Towards Causality with Liberal Oxygen Use?

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Studies of hyperoxia and poor outcomes have been proliferating in the medical literature. In *The Journal* alone Raman et al[1] and Numa and colleagues[2] each demonstrated a U-shaped relationship between pediatric intensive care unit admission arterial partial pressure of oxygen (PaO2) and mortality, and Sznycer-Taub[3] and Beshish[4] report large odds ratios of harm for hyperoxia on venoarterial extracorporeal membrane oxygenation and bypass respectively.

In a previous editorial[5] we called for reproduction of this association in other populations- including a hunt for unmeasured confounders. Further, we urged consideration of the factors that might help us understand if any *causal* association between hyperoxia and outcome was likely. The "*Bradford-Hill*" criteria are features that support likely causation in any observed association[6]. These include biological feasibility, an appropriate timing between the exposure and outcome, and a dose-response relationship. All of these have been described in the hyperoxia and harm relationship .

In this issue of *The Journal* Balcarcel et al[7] report on association between the cumulative exposure to *excessive* oxygen supplementation in the first twenty-four hours after admission to PICU and more severe subsequent multi-organ dysfunction and mortality in 5,406 mechanically ventilated children in two hospitals. The focus is not simply on the achieved oxygenation (saturation or partial pressure) or fraction of inspired oxygen but on a novel parameter "cumulative exposure to oxygen excess" (CEOE) defined as the mean hourly diference between the FiO_2 provided above 0.21, when the corresponding hourly SpO_2 was 95% or above during the first 24 hours of mechanical ventilation. In the high CEOE quartile they observed a increased risk of both MODS on day 7 and in-hospital mortality after adjusting for age, presence of MODS on day 1, study site and immunodeficiency status. The result was robust across a range of exploratory analyses including in the subset of cases without MODS on day 1 of mechanical ventilation, and those cases with confirmed or suspected infection.

The importance of this work maybe greater than providing a first estimate for the size of the association of excess oxygen dose and outcome. It may contribute to understanding the possible mechanisms (or confounders) in play between oxygen therapy and harm. We suggest that a (simplified) version of the causal relationships might look something like the figure. We show this only to illustrate the likely complexity of causation and confounders that are in play with even very well-conducted observational studies. Firstly this diagram indicates the possible confounder of *clinician concern*. Fear of hypoxia and its associated risks may lead staff to treat higher risk patients more intensively than is physiologically necessary. Some of this perception will not be captured in standard severity of illness or organ failure scores. A desire not to be 'close to the edge' may nudge up ventilator settings and oxygen exposure. This simple but unmeasurable, clinician-derived confounder may increase excessive oxygen exposure in cases at higher risk increased MODs and mortality. The mediators may be inappropriately higher ventilator pressures and tidal volumes (or delayed weaning) leading to poorer outcomes.

The simple causal path between hyperoxia and poor outcomes via oxidative injury is appealing but is likely overly simplisitic. Indeed it may not be present at all. Hyperoxia may reflect overly aggressive ventilation. This might occur more frequently when unit activity is higher and staffing numbers or expertise are lower than normal. In such a situation weaning may be less rapid and organ injury more frequent because of ventilator-induced lung injury via barotrauma/volutrauma and biotrauma driving systemic inflammation. Or perhaps quality of care in other ways maybe suboptimial at the same time when hyperoxia is not recognised. Although that seems unlikely in a high-resource setting, we have observed that our own practice is for much more liberal oxygenation than we intend.[8]

By focussing on excessive oxygen exposure rather than a predefined threshold for hyperoxaemia, Balcarcel et al have added credibility to such an indirect causal path between excessive oxygen exposure and poor outcome. The direct path remains credible.

There is a middle ground where excessive oxygen exposure such as reported by Balcarcel at el is the mediator of injury but only at the alveolar level. In this case oxidative injury would

occur to lung epithelium but systemic injury would follow from soluble damage associated molecular patterns arising from lung injury.

Our own approach to this complexity is pragmatic. We are conducting a multi centre randomised clinical trial of conservative (SpO_2 88-92) vs liberal (SpO_2 >94) peripheral oxygenation targets in critically ill children aiming to recruit 2040 participants (ISRCTN92103439). Our primary outcome measure is a composite of mortality and days of organ dysfunction, alongside measures of cost-effectiveness and functional outcomes. We will only be able to report on the combined effect of the choice of these two SpO2 targets *and* the intensive care strategies required to achieve them. While the randomisation will reduce the impact of several of the confounders in the causal network, it will not answer the mechanistic questions.

A true understanding of the risks and benefits of different levels of oxygenation will require mechanistic studies of the pathways leading to harm via increased oxidative stress or other routes. Eventually this knowledge might enable informed oxygen targeting to an individual critically ill child's needs. In the meantime Balcarcel and colleagues have reminded us of the huge complexity of even the simplest interventions in critical illness.

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Figure: Possible Causal Graphic Model of Oxygen Administration and Severity of Organ Failure

There are several ways in which increased oxygen may cause organ failure: either directly through increased oxidative stress or indirectly as a marker of more aggressive treatment than is required. An unmeasured confounder of clinician concern of a high-risk patient may prompt higher ventilator settings with an increased risk of ventilator induced lung injury, and increased oxygen exposure. Randomised trials of oxygen targets or studies that assess markers of oxidative injury may help clarify the causal relationships.