Risks and Benefits of Oxygen Therapy

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Mootha and Chinnery review the potential for hypoxia as therapy for mitochondrial disease. At first sight this is counter-intuitive. It seems improbable that reducing the availability of a substrate that enables high-energy phosphate production via oxidative phosphorylation would be of benefit. But recent clinical data beyond the field of inherited metabolic disease support this approach.

Firstly, increased oxygen delivery to supra-normal levels is associated with harm in stroke, sepsis, myocardial infarction and following cardiac arrest: all diseases characterised by initial cellular hypoxia.

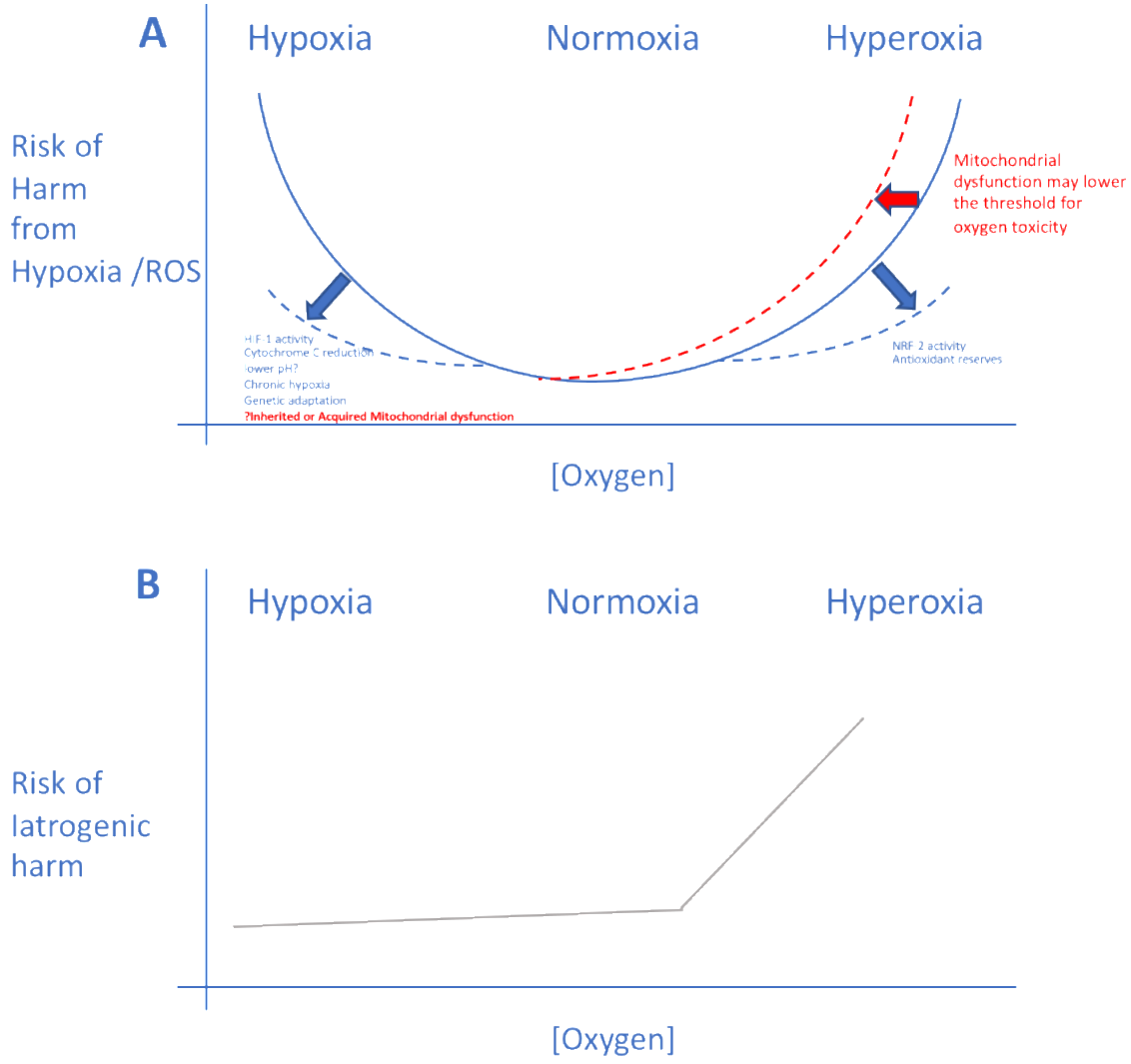
Secondly, "*permissive hypoxia"* is emerging as a potentially superior treatment strategy in critical illness. Infants with RSV bronchiolitis recover more quickly with lower peripheral oxygenation saturation (SpO2) targets. Trials of oxygen targets in critically ill adults indicate superiority, or at least non-inferiority, of the lower targets values. We recently completed a pilot trial of conservative vs. liberal oxygenation in 120 critically ill children (Oxy-PICU). Large scale 'definitive' trials are now being planned. However, in contrast, extremely premature infants (<28 weeks gestation) are harmed by permissive hypoxia.

But why might a lower oxygen target be beneficial in critical illness? One simple option is that a high oxygen level is not in itself harmful, but that the extra interventions provided to raise oxygen increase iatrogenic injury. High SpO2 or PaO2 may be proxies for 'overtreatment' with sedative, analgesics, higher ventilator pressures and tidal volumes. (Figure) This explanation has potential merit; other ICU treatments (blood transfusions, parenteral nutrition or insulin infusions) are harmful unless used very conservatively. However, the benefits of hypoxia observed in the mouse Leigh's model cannot be explained by decreased iatrogenic injury. Instead perhaps oxygen is directly toxic; and defences against this toxicity are easily overcome in mitochondrial diseases or critical illness (where secondary mitochondrial dysfunction is common). This may be relevant even at normal inspired oxygen concentrations. After all, the bio-geological history of oxygen on earth means that many structures – including mitochondria – evolved when absent or very low oxygen tensions prevailed.

The challenge remains in defining the thresholds of harm. Our clinical measures of PaO2 or SpO2 are far upstream of the oxygen present for OXPHOS: we cannot measure this directly and it will vary both between and within tissues. Indeed, that may not be enough to define risk anyway since OXPHOS (in isolated mitochondria at least) is itself influenced by local oxygen tension (and pH) over a far greater range than previously thought. (Wilson 2017) Highly sophisticated oxygen-sensing mechanisms trigger complex adaptive transcription responses in hypoxia (HIF-1) or hyperoxia (NRF-2). (Fratantonio et al. 2018) The sweet-spot for oxygen therapy in an individual is therefore likely to be complex. We manage other drugs with narrow therapeutic ranges by aiming to use the 'minimum-effective dose' with due consideration of dose-related side effects. This may be the future for oxygen therapy, but in order to do this we need to be able to define a threshold for effectiveness and accurately measure both effectiveness and hyperoxia-related side effects in acute settings.

Mootha and Chinnery's call for consideration of therapeutic hypoxia may have implications for a wider population beyond those with inherited mitochondrial disease. Upcoming trials of optimal targets of oxygen delivery in critical illness are already challenging the dogma of supplemental oxygen for all in clinical medicine.

Figure. **Possible Relationship between Oxygenation and Harm in Acute Severe Illness.** A) Both severe hypoxia and hyperoxia harm tissue in part, via reactive oxygen species. Oxygen-sensing mechanisms activate transcription regulators hypoxia-inducible factor-1 (HIF-1) to attenuate hypoxic injury and NRF-2 to ameliorate hyperoxic harm. The degree of harm therefore depends on many factors including timing and baseline mitochondrial function. B) Overly aggressive treatments contribute to iatrogenic harm -e.g. higher oxygen tensions in the context of severe acute respiratory distress syndrome may increase the risk of iatrogenic ventilatory-induced lung injury. The overall risks and benefits and oxygen therapy will arise from a combination of these effects.


A
Hypoxia
Normoxia
Hyperoxia
Risk of Harm from Hypoxia /ROS
Mitochondrial dysfunction may lower the threshold for oxygen toxicity
HIF 1 activity
Cytochrome C reduction
Lower pH?
Chronic hypoxia
Genetic adaptation
?Inherited or Acquired Mitochondrial dysfunction
NRF 2 activity
Antioxidant reserves
[Oxygen]
B
Hypoxia
Normoxia
Hyperoxia
Risk of Iatrogenic harm
[Oxygen]

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