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Hyperoxemia: The Poison is in the Dose

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To the editor,

The counterintuitive question of the link between hyperoxemia and increased mortality has frequently been raised in the last 10 years. Austin et al. randomized controlled trial in 2010 was the first study to demonstrate an excess of mortality with a short time exposure to liberal use of oxygen in patients with acute respiratory failure[1]. The results of the recently published meta-analysis by Chu et al. included 16037 patients from 25 randomized controlled studies were compelling. The authors showed an increased mortality in acutely ill patients when oxygen is delivered liberally (SpO_2 above 94-96%)[2]. In this meta-analysis, a dose-effect relationship was found for oxygen toxicity[2]. While the toxicity of severe hyperoxemia in intensive care units (ICU) is well established[3], the impact of moderate hyperoxemia is unclear. In a recent study published in the *American Journal of Respiratory and Critical Care Medicine*, Palmer et al. showed that even moderate hyperoxemia (defined as PaO_2 > 100 mmHg) was associated with increased mortality in ICU patients[4]. Interestingly, 77.5 and 90.6% of the patients included in this study were exposed to hyperoxemia after 1 or 7 days in ICU respectively. The authors could not find a dose-relationship effect for oxygen and mortality but they found a relationship between the duration of hyperoxemia exposure and mortality. However, it was unclear what was the range of PaO_2 in the population evaluated in Palmer's study[4] as no data on mean, median, interquartile of PaO_2 are provided. If the range of PaO_2 values is too narrow, no dose-effect relationship could be made. Indeed, it is possible in UK centers, that very high PaO_2 were rare, as UK practitioners are particularly aware of potential oxygen toxicity. It is also unclear if the parameter to define hyperoxemia was optimal ("hyperoxemia dose"). Helmerhorst demonstrated that the definition of hyperoxemia (first PaO_2, worst value, mean, AUC, during 24 hours or during the whole ICU stay..) influenced the impact on outcome a lot[3]. Helmerhost et al. study provided convincing data that moderate (Mean PaO_2 between 120 and 200 mmHg, related to 15% of patients) as well as severe exposure to hyperoxemia (Mean PaO_2 above 200 mmHg, related to 1% of the patients) were associated with increased mortality in ICU patients[3]. In

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Helmerhorst study both dose and time-response relationships were demonstrated between hyperoxemia and outomes (duration of mechanical ventilation, ICU and hospital mortality). Paracelse wrote in 1538, “all things are poison and nothing is without poison, only the dose permits something not to be poisonous”[5]. The dose and time relationship for oxygen toxicity is not surprising given the physiology of oxygen toxicity mediated by toxic metabolites of oxygen, the reactive oxygen species (ROS) or free radicals.

Production of ROS is dose dependant. Thanks to different mechanisms of protection against free radicals, including enzymatic (superoxide dismutase, catalase, gluthation peroxidase) and non enzymatic (vitamins A, C, E, …) antioxidants, the effects of free radicals can be reduced. “Our whole body is an anti-oxydant machine” adapted to a progressive increase in atmospheric oxygen concentration (during 4 billions of year) up to 40% during Palaeozoic era. Homo sapiens have lived in the last 300.000 years breathing an atmosphere of 21% oxygen concentration[6]. Only homo sapiens walking through hospitals are exposed to pure oxygen and hyperoxemia, leading to increased free radicals with systemic effects (cells and DNA damage, microvascular vasoconstriction, lung injury…). Continuing to overlook oxygen toxicity may not be ethical given the amount of data available. It is time in hospitals to finally achieve the goals of oxygen therapy and to provide the right dose of oxygen: to treat hypoxemia, to avoid hyperoxemia and to wean patients from oxygen.

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