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Hyperoxia – A Journey to the Centre of the Cell

An overview of hyperoxia, effect of reactive oxygen species on biological processes and tissues and effective strategies for oxygen therapy.

The reliance of life on oxygen is a modern and terra-centric view. Oxygen only appeared on the scene about 450 million years ago – wiping out many life forms or forcing them to trap oxygen with porphyrin rings – the ancestor of our own haemoglobin.

Therefore strategies to cope with low oxygen are numerous – from the bar headed goose at altitude over the Himalayas, to the naked mole rat shrouded in subterranean earth, to the deep diving turtle, which can withstand anoxia for 15 minutes.

Strategies for excess oxygen have had little selection pressure – or have they? Reactive oxygen species (ROS) are the main by-product that draw attention. How does inspired oxygen affect this? What do they do to cells, and to organisms? What protection do we have from them? What does the evidence say for our patients?

Current RCTs

Evidence at present tends towards increased harm from hyperoxaemia, particularly in respiratory patients. However one trial suggested increased rates of ischaemic gut in a conservative oxygen arm and was stopped early due to unlikelihood of finding a significant primary endpoint difference (mortality) (Barrot et al. 2020).

HYPERS2S (oxygen in septic shock), and OXYGEN-ICU suggest increased mortality in hyperoxia. SO2S (oxygen in stroke), ICU-ROX (oxygen in ICU), and AVOID (oxygen in MI requiring PCI) found no benefit of hyperoxia. The IOTA 2018 meta-analysis suggested a trend towards mortality in hyperoxia- albeit weighted heavily in OXYGEN-ICU which had some methodological flaws

Effect of FiO_2 on ROS Generation

Many of us will be familiar with the oxygen cascade – the journey from atmospheric concentration, to dilution with water vapour, respiratory tract mixing, diffusion across the lung surface, capture in blood, and delivery to the mitochondria. It is not clear how much inspired oxygen eventually reaches the mitochondrial electron transport chain (ETC), nor, how much of this is coupled to ATP production or, is leaked as ROS. The proportion varies by disease state and prior level of fitness.

For example, HIIT induces mitochondrial biogenesis genes that enable prompt repair and recovery from ROS-damage; furthermore it also induces the electron transport chain complexes to super-assemble into a formation that reduces ROS leak from the guilty party, which is often complex I. Thus, altitude trained athletes could use 60% oxygen with no measurable oxidative stress in blood or urinary measures of ROS production (Wilbur et al. 2004). However, the effect of cell stress/pathogen exposure/hypoxia on the mitochondrial ETC is often to break it between complex I. and II, reverse shunting oxygen back the way it has come and releasing it as a free radical (Liu et al. 2002). This is an alarmin signal that helps stabilise cell siege responses (for example an active subunit of HIFa, which transcribes an array of heat shock proteins, antioxidants and metabolic enzymes like pyruvate dehydrogenase, turning away from the Kreb's cycle). In this setting, ROS is enhanced by elevated FiO_2 (Yang et al. 2016).

Effect of ROS on Biological Processes Pertinent to Critical Care

ROS and other agents such as cyanide and hydrogen sulphide are actually used in health as short distance, rapid cell mediators, and are a completely normal and necessary part of cell function – coupling ATP production to consumption. However like all poisons, it is the dose that is important. Mismatch between ROS and antioxidant defence has become a focus of organ damage – see vitamin C advocation. However when a cell is stressed, iatrogenic intervention can confuse the cell siege strategy developed by pathogen exposure. In the setting of infection, giving a conflicting signal in the form of over-adequate oxygen, can generate ROS and further alarmins.

Effects of ROS on Tissues

Immune

The reverse electron transport mentioned above in the context of infection, is weaponised by neutrophils and other cells, to destroy invaders. Eukaryotic cells have better resistance to ROS than many invaders for a number of reasons, so ROS are a useful frenemy. One, DNA is inherently more stable than RNA in terms of oxidisation, inevitably why it arose, moreover keeping DNA tightly sealed in a lipid membrane means it is the nuclear envelope, ahead of the genetic material, that gets oxidised. Burst killing by neutrophils is infamous – visible

as pus. In fact, increasing FiO_2 enhances burst killing as one might expect (Tantingco and Ryou 2020), and was an historic argument for the use of supplementary oxygen in reducing wound infection.

However ROS and their oxidisation of anything within reach – especially membrane lipids, are prone to activating both apoptosis via mitochondrial damage, as well as pyroptosis via activation of innate immune components, such as the inflammasome.

One group actually found that repeated (but not sustained) cycles of hypoxia reduced ROS generation and the inflammatory phenotype of microglia (Tantingco and Ryou 2020). This is similar to the concept of remote ischaemic conditioning – a distal distress signal that prepares other tissues for siege. Repeated hypoxic exposure also appears to have beneficial effects on mitochondrial and skeletal metabolism – and is under investigation in sport performance fields. The key is that it is never sustained to the point of apoptosis. Cyclical permissive hypoxia is a novel concept. Similarly it was noted that in presence of lactate, oxidative phosphorylation increased with increasing oxygen, maintaining VO_2 max, whilst in presence of glucose, VO_2 was static. Cells require the correct substrate to utilise oxygen and limit ROS (Levasseur et al. 2006), and this is dynamic in stress.

Lung

FiO_2 is known to cause diffuse alveolar damage alone and in conjunction with mechanical ventilation (VILI); the two are synergistic. However hypoxia is of course, deleterious to the rest of the body, and as such, the lungs are often over-oxygenated to bypass an AA gradient or mismatch to improve blood oxygen content. The lungs are therefore a special focus of ROS interest. ROS are indicated in the mechanism of VILI (Zhu et al. 2018). Intriguingly, another source of oxidative stress in critical illness, is free heme. As a transition metal, its ability to flip between ferric and ferrous give it a unique tendency to oxidise its surroundings. It is therefore unsurprising heme stabilises siege players like HIFa, and also unsurprising that three of the proteins raised in inflammation are ferritin (binds heme), hepcidin, and heme oxygenase. The process by which heme causes cell death is called ferroptosis – mitochondria are especially susceptible, and they are also the site of its production. Chelation with deferoxamine (pre exposure rather during the insult) was able to markedly reduce VALI in mouse models (Zhu et al. 2018). This is tricky in a critical care setting, where we receive the insulted physiology after the event, however it could be a strategy before high risk anaesthetics and surgeries which are likely to require prolonged ventilation post operatively. As ICU patients are often also anaemic (although not pathologically so…), the body may already have chelated what it can.

> **"mismatch between ROS and antioxidant defence has become a focus of organ damage"**

Heart

Cardiac mitochondria are unique in that they use special peroxisomes to ship out ROS and manage the peroxide consequences of their hard work.

Brain

ROS are naturally an obvious problem with respect to hypoxia, ischaemia-reperfusion and sub arachnoid haemorrhage, the scope of which is extensive. Given the highly limited regeneration of neural tissue in the adult, attention has been given to keeping patients sedated with neuroprotective adjuncts, such as Xenon, whose neuroprotective properties seem to stem from repelling the excitotoxic effects of NMDA receptor stimulation.

Kidney

Acute Kidney Injury (AKI) has proved a valuable model in all the ways ROS cause renal dysfunction and various strategies have been used to try and reduce the issue (Tomsa et al. 2019).

Gut

As a highly metabolic tissue, prone to ischaemia, and also prone to resistant post-operative ileus, ROS are an important issue for the gut. Hypoxia here makes mucosal surfaces susceptible to erosion and invasion, the consequences of which bear hefty lethality and was a clinical concern in RCTs of conservative oxygen use in ICU. It is also in fly gut, that the ROS generation of sleep deprivation was proven to be fatal (Hindson 2020). A balancing act is plainly needed. Of note, ileus seems to be particularly related to NO more than mitochondrial ROS, as exogenously applied nitrite proved to be exceptional in a model of murine ileus (Cosyns et al. 2015), via inhibition of guanyl cyclase.

Defences Against ROS

ROS are an ancient foe and strategies are conserved across phyla, normally pertaining to antioxidant enzymes and free radical sinks. Classics are gluthionine, thioredoxin, superoxide dismutase, and manganese. Defects in all these systems tend to be associated with cardiac and CNS developmental issues/degeneration. They are the range of antioxidants switched on in arousal from hibernation (Yin et al. 2016), where metabolism climbs ten-to-hundred fold within hours.

Intriguingly, of the mammals, primates lost the ability to synthesise their own vitamin C and require it via diet. It is unclear then, if it is superfluous, or actively selected against. Numerous advantages for acquiring orally exist (Hornung and Biesalski 2019). Ascorbic acid levels are frequently quoted as reduced in sepsis (most antioxidants are

consumed) and has wide controversy in terms of improving outcome in any kind of inflammatory setting, with most large RCTs failing to show a mortality benefit. For example, ascorbic acid transporters are downregulated in disease (Hornung and Biesalski 2019), and for another, ROS are highly reactive and disappear in a very short distance – almost all intracellularly. The utility of enteral and IV antioxidants when ROS speciation occurs inside cells, could be viewed with cynicism. Mitochondrially-targeted antioxidants, however, may be another avenue. ROS-independent benefits of vitamin C may be circulatory and also related to vasopressor synthesis.

ROS tend to evoke an inflammatory reaction but also invoke stabilising intracellular networks – be it HIFa, heme oxygenase, heatshock proteins and mitochondrial proteins. As a dynamic illness, critical care admissions are likely in different seasons of wax and wane at any given time point.

Medical Interventions

Vitamin C remains controversial – the VITAMINS trial found no benefit, CITRUS-ALI found some survival benefit in a secondary endpoint, although there are some statistical flaws regarding survivor bias.

Novel interventions such as MitoQ (mitochondrial free radical scavenger) show promise in preventing organ damage in septic mice (Lowes et al. 2008). It is rarely as simple as ROS alone, as they are inextractably linked to metabolism, glycolysis and central mediators of them all, like mTOR (famous for improving animal survival when given the red grape extract resveratrol).

Additionally, paying attention to the beneficial effects of ROS (e.g. regulation of genes downstream from HIFa) has prompted development of both HIFa agonists, and antagonists to its oxygen sensitive component prolyl dehydroxylase (PHD). These are exceptional anti-inflammatory drugs (PHD inhibitors) – they show efficacy in protection from AKI in caecal ligation puncture models if delivered pre puncture, and reduce mortality from LPS-induced endotoxaemia, however, they increase mortality from polymicrobial sepsis because of a lack of inflammatory response (Vanderhaeghen et al. 2020). ROS are PHD inhibitors.

Other agents in development target the molecular clock – BMAL-1 and its nuclear transcription factor Rev-erb – be it plant or animal, UV light exposure and feeding has meant circadian enrichment of antioxidant genes, stress proteins, mitochondrial regulators and protectors.

Conclusion

Given that sepsis is a disease of exacerbated inflammation followed by inappropriate immune tolerance, timing is clearly everything with such drugs, and likely, also with oxygen. According to Vonnegut "science is magic that works".

Conflict of Interest

None. ■

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