EDITORIAL

COVID-19 ARDS: Can Systemic Oxygenation Utilization Guide Oxygen Therapy?

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Coronavirus disease-2019 (COVID-19) can cause acute respiratory failure with persistent hypoxemia. In the subset of patients who develop acute respiratory distress syndrome (ARDS) and progress onto mechanical ventilation, the morbidity and mortality are very high. COVID-19-induced lung disease is an unusual cause of respiratory failure and behaves differently to the ARDS due to other causes. These patients often require prolonged duration of mechanical ventilation and oxygen therapy, both of which carry their own risk. It remains unclear about the best target oxygen administration in classical ARDS or the subgroup of a patient with COVID-19-induced lung injury.

Oxygen is essential for aerobic metabolism and sustaining organ function and hypoxia is harmful, so in theory, more should be better. However, when it comes to oxygen therapy, more is not necessarily better as we do not normally exist in anhyperoxygenated state, and oxygen therapy is not without harm. Hyperoxia could lead to vasoconstriction, free radical generation, and consequent tissue damage, and denitrogenation of the lungs with resulting atelectasis and de-recruitment. Therefore, the efforts are on to find the balance, the sweet spot, for oxygenation targets.

Various trials have yielded conflicting results for optimal oxygen target for ARDS. The National Heart, Lung, and Blood Institute ARDS Clinical Trials Network had recommended a target PaO_2 between 55 mm Hg and 80 mm Hg.

However, in a recent multicenter randomized, liberal, or conservative oxygen therapy for acute respiratory distress syndrome trial ($LOCO_2$),[1] enrolled 205 adult patients who were intubated and receiving mechanical ventilation for less than 12 hours. The PaO_2 target for the conservative group was between 55 mm Hg and 70 mm Hg (SpO_2 target 88–92%) vs the liberal oxygen therapy group where target PaO_2 was between 90 mm Hg and 105 mm Hg (SpO_2 >96%). They found that there is no difference in 28 days mortality from any cause between the two groups, however, the 90-day mortality was more in the conservative group and the conservative group has more mesenteric ischemic events. Another trial, the ICU-ROX,[2] was a multicenter study that included approximately 1000 patients randomized into two groups. In both groups, the lower limit of saturation was 90%, conservative oxygen group the target SpO_2 is 90–97% with titration of FiO_2 to maintain this range vs liberal oxygen group where there was no upper limit of oxygen saturation. They found no difference in ventilator-free days at 28 days between the two groups.

Whereas, the Oxygen-ICU trial[3] which included 480 patients with an expected intensive care unit length of stay of 72 hours or longer, a conservative protocol for oxygen supplementation (SpO_2 94–98%) was associated with an absolute risk reduction for intensive care unit mortality of 8.6% compared with that for patients treated with conventional therapy (SpO_2 97–100%). There was also fewer incidence of shock, liver failure, and bacteremia in the conservative group. In a *post hoc* analysis, they found that there are less in-hospital mortality and more mechanical ventilation-free hours in the conservative oxygen group.

In a large systemic review and meta-analysis (IOTA),[4] Chu et al. analyzed 25 RCT and included 16037 patients. They found that there is a significant increase in the hospital mortality and 30-day mortality in the liberal oxygen group (target SpO_2 >96%) and concluded that supplemental oxygen might become unfavorable above a SpO_2 range of 94–96%.

So given the conflicting results, the general conclusion maybe to avoid extremely low (88%) or high (>96%) saturation and keep the target between 90% and 96% in patients with ARDS.

Coming to COVID-19 ARDS, hypoxia in COVID-19 infection is likely of multifactorial origin. The unique pathophysiologic mechanisms include relatively preserved lung compliance, lack of excessive dead space, presence of intra-pulmonary shunting, deranged hypoxemic vasoconstriction, and silent hypoxia, frequently termed happy hypoxia wherein patients initially do not complain of dyspnea as there is no concomitant elevation of $PaCO_2$ and/or work of breathing. The PaO_2/FiO_2 ratio remains low in COVID-19 until critical respiratory insufficiency occurs. The pathological shift to typical ARDS occurs as pulmonary circulation is progressively impaired due to thromboembolic phenomena and inflammation progressively affects alveolar-capillary cell membrane integrity producing inflammation, edema, and lung cell necrosis.[5,6]

SARS-CoV-2 virus enters the body via the ACE-2 receptor. Angiotensin II has proliferative, hypertrophic, and fibrotic effects

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and there is upregulation of the ACE-2 receptor on exposure to hypoxia which can lead to more severe disease. Indeed, delayed identification of hypoxia in pneumonia is associated with increased disease severity, increased rate of mechanical ventilation, and increased mortality.

So, what should be the ideal oxygen target in COVID-19? Different countries have different national guidelines for oxygen targets for COVID-19 ARDS. In the UK the target SpO_2 for the commencement of oxygen therapy is 91% and 94% in Singapore. They have found that the case fatality rate in Singapore is 0.08% and in the UK it is 13.4%. So, improving supplemental oxygen is likely to reduce mortality in COVID-19 pneumonia.

Surviving sepsis guideline for COVID-19 pneumonia suggests starting supplemental oxygen if the SpO_2 is less than 92% and recommended to start supplemental oxygen if the SpO_2 is less than 90%. They recommended to target SpO_2 should not be more than 96%.

Although monitoring the saturation and keeping the targets between 90% and 96% are practical and widely applicable. Does this translate to adequate oxygenation at the level of the tissues?

The authors show in their small hypothesis-generating study that calculating the oxygen extraction ratios (O_2ER) by simultaneously measuring the arterial blood gas, central venous blood gas, and central venous O_2 ($ScVO_2$). O_2ER is the fraction of the oxygen delivered to the capillaries that are taken up into the tissues and it is an index of the efficiency of oxygen transport. It is the ratio of O_2 uptake (VO_2) to O_2 delivery (DO_2); the normal ratio is 0.2–0.3, which corresponds to a $ScVO_2$ of 70–80%.

A high O_2ER (low $ScVO_2$) is a feature of "flow insufficient states", secondary to anything which causes a decreased cardiac output or an increased tissue oxygen demand.

A low O_2ER (high $ScVO_2$) is caused due to either a decreased tissue oxygen demand, or inefficient oxygen utilization by the tissues, or pathologically and disproportionately increased cardiac output.

In their small study of eight mechanically ventilated patients with severe ARDS where the saturation targets were kept between 92% and 96% and there were no signs of anaerobic metabolism; there a good proportion of patients in which the O_2ER was reduced suggesting that systemic O_2 utilization is abnormal in patients with severe COVID-19. In some patients the oxygen delivery can be excessive of the requirements and such patients may benefit from less aggressive interventions to maintain SpO_2.

SARS-CoV-2 is known to affect host mitochondrial function, although there is limited data on its final influence on cellular metabolism.

This hypothesis appears attractive but would be practically difficult to perform given the need for advanced monitoring and the need to repeatedly calculate the O_2ER as in reality the oxygen extraction of each tissue fluctuates constantly and will change as the disease progresses, besides having other limitations as using $ScVO_2$ as an acceptable surrogate for SvO_2 (which is true only in certain settings).

It may have a role in patients with "happy hypoxemia", where tolerance of lower SpO_2 goals based on systemic O_2 utilization may be beneficial in reassessing intubation and preventing the secondary complications of mechanical ventilation. Still, as the authors have pointed out, more studies and longitudinal data analysis would be required to confirm consistency of the results obtained and before exploring the practical utility of systemic oxygenation targets to titrate oxygen therapy in COVID-19 ARDS.

In conclusion, currently, we should keep a balance between liberal oxygen therapy and conservative oxygen therapy. We should avoid hyperoxia as well as hypoxia. Target SpO_2 between 92% and 96% is associated with good outcomes both in COVID-19 ARDS as well as in non-COVID ARDS.

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