Editorial

Oxygen: a powerful drug to handle with care

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Acute hypoxemia is common in hospitalized patients as the result of acute and/or chronic diseases that may involve different tissues and organs. Regardless of etiology, generous oxygen supplementation is normally used in hypoxemic patients as the first-line supportive therapy without considering the potential negative effects of exposure to high oxygen concentrations in inspired gases (FiO_2). A recent observational trial showed that health care personnel of the intensive care units is generally focused only on hypoxia: lower limits of peripheral oxygen saturation (SpO_2) are extensively prescribed whereas upper limits are rarely considered (1). Therefore, a large proportion of critically ill patients is frequently exposed to unnecessary prolonged periods of hyperoxemia (2,3). A recent prospective study showed that in ED the use of an initial FiO_2 at 0.4 rather than 0.6 was able to restore normoxia in almost all the hypoxemic patients and that two-third of them became hyperoxic even with 0.4 FiO_2 (4).

The oxidative stress induced by hyperoxia on pulmonary, cardiovascular, and neurological systems have been demonstrated in several in vitro, animal and human studies. Hyperoxic acute lung injury is the most known form of oxygen-related toxicity but many other organs and systems may be impaired. In fact, sustained hyperoxia exerts detrimental effects at the cellular level, particularly in the mitochondria that usually plays a key role in detoxifying cells from reactive oxygen species (ROS). High amounts of oxygen are hard to handle by the mitochondria and may lead to an imbalance between pro- and anti-oxidant molecules with significant damages to cell components leading to activation of apoptotic pathways, loss of cellular homeostasis and cell death (5). Moreover, oxidative stress may induce the formation of reactive nitrogen species and the decrease of nitric oxide production with significant alteration in microcirculation and tissue perfusion.

For the above reasons, oxygen should be considered a powerful drug requiring careful management to avoid under or overdosing and titration of oxygen therapy is strongly recommended, particularly in the emergency department (ED) and in the intensive care unit (ICU) (6). As expected by considering the pathobiology mechanisms, a retrospective cohort study demonstrated a U-shape relationship between PaO_2 levels and hospital mortality in patients admitted to ICU (7), suggesting that both ipo- and hyperoxemia may cause an increased risk of mortality compared to normoxia. Normoxia is commonly defined as a PaO_2 value ranging from 60 to 100 mmHg and different criteria have been used in clinical studies to define hyperoxemia leading to heterogeneous results difficult to compare. A recent cohort study showed that the relationship between PaO_2 levels and patients' outcome depend on the different metrics applied, with metrics of central tendencies (e.g., mean and median PaO_2) showing the strongest correlation with outcome. Although results were more consistent in patients with PaO_2 >200 mmHg, a linear relationship was also observed between the extent of hyperoxemia exposure and mortality even for lower levels of PaO_2 (8).

Due to the large use of oxygen therapy in emergency conditions, the main body of literature on the effects of hyperoxia refers to critically ill patients as for instance

patients with cardiac arrest, myocardial infarction, mechanical ventilation, sepsis, traumatic brain injury and stroke. Oxygen supplementation is currently administered in patients with acute coronary syndrome, regardless on SpO_2 values, and it is a milestone in therapeutic algorithms in case of acute myocardial infarction. Similarly, oxygen therapy at high FiO_2 is routinely used both in in-hospital and out-of-hospital cardiac arrest in accordance with the current American Heart Association guidelines that recommend using FiO_2 of 100% during cardiopulmonary resuscitation in order to maximize the likelihood of achieving return of spontaneous circulation (9). Nevertheless, it should be recalled that many studies suggest that unnecessary exposure to O_2 therapy can worsen the size of myocardial ischemia (10,11) and the ischemia-reperfusion brain injury with poor neurological outcome after cardiac arrest (12,13). Due to the common beliefs and the behavior of healthcare staff, mechanically ventilated patients are at risk to be exposed to significant period of useless hyperoxia during ICU stay (2). In this setting, several recent studies indicate that mild hyperoxemia seems to increase the mortality risk, mainly in sickest patients with respiratory dysfunction and sepsis (14-17). The effects of oxygen conservative strategies compared to more liberal strategies in ICU patients will be clarified soon by numerous ongoing large randomized controlled trials (ACTRN12615000957594, NCT02378545, NCT03174002, EUDRACT 201800252535). In patients with stroke and traumatic brain injury the use oxygen supplementation remains still controversial because of low number of trials and high inconsistency between each other (18,19). To sum up the data available on critically ill patients, a recent study meta-analyzed the results of 25 randomized controlled trials on 16,037 patients and concluded that oxygen therapy might become potentially harmful when targeted to SpO_2 values above 96% with recommendation for a conservative use of oxygen therapy (20).

Although adverse effects caused by un-needed oxygen therapy are expected to be similar to those observed in critically ill patients, differences in clinical and pathophysiological context and in time and level of exposure between intensive and non-intensive units may mitigate the negative impact of hyperoxia in patients admitted to general wards. Unfortunately, few data are available on the use of oxygen therapy and on its effects in patients admitted to non-intensive wards. This gap has been partially closed by a recent observational study aimed to investigate potential harmful effects of hyperoxaemia in non-critically ill patients who receive oxygen-therapy in non-invasive way (21). This single center South-Korean clinical experience retrospectively evaluated the relationship between early hyperoxaemia (i.e., first 3 days after ED admission) and patients' outcome in 10,141 consecutive patients admitted to general wards after ED visit with at least two arterial blood gas analysis in the first 72 hours after admission. Noteworthy, hypoxemic patients (maximum PaO_2 <60 mmHg) were excluded from the study in order to assess only the difference between hyperoxemia and normoxemia. Even patients who died or showed complications (i.e., ICU transfer and respiratory, cardiovascular, hepatic, renal and coagulation dysfunction) in the first 5 days after hospital admission were excluded (18% of enrolled patients) to avoid confounding factors in the evaluation of delayed effects of hyperoxia. Indeed, this exclusion hindered the assessment of the possible short-term negative effects of hyperoxia described in animal models, healthy volunteers and in critically ill patients, mainly with the use of very high FiO_2 (22,23). In the study by Jeong *et al.* (21), the oxygenation state was evaluated using different PaO_2 metrics as for instance maximum, median, average and area under the curve (AUC) of the first 72 hours from ED arrival and for each variable the upper quintile was compared to the others. Unadjusted and adjusted analysis showed that exposure to hyperoxemia in the first 3 days after hospital admission seems to increase 90-day mortality, ICU admission and occurrence of organ dysfunctions after five days from the hospital admission. As expected, the authors noted that the total oxygen exposure measured by PaO_2 AUC-72h, rather than maximum PaO_2, was significantly related to outcome. Interestingly, data also suggest a possible association among hyperoxemia, liver and cardiovascular dysfunctions, already reported in critically ill patients (15), as well as the potential negative effects of high PaO_2 exposure on haemostasis.

Although observational and retrospective, and with some limitations in patient selection and definition of hyperoxemia, the study by Jeong *et al.* provides considerable new information on the effects of hyperoxemia in patients without significant critical illness admitted to general wards (21). The data confirm the findings observed in critically ill patients of harmful effects induced by non-appropriate and overdosed O_2 therapy even for short exposure. As occurred in the last years in ICU and ED, general wards healthcare staff should reconsider the management strategy of O_2 therapy by using specific

protocols to prevent hypoxia as well as (mild) hyperoxia with pre-defined O_2 doses based on the careful monitoring of SpO_2. Further high-quality studies are needed to definitively confirm data observed in patients admitted to general wards, but in the mean time we strongly recommend to handle O_2 with care.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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