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CORRESPONDENCE

Pro/con debate
Conservative oxygenation in the intensive care unit: Con

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In the last decade, the attitude towards oxygen therapy for ICU patients has changed. Whereas in earlier times we used to administer oxygen superfluously to prevent hypoxaemia, recently we have become increasingly aware of the potential harmful effects of hyperoxaemia.[1] Many papers urge us to aim for tight oxygen control. However, we have to be careful not to jump to conclusions, as was the case for tight glucose control.

Numerous adverse effects of hyperoxia have been reported, pathophysiologically based on an increase in oxidative stress and inflammation. Among the most frequently reported are pulmonary side effects, such as tracheobronchitis, resorption atelectasis and pulmonary oedema. These effects are directly proportional to PaO_2 (especially with FiO_2 ≥0.6) and exposure time.[2] Furthermore, hyperoxia can induce systemic vasoconstriction, in particular in the coronary and cerebral vessels, leading to a decrease in cardiac output and organ perfusion and an increase of ischaemia/reperfusion injury.[3]

However, besides negative effects, also positive effects can be ascribed to hyperoxia. The reported vasoconstriction may be beneficial. Preclinical studies indicate that hyperoxia-induced vasoconstriction may stabilise macrocirculatory and microcirculatory haemodynamics with improved kidney and brain redox state,[4] although these findings were not confirmed by clinical studies.[5] Hyperoxia can be protective in haemorrhagic shock, preventing myocardial ischaemia and redistributing blood flow in preference of the renal or hepatosplanchnic system with improvement of organ function.[3] In addition, hyperoxia may enhance bactericidal effects of neutrophils by enhanced reactive oxygen species (ROS) formation and inhibit bacterial replication, thereby reducing the risk of surgical site infection, in particular following colorectal surgery.[6]

At present, good quality clinical data about the effect of hyperoxia remain limited. Many studies and reviews suggesting that hyperoxia leads to worse outcome and increased mortality are based on observational data, frequently obtained in a retrospective design. Thereby, hyperoxia could just have been a marker for severity of illness.[7] Mostly, only the blood gas measurements of the first 24 hours were taken into account[8-10] and classification of hyperoxia based on a single blood gas analysis (highest A-a gradient,[9] lowest P/F ratio11). Therefore, the effect of cumulative oxygen exposure during the entire ICU or hospital stay in these studies was unknown.

In the observational studies that differentiated between mild, moderate and severe hyperoxia, severe hyperoxia was rather consistently associated with worse outcome,[10,12,13] whereas mild to moderate hyperoxia improved outcome in a number of studies.[10,12] For example, after cardiac arrest, severe hyperoxia (defined as PaO_2 >300 mmHg) was associated with increased mortality, whereas moderate hyperoxia (PaO_2 100-299 mmHg) was associated with improved organ function.10 Two retrospective studies of patients with traumatic brain injury suggested that a PaO_2 of 110-487 mmHg12 and 250-486 mmHg, respectively, was associated with the best outcome.[13]

Furthermore, the nadir of mortality in several observational studies appeared to be in the mild hyperoxic, rather than the physiological or subnormal range. In one of the most important landmark trials with regard to hyperoxia in ICU patients, the nadir of the U-shaped curve of mortality was at 110-150 mmHg,[11] which was supported by the results of two large observational cohort studies of the same group showing the lowest mortality at a mean PaO_2 of ~150 mmHg over the total ICU length of stay in ICU patients[14] and a PaO_2 of 180-200 mmHg (estimated in the blood gas with the worst P/F ratio in the first 24 hours) in cardiac arrest.[15] Thereby, these results suggest that mild to moderate hyperoxia might be equal to or superior to normoxia in terms of outcome.

Moreover, subgroup analysis in a recent review of observational cohort studies showed a statistically significant adverse clinical outcome in patients with hyperoxia compared to nomoxia for cardiac arrest and ischaemic stroke, but not for traumatic brain injury, intracranial haemorrhage or after cardiac surgery

(the numbers of patients with haemorrhagic shock, sepsis or multiple trauma were too low or not quantified).7 This suggests that the optimal PaO_2 range may differ depending on the underlying pathophysiological problem of the patient.

The results of these observational studies urged the need for good quality randomised controlled trials (RCTs) in carefully selected patient groups to estimate optimal oxygenation targets. In recent years, the results of the first RCTs investigating different oxygenation strategies have become available, yielding equivocal results. Some RCTs found a worse outcome with hyperoxia, whereas other trials did not show any difference between normoxia and hyperoxia. With regard to myocardial infarction, the AVOID study (investigating non-hypoxaemic patients comparing 8 l O_2/min to air) showed increased myocardial injury,[16] but a recent Swedish trial (comparing 6 l O_2/min to air) did not find a difference in mortality or high-sensitive troponin T levels.[17] In patients with stroke, an RCT studying high flow oxygen at 30-45 l/min for 8 hrs was terminated prematurely due to increased mortality in the hyperoxia group, although deaths were not attributed to treatment (NCT00414726). However, in a very large study of 8000 non-hypoxic patients with stroke, low-dose oxygen (2 l O_2/min) did result in a different outcome compared with ambient air[18] In these four studies, oxygen was applied in a fixed dose without an upper limit in PaO_2 or SpO_2, so the achieved levels of PaO_2 may have varied considerably. Two RCTs in ICU patients compared conservative vs. conventional oxygen therapy and titrated the FiO_2 based on the SpO_2 and PaO_2. In the largest RCT in ICU patients until present (comparing SpO_2 94-98% vs. SpO_2 >97%), there was a substantial decrease of mortality in the conservative group (11 vs. 20%).[19] However, control of blood gas analysis was scarce, the SpO_2 was not reported and the study was terminated prematurely. Another RCT comparing target SpO_2 of 88-92% vs. >96% did not observe a significant difference in mortality; however, this was a small pilot not powered for mortality.[20] The potential downside of tight oxygen control is the increase in subnormal PaO_2 levels. Subnormal levels such as accepted for ARDS patients (down to 55 mmHg) may lead to long-term cognitive dysfunction.[21] Since pulmonary effects mostly appear at higher FiO_2 levels (FiO_2 >60%, almost no difference in cytokine levels at FiO_2 of 30-50%[2,22]), it is commonly unnecessary in patients without ARDS or other severe pulmonary problems to allow the PaO_2 level to decrease to this extent to avoid high FiO_2 levels. Long-term cognitive effects were not estimated in these two RCTs.

In conclusion, although severe hyperoxia is rather consistently associated with adverse outcome and should be avoided, optimal oxygenation targets in ICU patients remain to be determined. Some observational studies have shown beneficial effects of mild to moderate hyperoxia suggesting that optimal targets might not be in the normoxic, but in the mild supraphysiological range. The few RCTs at present find equivocal results. Future trials should not investigate the effect of a fixed oxygen suppletion, but should compare predefined SpO_2 or PaO_2 values. Also, estimating long-term effects of subnormal PaO_2 levels on cognitive function is necessary to assess optimal PaO_2 levels for different subgroups.

Disclosures

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