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LETTER TO THE EDITORS

Risks and benefits of oxygen therapy

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Mootha and Chinnery review the risks and benefits of oxygen administration in mitochondrial disease. They highlight probable harm from hyperoxia and possible benefit from hypoxia. 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 (Chu et al. 2018).

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 (Cunningham et al. 2015). Trials of oxygen targets in critically ill adults indicate superiority, or at least non-inferiority, of the lower targets values (Panwar et al. 2016; Girardis et al. 2016). We recently completed a pilot trial of conservative vs. liberal oxygenation in 120 critically ill children (Oxy-PICU) (Jones et al. 2017). Large-scale 'definitive' trials are now being planned (Peters et al. 2017). However, in contrast, extremely premature infants (< 28-week gestation) are harmed by permissive hypoxia (BOOST II United Kingdom Collaborative Group et al. 2013).

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 SpO_2 or PaO_2 may be proxies for 'overtreatment' with sedative, analgesics, higher ventilator pressures and tidal volumes (Fig. 1). 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 the mouse Leigh's model cannot be explained by decreased iatrogenic injury (Jain et al. 2016; Ferrari et al. 2017). Instead perhaps oxygen is directly toxic; and defences are easily overcome in mitochondrial diseases or critical illness with secondary mitochondrial dysfunction. 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 PaO_2 or SpO_2 are far upstream of the oxygen presented 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 influenced by local oxygen tension (and pH) over a far greater range than previously thought (Wilson 2017). Highly sophisticated oxygen-sensing mechanisms trigger adaptive transcription responses in hypoxia (HIF-1) or

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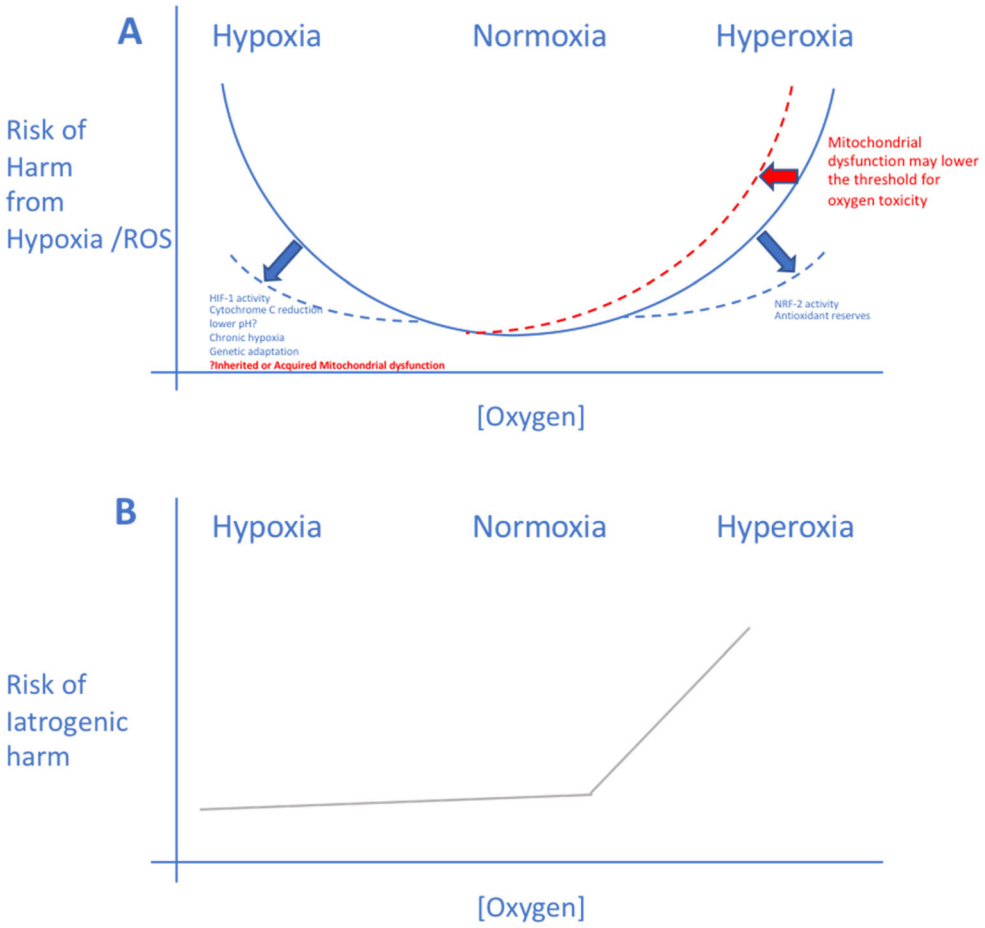

Fig. 1 Possible relationship between oxygenation and harm in acute severe illness. **a** Both severe hypoxia and hyperoxia harm tissue in part, via reactive oxygen species. Oxygen-sensing mechanisms activate transcription regulators hypoxia-inducible factor-1 (HIF-1) to attenuate hypoxic injury and NRF-2 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

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'. This may be the future for oxygen therapy.

Mootha and Chinnery's call for reconsideration of oxygen therapy is relevant for a wider population beyond those with inherited mitochondrial disease. The mechanisms for harm may be common to both populations. Trials of oxygen targets in critical illness are already challenging the dogma of 'supplemental oxygen for all' in clinical medicine.

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Compliance with ethical standards

Conflict of interest Mark Peters, Gareth Jones, Simon Eaton, Daisy Wiley and Samiran Ray declare that they have no conflict of interest.

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