How much is too much of a good thing?

Nepean WTET summary 14/4/20

Rationale and Background

- Administration of supplemental oxygen is one of the most common therapies in ICU practice, most frequently used to manage hypoxaemia which can lead to tissue hypoxia and end organ dysfunction or failure. Oxygen usually forms part of a supportive management strategy whilst the underlying pathology is identified and targeted treatments given.
- Oxygen content of blood is predominantly dependent on \([\text{Hb}]\) and \(\text{SaO}_2/\text{SpO}_2\). Delivery of which at a tissue level is dependent on cardiac output, tissue perfusion (to include MAP) and a balance between supply-demand (increase demand in hypermetabolic states).
- \(\text{PaO}_2\) contributes little to oxygen content but impacts autoregulatory mechanisms (in particular of cerebral and pulmonary vasculature) which can increase/decrease blood flow respectively if dissolved concentrations (\(\text{PaO}_2\)) are low.
- Alveolar oxygen concentration is dependent not only on \(\text{FiO}_2\) but also minute ventilation e.g. supplemental \(\text{O}_2\) may slightly delay but won’t prevent a hypoxic cardiac arrest from apnoea.
- High \(\text{FiO}_2\) (even when indicated) can lead to absorption atelectasis and increased shunt – thereby paradoxically worsening gas exchange and hypoxia.
- Hyperoxia is associated with increase free radical oxygen species generation which if marked and/or prolonged deplete anti-oxidant scavenging stores and cause apoptosis and cell death.
- Both hypoxia and hyperoxia are therefore harmful and it is important to titrate this commonly used therapy to appropriate goal posts.

Advantages and Disadvantages of each strategy

- Potential harm of trend towards overly conservative \(\text{O}_2\) target
  - Organ dysfunction and/or failures
  - Increased ICP, worsening pulmonary hypertension
- Potential harm of trend towards overly liberal \(\text{O}_2\) target
  - Evidence of harm in a number of studies in non-critical ill eg:
    - AVOID trial (STEMI randomised to supplemental \(\text{O}_2\) to all versus supplemental \(\text{O}_2\) only if \(\text{SpO}_2 <94\%\) to target \(\text{SpO}_2 94\%) \rightarrow\) showed increase infarct size with hyperoxic arm at 6m \(\rightarrow\) changed practice!
    - Similar studies in stroke population \(\rightarrow\) increased infarct size with hyperoxia
    - CNS toxicity includes seizures (mostly hyperbaric studies)
  - Contraindicated in specific conditions (accelerates fibrosis) eg paraquat poisoning and bleomycin toxicity
  - High \(\text{FiO}_2\) may cause absorption atelectasis, worsening shunt and hypoxia
  - Hyperoxic acute lung injury (HALI); prolonged high concentrations of oxygen have been shown in healthy animals to cause a clinical picture in keeping with ARDS

Evidence

- Oxygen-ICU JAMA 2016
  - RCT, Single center non-blinded, Italian, \(n=434\)
  - ICU patients expected >72h randomised to target \(\text{SpO}_2 94-98\%\) vs 97-100\%
Conservative strategy significantly reduced ICU mortality (11.6% vs 20.2%)

- HYPERS2S Lancet 2017
  - Hyperoxia and hypertonic saline in septic shock; 2x2 MC RCT
  - Stopped early (n=442) due to high mortality in hyperoxia group

- IOTA Lancet 2018
  - Meta-analysis, 19 trials, n>15000
  - Increased mortality with hyperoxia secondary to liberal oxygen strategy

- LOCO2 NEJM 2020
  - MC RCT 13 French ICUs 2016-2018
  - Liberal (PaO₂ 90-105mmHg / SpO₂ =/>96%) vs conservative (PaO₂ 55-70 / SpO₂ 88-92%) O₂ therapy for 7d within 12h of invasive ventilation with ARDS (NB excl. COPD)
  - Stopped early, after n=201 (power calculation n=850), no difference in 28d mortality, increased 90d/6m mortality in conservative group with more mesenteric ischaemia

- ICU ROX NEJM 2020
  - ANZICS MC RCT; MV<2h expected >48h, n=1000
  - Conservative (SpO₂ 91-96%) vs liberal (91% to no upper limit)
  - No difference in ventilator free days at d28, or secondary outcomes (90/180d mortality)
  - Subgroup; signal of benefit (restrictive O₂) in hypoxic-ischemic encephalopathy
  - Not ethical to give liberal arm as high a target as in oxygen-ICU (proven harm), therefore with smaller differences between liberal and conservative arm this study may not large enough trial to answer this question. Common therapy and so important question → ICU megarox

Summary (my practice)
- In the general ICU population I try to avoid both hyperoxia and hypoxia most of the time (e.g. I do allow transient hyperoxia as part of pre-oxygenation for intubation)
- I carefully consider all aspects of how oxygen delivery may be affected (down to cellular dysoxia in sepsis for example), where the pathologies may lie and how they can be treated and optimised
- Overall I consider on a case-by-case basis the balance of benefit versus harm of a relative conservative versus relative liberal approach to oxygen targets - accepting that very tight parameters are not achievable on a practical level all of the time
- Specific indications for minimising / avoiding supplemental O₂:
  - Bleomycin toxicity / paraquat poisoning
  - STEMI, CVA with SaO₂/SpO₂ >94%
- Specific indications for tolerating / targeting hyperoxia:
  - Life-threatening anaemia with contraindication to transfusion (e.g. Jehovas Witness)
  - Carbon monoxide poisoning
  - Raised ICP, TBI (target PaO₂ >70mmHg)
  - Acute/severe pulmonary hypertension (target PaO₂ >70mmHg)
  - May consider for conservative management of simple pneumothorax (de-N₂)
- I sometimes use response to titration of FiO₂ as a diagnostic tool – where large changes in FiO₂ yield little change in SpO₂ I think of predominant shunt pathologies
- My usual practice outside of specific indications otherwise, is to target SaO₂/SpO₂ 90-94% (unless chronically hypercapnoeic, in which I target 88-92%). I give the minimum FiO₂ needed to achieve this target understanding reductions in FiO₂ even where systemic hyperoxia not an issue, may reduce HALI and absorption atelectasis
- I try and balance these two strategies and their potential harms. I await new evidence (ICU megarox) to inform / guide my practice further (with particular attention to emerging subgroups).