access to most of the body
- recommend for a $\text{FiO}_2 < 0.40$
- suitable for a chronically ill or stable infant in the crib
Oxygen via incubator

- provide a stable concentration, visibility and access to most of the body
- recommend for a FiO2 < 0.40
- recommend for a stable infant in the incubator
Oxygen monitoring

Oxygen analyzer

Arterial PaO$_2$ VS Oxygen saturation
Oxygen monitoring

- \( \text{PaO}_2 \)
- transcutaneous oxygen monitoring (\( \text{SpO}_2 \))
- oxygen content
  - \( \text{PO}_2 \) 100 mm Hg hemoglobin carries approx. 100 times more oxygen in plasma
  - 2 components of oxygen load
    - oxygen bound to hemoglobin
      - (1g. of Hb binds 1.34 ml. oxygen)
    - oxygen dissolved in plasma
      - (0.3 ml \( \text{O}_2 \)/100 ml)
Arterial PaO$_2$

- tissue oxygenation depends on PaO$_2$ or the saturation between tissue and blood
- in term of the saturation, change from fetal hemoglobin to adult hemoglobin should be considered in the newborn infants
  - naturally occurred
  - repeated transfusion during intensive care period
Oxygen saturation

- limitation to detect hyperoxia (\(\text{PaO}_2 > 12 \text{ kPa}; \text{SpO}_2 > 97\%\))
- sensitive to detect tissue hypoxemia when \(\text{PaO}_2\) is at the critical level (\(\text{PaO}_2\) is on the steep portion of the curve)
Oxygen saturation: limitation and recommendation

- no definite criteria for hypoxia
- to avoid hypoxia, saturation should be kept at the level of \( \text{PaO}_2 \) 50 kPa
- saturation should be intermittently compared with \( \text{PaO}_2 \) obtained from ABG
- lower acceptable limit of saturation: 85%
- upper acceptable limit of saturation: 97%
Oxygen saturation

- **advantages**
  - noninvasive
  - rapid response time
  - no tissue damage
  - sensitive to detect hypoxia

- **disadvantages**
  - varied with patient activity
  - influenced by edema, phototherapy, perfusion
  - insensitive to detect hyperoxia
Complications

- burns
- factors influence
  - skin maturation
  - tightness
  - duration of probe attachment
Oxygen toxicity
Development of oxygen radical defense systems

- Concentration of oxygen scavengers and antioxidant enzymes increase in lungs and kidney during pregnancy.
- Level of total antioxidant was lower in the preterm infants than the adult or term infants.
- VLBW infants have a higher capacity to produce oxygen radicals by the respiratory burst than term infants.
Oxygen free radical reperfusion injury

- accumulation of lipid peroxidation products following reperfusion
- protection by the administration of nonenzymatic antioxidants including vitamin E, glutathione, dimethylsulfoxide or enzymatic antioxidants
- the direct identification of free radicals by electron spin resonance spectroscopy
Actions of free radicals

Role of hypoxanthine - xanthine oxidase system

- hypoxanthine is the end product of the purine catabolism in most human organs
- hypoxanthine is a break down product from ATP, AMP
- during hypoxia, hypoxanthine is accumulated
- when hypoxanthine is oxidized to uric acid, oxygen radicals are formed
Mechanism for ischemia/reperfusion injury

ischemia

ATP

AMP

hypoxanthine

XD

protease

XO

$O_2^- + H_2O_2 + urate$

oxygenation
Oxygen toxicity

Neonatal free radical disease

- respiratory tract: bronchopulmonary dysplasia
- retina: retinopathy of prematurity
- brain: intraventricular hemorrhage, PV L
- gastrointestinal tract: necrotizing enterocolitis
- KUB: acute tubular necrosis
Oxygen free radicals

\[ \text{O}_2 + 4 \text{H}^+ + 4 \text{e} \rightarrow 2 \text{H}_2\text{O} \]

\[ \text{O}_2 + \text{e}^- \rightarrow \text{O}_2^- \quad \text{(superoxide radical)} \]

\[ \text{O}_2 + \text{e}^- \rightarrow \text{H}_2\text{O}_2 \quad \text{(hydrogenperoxide)} \]

\[ \text{H}_2\text{O}_2 + \text{e}^- \rightarrow .\text{OH} \quad \text{(hydroxyl radical)} \]

\[ .\text{HO} + \text{e}^- \rightarrow \text{H}_2\text{O} \quad \text{(water)} \]
Chemical mechanism of oxygen toxicity

Principle mechanism

- univalent reduction of molecular oxygen
- formation of free radical intermediates

Reactive O$_2$ metabolites

- Superoxide free radical (O$_2^-$)
- Hydrogen peroxide (H$_2$O$_2$)
- Hydrogen free radical (OH$^-$)
- Singlet oxygen (1O$_2$)
Actions of free radicals

- injure biological membranes by lipid peroxidation
- inactivate enzyme
- denature proteins
- break double strand of DNA
Antioxidant enzyme defense system

- Superoxide dismutase (SOD) detoxified $O_2^-$
- Catalase detoxified $H_2O_2$
- Glutathione peroxidase (GP) detoxified $H_2O_2$
- G-6-PD provided NADPH reduced glutathione
Actions of free radicals

Role of Iron

• nutritional iron deficiency in premature infants may be protective in oxygen radical-mediated injury

• lactoferrin and transferrin-like-iron-binding protein present in breast milk may have protection from oxygen radical injury

• low serum level of apotransferrin and ceruloplasmin in the premature infants may potentiate this type of injury
Actions of free radicals

Role of the activated leukocyte

- On exposure to bacteria, the oxygen uptake of neutrophils is increased as much as 50-fold
- A large amount of superoxide and hydrogen peroxide radicals are formed
- Leukocytes attack bacteria with oxygen radicals
- This phenomenon is called respiratory burst
Effects of alveolar macrophage

Exposure to prolonged high inspired oxygen

- influx of polymorphonuclear leukocytes
- impaired antiprotease defense system
- release of proteolytic enzyme
- proteolytic damage in alveolar wall
Pulmonary change of oxygen toxicity

- atelectasis (surfactant inactivation)
- edema
- alveolar hemorrhage
- inflammation
- fibrin deposition
- thickening and hyalinization of alveolar membrane
- tracheal, bronchiolar and type 1 alveolar lining cells were damaged
Free radical scavengers and antioxidants

Antioxidants

- vitamin E
- bilirubin
Free radical scavengers and antioxidant enzymes

Free radical scavengers

- mannitols
- superoxide dismutase
- bilirubin
- uric acid
- dimethyl sulfoxide
Factors that determine oxygen toxicity

- maturation
- nutritional and endocrine status
- duration of exposure to oxygen
- other oxidants

A safe level of inspired oxygen has not been established, any concentration in excess of room air may increase the risk of lung damage when administered over a period of time.
Policy for preventing ROP

- All infants who are at risk will be monitored with an oxygen saturation monitor.
- The upper limits for the monitor alarm will be routinely set at 95%.
- Daily attempts should be made to lower the FiO2 in stable, convalescing infants with O2 saturations in the low to mid 90’s.
- Correlating arterial samples will be obtained/attempted twice weekly.
ROP: oxygen monitoring policy

- administer oxygen via a hood as a primary mode of delivery for infants < 1500 g
- use oximetry to determine the optimum flow and distance from the face when using short term blow by O₂.
- monitor infants at risk by setting a strict upper limit for the oximeter of 95%
- If possible a calibration PaO₂ should be obtained twice weekly; simultaneous FiO₂, SaO₂ and PaO₂ will be recorded
ROP: oxygen monitoring policy

- obtain an arterial blood gas when an "at-risk" infant who was previously in room air is retreated with oxygen.
- if the arterial PaO₂ > 90 mm Hg, notify a physician and document the response
- adjust FiO₂ based on ordered parameters using oximetry and/or transcutaneous monitoring.
- ensure that an ROP check has been done at six weeks of age on infants ≤1500 g.
Prognostic factors

- **P(A-a)O\(_2\)** difference
  - in infants with PPHN, the mortality was 79% if P(A-a)O\(_2\) was equal to 610 mm Hg for 8 consecutive hrs

- **Oxygen index (OI)**
  - definition: MAP x FiO\(_2\)/ PaO\(_2\)
  - OI>40: 80% mortality
  - OI>25: 50% mortality
Alveolar-arterial oxygen pressure difference

- determine ventilation/perfusion (V/Q) mismatch
- normal value for adult in RA: 10-20 mm Hg
- normal value in the neonate
  - 40-50 mm Hg at birth
  - 300 mmHg (FiO₂ 1.0)
Alveolar-arterial Oxygen Pressure Difference

- $P(A-a)O_2$ – alveolar-arterial oxygen pressure difference
  - correlate with severity of lung disease
  - method of calculation
    - $PAO_2 = [FiO_2 \times (P_{\text{atm}} - P_{H_2O})] - PCO_2$
- Exp. $PaO_2 = 673$ mm Hg
  (FiO$_2$ 1.0; PCO$_2$ 40 mmHg)
Etiology of high P(A-a)O$_2$ difference

- diffusion block at the alveolar-capillary level
- V/Q mismatch in the lung
  - a result of ventilated areas poorly perfusion
  - perfused areas poorly ventilated intracardiac
- fixed right-to-left shunt
Graph for estimation the shunt at different inspired oxygen