Hyperoxemia: The Poison Is in the Dose

To the Editor:

The counterintuitive question of the link between hyperoxemia and increased mortality has frequently been raised in the last 10 years. The Austin and colleagues' randomized controlled trial in 2010 was the first study to demonstrate an excess of mortality with a short exposure to liberal use of oxygen in patients with acute respiratory failure (1). The results of the recently published meta-analysis by Chu and colleagues, which included 16,037 patients from 25 randomized controlled studies, were compelling. The authors showed an increased mortality in acutely ill patients when oxygen was delivered liberally (oxygen saturation as measured by pulse oximetry >94–96%) (2). In this meta-analysis, a dose–effect relationship was found for oxygen toxicity (2). Although the toxicity of severe hyperoxemia in the ICU is well established (3), the impact of moderate hyperoxemia is unclear.

In a recent study published in the *Journal*, Palmer and colleagues showed that even moderate hyperoxemia (defined as Pa_{O_2} >100 mm Hg) 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 and 7 days in the ICU, respectively. The authors could not find a dose–effect relationship for oxygen and mortality, but they found a relationship between the duration of hyperoxemia exposure and mortality. However, in the population evaluated in the study by Palmer and colleagues (4), the range of Pa_{O_2} was unclear, because no data on the mean, median, or interquartile range Pa_{O_2} values were provided. If the range of Pa_{O_2} values is too narrow, no dose–effect relationship can be established. Indeed, it is possible that in United Kingdom centers, very high Pa_{O_2} values are rare because United Kingdom practitioners are particularly aware of potential oxygen toxicity. It is also unclear if the parameter used to define hyperoxemia ("hyperoxemia dose") was optimal. Helmerhorst and colleagues demonstrated that the definition of hyperoxemia (first Pa_{O_2}, worst value, mean, area under the curve, during 24 h or during the whole ICU stay) influenced the impact on outcome a lot (3). The Helmerhorst and colleagues study provided convincing data that moderate (mean Pa_{O_2} between 120 and 200 mm Hg in 15% of patients) and severe exposure to hyperoxemia (mean Pa_{O_2} >200 mm Hg in 1% of the patients) were associated with increased mortality in ICU patients (3). In the Helmerhorst study, both dose–response and time–response relationships were demonstrated between hyperoxemia and outcomes (duration of mechanical ventilation as well as ICU and hospital mortality).

Paracelsus wrote in 1538, "All things are poison, and nothing is without poison, only the dose makes the poison" (5). The dose and time relationship for oxygen toxicity is not surprising, given the physiology of oxygen toxicity mediated by toxic metabolites of oxygen, reactive oxygen species, or free radicals.

Production of reactive oxygen species is dose dependent. Thanks to different mechanisms of protection against free radicals, including enzymatic (superoxide dismutase, catalase, and glutathione peroxidase) and nonenzymatic (vitamins A, C, E, and so forth) antioxidants, the effects of free radicals can be reduced. "Our whole body is an antioxidant machine" adapted to a progressive increase in atmospheric oxygen concentration (during the course of 4 billion yr) up to 40% during the Paleozoic Era. *Homo sapiens* have lived during 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 (cellular and DNA damage, microvascular vasoconstriction, lung injury, and so forth). Continuing to overlook oxygen toxicity may not be ethical, given the amount of data available. It is time for 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. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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