VIEWPOINT

Conservative Oxygen Therapy is the Way Forward in Critical Illness

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Introduction

The common causes of hypoxemic respiratory failure in intensive care unit (ICU) include ventilation-perfusion mismatch, diffusion defects, and shunting. Oxygen therapy is one of the quintessential aspects of the management of hypoxemic respiratory failure to optimize oxygen delivery to tissues. However, ever since the discovery of oxygen in 1774, reports of oxygen toxicity started coming up within a decade of its usage. In 1783, Antoine Lavoisier noticed toxicity of oxygen administration in animals if used at high concentrations and for prolonged duration, which was followed later by similar reports of oxygen toxicity in humans.[1] In a landmark retrospective study in 2008 by de Jonge et al. in around 36,000 patients, a U-shaped association was found between hospital mortality and arterial partial pressure of oxygen (PaO_2) within the first 24 hours of mechanical ventilation, highlighting that not only hypoxia but also hyperoxia can negatively impact the patient outcomes.[2] This makes us wonder whether oxygen is a friend or a foe.

Definitions

Hyperoxemia is defined as partial pressure of arterial oxygen (PaO_2) above 100 mm Hg and any amount of supplemental oxygen above 21% may culminate in hyperoxemia. Tissue hyperoxia, on the other hand, is defined variedly depending upon the baseline perfusion at microcirculatory and macrocirculatory levels.[3]

Pathophysiology of Hyperoxia

High oxygen concentrations lead to the generation of superoxide free radicals, mediated by the presence of free electrons in oxygen, which in high doses overwhelm the body's intrinsic antioxidant capacity and result in organ dysfunction by the following mechanisms:[3]

- Resorption atelectasis.
- Vasoconstriction.
- Reactive oxygen species mediated pulmonary and systemic oxidative stress.

Hyperoxia and Subgroups of Critically Ill Population

Acute Brain Injury

In patients with acute brain injury, high oxygen therapy may benefit by increasing the brain tissue oxygen tension. On the contrary, brain dysfunction may also get worsened by hyperoxia secondary to cerebral oxidative injury and cerebral vasospasm, as seen in patients with traumatic brain injury and stroke in several observational studies at PaO_2 >150–200 mm Hg. Moreover, in post-cardiac arrest patients, hyperoxia may exacerbate the ischemia-reperfusion injury in brain parenchyma (oxygen paradox).[3] A recent systematic review published in 2020, in fact, recommends normoxemia and normocapnia as the post-resuscitation oxygenation and ventilation targets in cardiac arrest survivors.[4]

Acute Respiratory Distress Syndrome (ARDS)

In moderate-severe ARDS, patients are generally protected from the harmful effects of systemic hyperoxemia owing to impairment of pulmonary gas exchange. However, detrimental effects of high FiO_2 can happen in the lungs per se, which tend to worsen further in the absence of lung protective ventilation.[3]

Acute Myocardial Infarction (MI)

As observed in patients with brain dysfunction, oxygen therapy, on one hand, may mitigate the oxygen demand and supply mismatch in myocardium but, on the other hand, may also precipitate ischemia by triggering coronary artery vasospasm. Besides, the determination of the role of oxygen in suspected acute myocardial infarction (DETO2X-AMI) randomized trial published in 2017 found no mortality benefit of routine supplemental oxygen administration in patients with suspected MI, who were not hypoxemic.[5]

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Perioperative Settings and Surgical Site Infections

In perioperative period, high FiO_2 is believed to reduce surgical site infections but no significant benefit was replicated in the landmark PROXI trial.[6]

Review of Literature on COT vs Liberal Oxygen Therapy

The oxygen ICU trial by Girardis et al. in 2016, which was the first randomized trial comparing the effect of conservative vs liberal oxygen therapy on ICU mortality, concluded that in critically ill patients with ICU stay ≥72 hours, conservative oxygen therapy (COT) [PaO_2 70–100 mm Hg and oxygen saturation (SpO_2) 94–98%] *vis-à-vis* conventional therapy (PaO_2 up to 150 mm Hg and SpO_2 97–100%) resulted in lower ICU mortality.[7] Subsequently, in the hyperoxia and hypertonic saline in patients with septic shock (HYPERS2S) multicentric trial by Asfar et al. in 2017, arterial hyperoxia [at fraction of inspired oxygen (FiO_2) 1.0] was found to increase mortality in patients with septic shock and the trial had to be prematurely stopped for safety issues.[8] Thereafter, improving oxygen therapy in acute-illness (IOTA) systematic review and meta-analysis in 2018 comparing high vs low FiO_2, inclusive of 25 randomized controlled trials (RCTs) and around 16,000 patients, showed that liberal oxygen therapy (high FiO_2) increased mortality in acutely ill adult patients, although most of these patients were those of stroke and MI and only a few were critically ill.[9] Recently, in the last 2 years, four RCTs on conservative vs usual care/liberal oxygen therapy[10–13] have come up but with an overall neutral opinion. Among the notable findings is a benefit of COT in patients with hypoxic ischemic encephalopathy as seen in intensive care unit randomized trial comparing two approaches to oxygen therapy (ICU-ROX) trial and a possible harm of COT in terms of intestinal ischemia and tachyarrhythmias as seen in liberal oxygenation vs conservative oxygenation ($LOCO_2$) trial (target SpO_2 <88%). The details of these recent trials have been summarized in Table 1. However, the trials are not without limitations, which are as mentioned below:

- Blinding was not done.
- There is a lack of uniform definition regarding conservative and liberal oxygen therapy.
- Adherence to targets is questionable as intermittent sampling was done in most of the trials.
- Oxygen saturation and PaO_2 may not correlate in certain conditions:
  - Tissue hypoperfusion.
  - Racial difference.
- Global vs. "regional" oxygenation was not assessed.
- Adequacy of lung protective ventilation and other aspects of oxygen delivery optimization (e.g., hemoglobin levels) was not mentioned.
- Heterogeneity of treatment may be seen in critical illness
- Varying outcomes were compared, for example, mortality, ventilator-free days, $SOFA_{RANK}$.

Permissive Hypoxemia and Adaptation to Hypoxia

Humans have evolved at only 21% atmospheric oxygen with mitochondrial biogenesis in a relatively hypoxemic environment.

Table 1: Comparison of recent RCTs on oxygen therapy in critical illness

	ICU-ROX	*$LOCO_2$*	*HOT-ICU*	*Dutch trial*
First author; journal	Mackle D; Australia New Zealand; NEJM 2020; MC RCT	Barrot L; France; NEJM 2020; MC RCT	Schjorring OL; Europe; NEJM 2021; MC RCT	Gelissen H; Nertherlands; JAMA 2021; MC RCT
n	1000	205	2928	574
Inclusion	Age >18 years; MV; general ICU	ARDS (P/F: 110–120); MV	O_2 @ 10 L/min; FiO_2 >0.5; MV 57% (baseline P/F similar to $LOCO_2$ trial)	SIRS ≥2; general ICU; MV 75%
Subgroups	Hypoxemia (70%); acute brain disease (40%); after surgery (30%)	Pneumonia (78%)	Pneumonia (57%); ARDS (12%); cardiac arrest (10%); MI (6%)	Systemic infection (35%); pneumonia (34%); cardiac arrest (18%); acute abdominal infection/infarct (17%)
COT	SpO_2: 90–96% (at lowest FiO_2)	SpO_2: 88–92% (7 days); PaO_2: 55–70 mm Hg	PaO_2: 60 mm Hg (for 90 days)	PaO_2: 60–90 mm Hg
Liberal	"Usual" O_2 therapy; no upper limit SpO_2; FiO_2 >0.3	SpO_2: ≥96%; PaO_2: 90–105 mm Hg	PaO_2: 90 mm Hg	PaO_2: 90 mm Hg
Primary objective	VFD (alive and free from MV)	28-day mortality	90-day mortality	$SOFA_{RANK}$ (non-resp. cumulative daily SOFA D1–D14)
COT vs liberal oxygen	Similar	High mortality in COT; trial prematurely stopped	Similar	Similar
Benefit or harm	Possible benefit of COT in suspected HIE	Intestinal ischemia and tachyarrhythmia in COT	SAEs (intestinal ischemia, MI, new shock, ischemic stroke) "similar" (unlike $LOCO_2$ trial)	Mild hypoxemia more often in COT but "severe hypoxemia similar in both groups"

ARDS, Acute respiratory distress syndrome; COT, Conservative oxygen therapy; HIE, Hypoxic ischemic encephalopathy; HOT-ICU, Handling oxygenation targets in the ICU; ICU, Intensive care unit; ICU-ROX, Intensive care unit randomized trial comparing two approaches to oxygen therapy; $LOCO_2$: Liberal oxygenation vs conservative oxygenation; MC RCT, Multicentric randomized controlled trial; MI, Myocardial infarction; MV, Mechanical ventilation; P/F, PaO_2/FiO_2 ratio; PaO_2, Partial pressure of arterial oxygen; SAE, Serious adverse event; SIRS, Systemic inflammatory response syndrome; SOFA, Sequential organ failure assessment; SpO_2, Oxygen saturation; VFD, Ventilator-free days

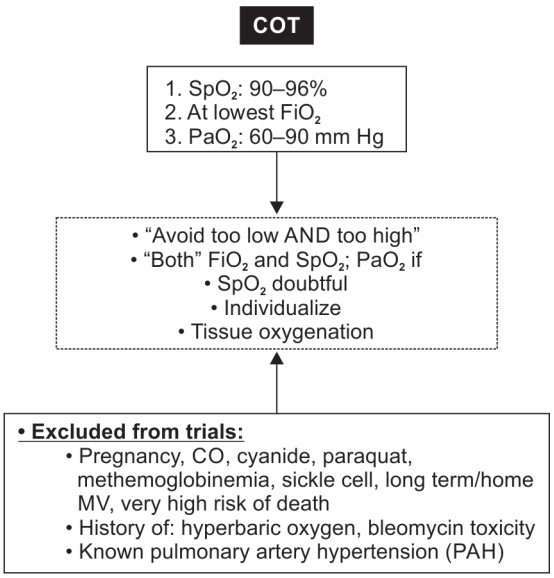

Fig. 1: How to apply conservative oxygen therapy (COT) in critical illness as inferred from trials. FiO_2, Fraction of inspired oxygen; SpO_2, Oxygen saturation; PaO_2, Partial pressure of arterial oxygen; CO, Carbon monoxide poisoning

Thus, it is quite possible that adaptability to hypoxia may be seen in certain phenotypes and genotypes of patients—high altitude dwellers, for example, Tibetan population and some patients with subacute or chronic hypoxemia. This phenomenon highlights further the possibility of varying oxygen requirements and thus, the need for personalized oxygen therapy.[14]

Conclusion

Individualization of oxygen therapy is essential in heterogeneous critically ill patients as oxygen is a double-edged sword. It is essential to avoid not only "too low" but also "too high" oxygen therapy. Recent trials have a neutral opinion in the context of conservative or liberal oxygen therapy, but these trials have certain limitations. At least we can say that COT as compared to liberal oxygen therapy is non-inferior and safe, if no contraindications exist. To conclude, till the results of further large-scale multicentric trials come up, COT targeting normoxemia may be the future in critical illness if provided in the "right amount, right patient, right time, right monitoring, fine balance." Figure 1 shows an approach to apply COT in critical illness as inferred from trials.

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