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Oxygen: A Luxurious Life Giving and Potentially Toxic Gas:

Commentary on: "Hyperoxia is Associated with Poor Outcomes in Pediatric Cardiac Patients Supported on Veno-arterial Extracorporeal Membrane Oxygenation (VA-ECMO)"

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Oxygen appeared in the Earth's atmosphere about 2.8 billion years ago as a result of production by cyanobacteria and by photosynthesis. Once oxygen took residence on Earth, only organisms that were capable of eliminating its toxic products. i.e. reactive oxygen species (ROS), using their antioxidant systems managed to survive (1,2). The discovery and description of oxygen is attributed to Joseph Priestley in 1774. Breathing the gas himself, Priestley reported that he felt "peculiarly light and easy for some time afterwards. Who can tell but that in time, this pure air may become a fashionable article in luxury…" (3). Recent studies on potential toxic effects of oxygen due to hyperoxemia after ischemia reperfusion have reinvigorated the interest in this aspect of patient management and created controversy. In this issue of the journal, Sznycer-Taub et al., report their findings on the topic of hyperoxia in infants with congenital heart disease who are placed on VA-ECMO in the post-operative setting (4). Sznycer-Taub and colleagues' study is the first report on this topic in patients supported on ECMO. In this retrospective single center study of 93 high risk infants requiring VA-ECMO in the post-operative period for cyanotic and noncyanotic congenital heart disease (CHD), the authors found that: 1) Mortality at 30 days post-surgery (primary outcome) was 38%, similar to what has been reported in other studies; 2) PaO_2 of 193 mmHg within 48h of ECMO was able to discriminate survival vs. death at 30 days based on ROC curve; 3) PaO_2 >193 mmHg within first 48h of ECMO cannulation as well as duration of ECMO ≥ 7 days were both independent risk factors for mortality. Among the secondary outcomes tested: the need for dialysis was associated with hyperoxia but neurological injury was not.

The definition of hyperoxia is not uniform in the literature. While a PaO_2 of > 300 mmHg is the most commonly used value to define the presence of hyperoxemia, it varies from >100 to >487 mmHg depending on the study (5). The authors indicated in their response to the

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review (although not included in the manuscript) that a mean PaO_2 in the first 48 hours of > 300 mmHg was also significantly associated with 30 day mortality in the univariate analysis (OR 2.6, 95% CI 1.02–6.9; p = 0.048). It is possible that what is considered as hyperoxia could change based on the age and presence of cyanotic CHD. An area under the curve analysis of the PaO_2 values would have helped to evaluate a dose-response relationship. However such an analysis was not performed in this study since the number of arterial blood gases obtained and the time points of their collection were variable due to the retrospective nature of the study.

In the postoperative period in CHD patients, there are many factors that can affect patients' PaO_2 on ECMO. Right ventricular function and ejection, lung parenchymal disease and overall ECMO flows are among those important factors. In pediatric heart surgery, long surgical durations with prolonged cross-clamp times are associated with postoperative low cardiac output syndrome secondary to both ventricular dysfunction and increased inflammatory response and acute lung injury (6)(7). In the setting of poor ventricular function and overall postoperative low cardiac output higher ECMO flows are required to restore appropriate hemodynamics. Patients with depressed ventricular function and high ECMO flows do not eject much blood through their lungs and thus measured PaO_2 may be higher than those in which native lung circulation is preserved (8). The authors acknowledged this issue and stated that neither ventricular dysfunction assessed by echocardiography nor high ECMO flows did correlate with higher PaO_2 in the first 48h. However, due to the retrospective nature of the study not all patients might have had this assessment within the first 48h and information on effective ventricular ejection is lacking. Evaluation of ventricular function while on ECMO still remains a challenge being grossly affected by ECMO flows and different loading conditions (9). Authors used *ECMO minimum flows* ≥120 cc/kg/min to identify those patients with higher ECMO flows. However, using a different measure such as overall mean ECMO flows during the first 48hours or simply performing an analysis of ECMO flows based on cardiac index might have yielded different results. ECMO flows of 120 ml/kg/min for a 3 kg neonate represent a cardiac index of less than 2 l/min/m^2 and might not represent a true "high flow" state in the setting of poor ventricular function and severe inflammatory response. Thus prospective studies will be required to further evaluate the relationship between the ECMO flows and hyperoxia controlling for factors such as ventricular ejection and underlying lung disease before a cause and effect relationship between hyperoxia and overall outcomes is established.

As for the possible mechanisms of injury by hyperoxia the authors discussed generation of reactive oxygen species (ROS) and activation of inflammatory and thrombotic cascades. It is not known whether there was an association between thrombosis or bleeding complications and hyperoxia in the current study. There is paucity of information on assessment of markers of oxidative stress and inflammation. Oxygen supply in excess of demand can accelerate formation of ROS via a number of sources– mitochondria and neutrophil NADPH oxidase being the major sources for generation of ROS, mainly superoxide and its dismutation product hydrogen peroxide (10). In addition several enzymatic systems such as cyclooxygenases and lipoxygenases utilize molecular oxygen to oxidize arachidonic acid in their catalytic cycle to form lipid mediators, such as prostaglandins, thromboxanes,

leukotrienes etc., with strong effects on vascular tone, platelet function and inflammatory processes (11). These mechanisms may contribute to oxygen toxicity during reperfusion after ischemia such as in the cyanotic CHD patient undergoing CBP. Understanding the mechanism of injury by hyperoxia may help in identification of therapeutic targets. In infants and children with CHD, CBP could worsen the already existing developmental deficiency of reductants and antioxidant enzyme systems leaving them vulnerable to toxic effects of excess oxygen (12, 13). Thus a combination of titrated oxygen therapy with targeted antioxidants may be particularly beneficial in CHD patients after surgery.

While advocating for a prospective study to evaluate the effect of hyperoxia on mortality, the authors also call for "a change of practice in management of infants with congenital heart disease who are placed on VA-ECMO in the post-operative setting" to avoid hyperoxia. It is possible that there is little justification for hyerpoxygenation on ECMO in the post-operative setting in infants who would have remained cyanotic due to their underlying anatomy and staged nature of the correction have they not needed ECMO support post-operatively. Titrating the oxygen content of the sweep gas of the oxygenator can achieve more physiologic PaO_2 levels. Interestingly the practice of titrating sweep gas to a targeted, presumably more physiological PaO_2 on VA-ECMO in the post-operative setting is not universal—with one-third of the pediatric cardiac intensive care units in the country maintaining high PaO_2 levels according to an informal survey the authors' conducted. In the current study, only 11% of the patients had sweep gas titration. Thus there might be clinical equipoise for future prospective studies to adequately investigate a cause and effect relationship between hyperoxia and outcome and whether a dose-response relationship exist between PaO_2 and outcome. Such studies should ideally include advanced physiological monitoring such as assessment of cerebral, renal and coronary blood flow in addition to MAP, CVP, SvO_2, FiO_2, PEEP, lactate, and hematocrit–clinical variables that might affect oxygenation. Incorporation of biochemical markers of redox status and imaging data in such a study could enhance our understanding of the mechanisms of the deleterious effects of hyperoxia ultimately leading to targeted interventions.

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