# Oxygen toxicity

Dr. k. bhavana

Post graduate

Department of respiratory medicine

Narayana medical college and hospital.

# Introduction

- Oxygen therapy is administration of o2 at a concentration greater than room air (21%) with a goal of treating / preventing symptoms and manifestations of hypoxia.

- Oxygen toxicity is a condition resulting from the harmful effects of breathing molecular o2 at increased partial pressure.

- Oxygen toxicity is generally associated with following conditions

1. one where the patient is exposed to very high concentrations of o2 for brief periods of time.

   e.g.: hyperbaric oxygen therapy

   which shows acute toxicity with CNS manifestations predominantly.

2. other where lower concentrations of gas are used but for longer duration

   which causes chronic side effects predominantly pulmonary features.

# History

- Priestley who discovered oxygen, was himself among the first to suggest that there may be adverse effects of this pure air, when in 1775 he observed a candle burn out faster in oxygen than in air.

- important contribution in the field of oxygen toxicity is

In 1878 paulbert demonstrated convulsions, hence CNS toxic effects of oxygen are called **BERT EFFECT**.

In 1899 J lorain smith noticed fatal pneumonia in rats after 4 days of exposure to 73% o2 at 1 ATA. Hence pulmonary oxygen toxicity is called **SMITH EFFECT.**

- At sea level the partial pressure of O2 in environment air is approximately 160mm of hg (21.3 Kpa)

on inspiration the air is humidified and mixed with exhaled CO2

So partial pressure of O2 at alveolus is 100 mm of hg (13.3 Kpa)

Average thickness of alveolar capillary membrane is 0.3 µm with surface area of respiratory membrane is 50 to 100 $m^2$

Partial pressure of O2 in pulmonary capillary is approximately 90 mm of hg (12 Kpa)

- I gram of Hb binds 1.39ml of O2
- Delivery of O2, DO2ml/min is normally 1000ml /min
- 25% of DO2 i.e. 250ml/min is oxygen consumption , this varies with organs it can be 70% to 80% during exercise.
- Remaining 750ml/min is total reserve, this reaches back to lung as venous blood.
- In tissues mitochondria uses this for aerobic respiration.
- So 160mm of hg O2 at mouth can fall upto 1mm of hg in some mitochondria
- If < 1mm of hg demand for O2 exceeds the supply and ATP production decreases.

- Medical oxygen supply is a compressed gas .
- Pipeline supply to the wall is approximately 4 Bars of pressure (3040mm of hg).
- Cylinder supply pressure when full can be 137 Bars (104-120 mm of hg).
- Studies have shown that a high $PaO_2$ level within the first 24 hours is an independent factor for hospital mortality.

# Toxicity depends on

- Pressure
- Time
- Oxygen concentration.

- O2 can be toxic to lungs when high FiO2 (0.60) is administered over extended exposure time (>/= 24 hours) at normal barometric pressure (1ATA).

- SO PaO2 at 50-300 Kpa for hours / days can be toxic.

- O2 toxicity can be minimized by keeping the PaO2 ,80mm of hg 0r FiO2 <0.40 to 0.50.

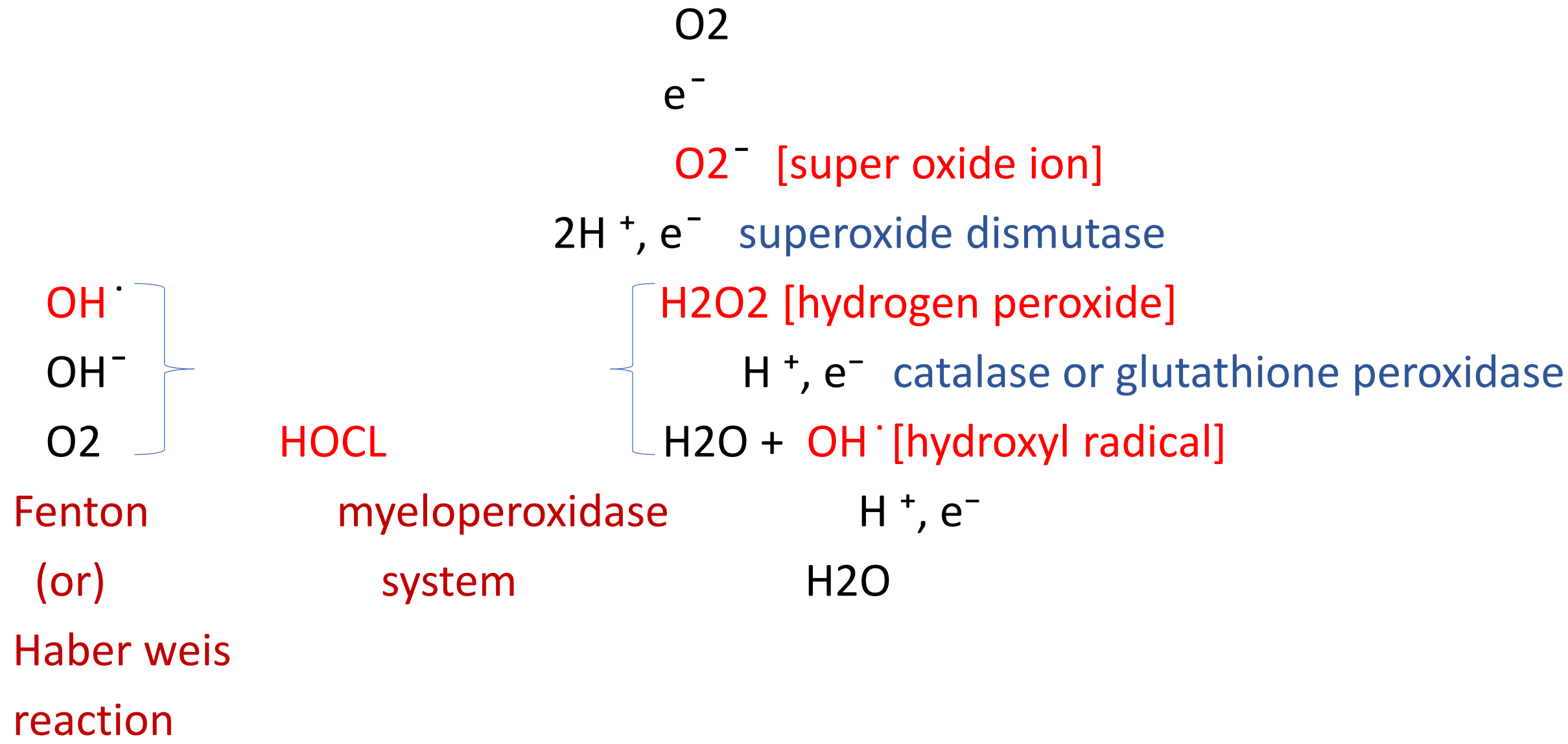
- When humans are exposed to 100% O2 at 101Kpa for 24 hours first symptoms were described as mild substernal tickling or tracheal irritation

# HIGH RISK GROUPS

- Long term ventilation with high Fio2.
- Those on high concentration of supplemental o2 for long duration (100% o2 for >8-12 hours).
- Infants and neonates getting 100% o2 for >2-3 hours.
- Premature babies.

- Patient on mechanical ventilation with exposure to levels >50%
- Exposed to chemicals that increase risk of o2 toxicity like chemo therauptic agents like bleomycin.
- Hyperbaric oxygen therapy.
- Under water divers.

# Mechanism of reactive oxygen species formation



- reactive oxygen species are

  super oxide ion $O_2^-$

  hydrogen peroxide $H_2O_2$

  hydroxyl radical $OH^{\cdot}$

  hypochlorous acid HOCL

# Sources of electrons

- Mitochondrial enzymes
- NADPH oxidase system
- Xanthine oxidoreductase
- Ferrous ion
- High PO2
- Exogenous compounds

# Sources of electrons for the reduction of O2

- Mitochondrial enzymes

during normal

oxidative respiration

(or)

glycolysis

NADH

oxidoreductase

releases electrons

[taken care by SOD]

few are pumped out by

mitochondrial permeability

(mPTP)

in cytoplasm they are taken

care by SOD

- If excess ROS are formed in mitochondria then prolonged opening of Mptp which leads to damage to mitochondria and cells.

- NADPH oxidase system

major electron donor in neutrophils and macrophages [phagocytic cells]

NADPH oxidase is present in phagocytic vesicle.

various stimuli like

bacteria

endotoxin

immunoglobulins

interleukins

activate

phagocytic

cells

which have phagocytic vesicles with NADPH oxidase

they donate electrons

superoxide ion

hydrogen peroxide

HOCL

- This super oxide ion helps in killing of bacteria

- So inappropriate activation of NADPH oxidase in marginal neutrophil

  can damage the endothelium of lung leading to acute lung injury.

- Xanthine oxidoreductase & reperfusion injury

Hypoxanthine → xanthine → uric acid

XOR XOR

XOR uses NADH as cofactor

In the case of hypoxia/ischemia NADH decreases so XOR uses $NAD^+$ and dioxygen ion as co factor which leads to formation of hydrogen peroxide and superoxide ion.

so during reperfusion extensive production of ROS happens.

- Ferrous ion

  $Fe^{2+}$ to $Fe^{3+}$ delivers a electron

  so it is a catalyst in Fenton reaction

  similar reaction also seen during conversion of hemoglobin to methemoglobin

- high PO2

  by law of mass action.

  normal tissue defenses are active only till PO2 till 60KPa (450mm of Hg)

- Exogenous compounds

  drugs , toxic substances act as an analogue for NADPH oxidase

  e.g.; bleomycin, nitrofurantoin.

# Harmful effects of reactive oxygen species

- They mainly effects DNA, lipids, sulphydryl containing proteins.
- All three are also sensitive for ionizing radiation
- DNA

  both mitochondrial and cytoplasmic DNA is damaged.

  repair errors, double strand breaks.

  activation of transcription factors and signal proteins.

- Lipids

  lipid peroxidation– it attaches to unsaturated fatty acids and damages the particular lipid and also generates another ROS.

  result– disrupts cell membrane  loss of integrity of the alveolar/capillary barrier in pulmonary oxygen toxicity

- Proteins– damages sulfhydryl proteins and results in formation of di sulphide bridges which inactivates wide range of proteins.

So till these leads to

inactivation of neurotransmitters

inhibition of proteins

release of cytokines

exertion of direct cytotoxic effects

Cell dysfunction inflammation malignancy (or)cell dealth

- All these are formed in a normal subject too but these are counterattacked by antioxidant systems in the case of excess O2 supply the balance between the oxidative and antioxidative systems is disrupted causing excess reactive oxygen species production and thereby oxygen toxicity.

# Defenses against reactive oxygen species

- Anti oxidant enzymes
  1. superoxide dismutase

3 types – extracellular
cytoplasmic containing manganese
mitochondrial containing copper and zinc.

stimulated by inflammatory factors like
hyperoxia
interferon
tumor necrosis factor
interleukin
lipopolysaccharide

2. catalase– cellular

extracellular

3. glutathione peroxidase

- Endogenous antioxidants
  1. ascorbic acid– removes hydroxyl free radical
  2. vitamin E– prevents lipid peroxidase chain.
  3. glutathione– high concentration on airway lining.
  4. surfactant– may act as an anti oxidant.

- exogenous anti oxidants
  1. allopurinol– may have an inhibitory action on many enzymes.
  2. iron chelating agent– stop ferrous ion which is a potent source of electrons for conversion of O2 to free radicals.
  3. mitochondrial targeted anti oxidants– experimental, may counterattack diaphragm weakness.
  4. in vitro– n-acetyl cysteine, beta carotene, dimethyl sulph oxide.

# Systemic effects of ROS

- RESPIRATORY EFFECTS

1. Lorrain smith effect

-- first described by J. Lorrain smith in 1899.

-- reduction of vital capacity of the patient is an indicator to monitor pulmonary toxicity.

-- the alveolar epithelial and alveolar capillary endothelial cells are vulnerable targets for O2-free-radical-induced injury caused by hyperoxia.

-- lung passage way congestion, pulmonary oedema, and atelectasis caused by damage to the linings of the bronchi and alveoli.

-- initially other body tissues are not effected due to hemoglobin-O2 buffer system but above a critical PaO2 this buffer system fails and the tissuePO2 rises.

-- at high levels of O2, protective endogenous antioxidant enzyme systems becomes consumed by ROS leading to cell death.

-- toxicity progress in overlapping phases with

initiation- lung fails to clear itself of mucus.

inflammation or exudative- destruction of the pulmonary lining and migration of leukocyte derived inflammatory mediators to the sites of injury.

proliferative- subacute, cellular hypertrophy, increased secretions from surfactant secreting alveolar type 2 cells and increased monocytes.

fibrotic- irreversible and permanent, collagen deposition, thickening of the pulmonary interstitial space and lung becomes fibrotic.

-- chest x-ray may show an alveolar interstitial pattern in an irregular distribution with evidence of a moderate volume loss from atelectasis.

- In short ROS damages the alveolar and capillary epithelium leading to capillary leakage causing interstitial oedema and later pulmonary oedema .
- Type 1 alveolar cells are effected first replacing them with type 2 alveolar cells which are cuboidal thereby the thickness for gaseous exchange increasing.

- Other pulmonary defects are

V/Q mismatch

ventilatory drive

Haldane effect– increasing $FiO_2$ decreases the $CO_2$ hemoglobin buffering capacity of hemoglobin, thus potentially leading to an increase in $PaCO_2$ and acidemia.

absorption atelectasis

increase in the work of breathing due to higher density of the oxygen compared with air.

tracheobronchitis : mild tickle on inhalation and progresses to frequent coughing.

bronchopulmonary dysplasia in neonates

ARDS

- CNS effects

-- first described by Paul Bert in 1878 hence called BERT EFFECT.

-- initially localized muscular twitching, especially about eyes, mouth and forehead. Small muscles of hand may also be involved.

-- incoordination of diaphragmatic activity in respiration may occur.

-- vertigo, nausea, followed by altered behavior, clumsiness, finally convulsions.

-- generalized tonic clonic seizures are seen.

-- CNS toxicity is hastened by factors such as raised PCO2, stress, fatigue and cold.

- Ocular effects

  myopia

  cataract

  retinal detachments

  retrolental fibroplasia/ retinopathy of prematurity

# Prevention and monitoring

- The abrupt stoppage of oxygen at the onset of toxicity may at times aggravate the symptoms, the OXYGEN OFF EFFECT.

- Indicator to monitor the pulmonary toxicity is reduction of vital capacity.

- 10% reduction is maximum acceptable.

- Dynamic lung compliance and the diffusing capacity for carbon monoxide are also seen reduced.

- Unit of pulmonary toxicity dosage (UPTD) is a theoretical concept, one minute of 100% oxygen at 1 atmosphere is taken to produce 1 UPTD. A UPTD of 1425 will produce a 10% reduction in the vital capacity.

- Spirometry findings

FVC, FEV1, MEF – decreases,

easy to use, can be measured by portable spirometry.

but effort dependent, needs proper trained lung function technician, co operative subjects, not able to detect small changes.

large individual variation.

influenced by exercise.

inappropriate for short in water oxygen exposure.

LUNG COMPLAINCE– measured in both conscious and unconscious.
differentiate emphysema and fibrosis.
but technically demanding.
performed in laboratory or hospital setting
reproducibility is less.

DLCO– differentiate between alveolocapillary membrane derived injuries
and pulmonary capillary blood volume derived injuries.
monitor development and recovery.
more sensitive than VC.
cannot measure directly after oxygen exposure need a ten minute break ,
need a technician

- Management of oxygen toxicity is purely supportive, prevention and monitoring Is of great importance.
- Close monitoring of patients on O2 therapy is needed.

# Take home message

- Oxygen is commonly used as a part of therapy of many disorders.
- This gas can have toxic effects if used injudiciously.
- These toxic manifestations usually involve the CNS, lungs and the eyes.
- The management of the condition is purely symptomatic and the emphasis should lie on its prevention.
- Individual susceptibility being very variable, it is imperative for all clinicians to be aware of and equipped to manage the crisis should it arise.

Thank you