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Review Article

Anaesthesia Section

It is Time to Revise the Ventilation Strategy in COVID-19 Affected Patients

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ABSTRACT

COVID-19 infection has emerged as a pandemic. This infection is new to the world, and the management strategy is evolving daily. As per the current guidelines, the patients of COVID-19 infection requiring mechanical ventilation should be treated on the lines of management of Acute Respiratory Distress Syndrome (ARDS). However, it seems that the management of ventilation in the case of COVID-19 needs to be modified. With growing experience, many hospitals have turned to Non-Invasive Ventilation (NIV) to ward-off severe respiratory failure and in keeping with the inadequate resources. The controversy in using NIV is whether the benefits of using such interventions are more than the potential risks of aerosolisation of the virus. There is a hope that helmet-based ventilation may help reduce the risk of nosocomial infection. Autopsy findings demonstrated that besides ARDS, the alveolar capillaries were clearly thickened, with fibrin thrombi within the capillaries and small vessels and surrounding oedema present in COVID-19 affected lungs. This virus attacks the beta chain of haemoglobin, dissociates heme, removing iron converting it to porphyrin. The cause of desaturation is the failure of the blood to carry oxygen leading to multiorgan failure and mortality. The cause of lung damage seen on Computerised Tomography (CT) scans is the release of oxidative iron, which in turn overcomes the natural defenses against pulmonary oxidative stress and causes what is known as the Cytokine Storm. The question is whether mechanical ventilation is harming the patient by traumatising their lungs leading to increased mortality. Prone ventilation is the next preferred step for COVID-19 patients who fail to achieve adequate oxygenation with low tidal volume ventilation. Hyperbaric oxygen therapy can help the leftover functioning haemoglobin to carry more oxygen. Blood transfusion and plasmapheresis provide symptomatic relief. Thrombolytic therapy is also being tried with some benefits. These may be promising in treating patients with COVID-19 infection. Researches are required on the other probability and to test newly emerging treatment modalities.

Keywords: Atypical acute respiratory distress syndrome, Heme theory, Newer treatment modalities, Non-invasive ventilation

INTRODUCTION

COVID-19 infection outbreak has affected the whole world. Most of the patients with COVID-19 develop only mild or uncomplicated illness [1]. However, approximately 14% of the infected patients develop a severe disease requiring hospital admissions and oxygen support, and 5% of them will need intensive care [1]. In severe cases, COVID-19 patients land up in complications like ARDS, sepsis and septic shock, multiorgan failure, including acute kidney injury and cardiac injury [2].

As per the current guidelines, the patients of COVID-19 infections requiring mechanical ventilation are managed like those with ARDS. However, with evidence coming from different hospitals across different countries, it seems that the way of managing ventilation in the case of COVID-19 should be modified [3].

WHO Guidelines Regarding Non-Invasive Ventilation (NIV) in COVID-19 Patient

The guidelines by the World Health Organization (WHO) suggest titrating the lowest possible Fraction of Inspired Oxygen (FiO_2) necessary to meet the requirement of oxygenation. The target should be SpO_2 between 90 and 96 percent, whenever possible [4]. Oxygen supplementation with a low flow system via nasal cannula up to 6 L/min is considered appropriate. It is believed that the risk of dispersion increases as the flow increases, augmenting the contamination of the surrounding environment. Ventilating patients with higher oxygen requirements via High Flow Nasal Cannulae (HFNC) or the initiation of NIV in patients with COVID-19 is controversial [5,6]. It is advocated that the decision to initiate non-invasive modalities, HFNC or NIV, should be made by balancing the risks and benefits to the patient, the risk of exposure to healthcare workers, and the best use of resources.

As per the existing guidelines, in patients with COVID-19 who have acute hypoxemic respiratory failure and higher oxygen needs than what low flow oxygen can provide, non-invasive modalities rather than proceeding directly for intubation are advised selectively in young patients without comorbidities who can tolerate nasal cannulae. According to the guidelines, some patients may merit avoidance of HFNC and may benefit from proceeding directly to early intubation, e.g., elderly or confused patients with comorbidities and several risk factors for progression. A low threshold to intubate such patients is advocated, mainly if they show any signs of rapid progression [4].

Considering these as aerosol-generating procedures, when HFNC or NIV is used, airborne precautions should be undertaken in addition to standard care, i.e., airborne infection isolation room (a negative pressure room), full personal protective equipment. If NIV is initiated, a full-face mask, preferably with a good seal and not having an anti-asphyxiation valve or port, a dual limb circuit with a filter on the expiratory limb as compared with single limb circuitry to decrease dispersion is preferred. It has been suggested to start with Continuous Positive Airway Pressure (CPAP) using the lowest effective pressures (e.g., 5 to 10 cm H_2O) [4]. Most experts with experience of managing COVID-19 patients recommend "early" intubation. However, the definition of what constitutes "early" is unclear. Intubation is the highest risk procedure for droplet dispersion in patients with COVID-19 [6].

Newer Trends towards Non-invasive Ventilation (NIV)

With growing experience amid COVID-19 pandemic, many hospitals have opted for noninvasive modalities to manage severe respiratory failure. Inadequate resources also force them to do so [7]. Although this practice is considered controversial among some US caregivers, it is being widely used in China and becoming popular in Europe [8]. The European Society of Intensive Care Medicine (ESICM) is now recommending it [9].

It is controversial if NIV or HFNC should be the first option. NIV devices support breathing by reducing the effort required and maintain the inflation of the alveoli, thus increasing oxygenation. In the context of the Italian experience of the covid-19 outbreak, Continuous Positive Pressure (CPAP) was found beneficial in reducing admissions and the number of intubations in the Intensive Care Unit (ICU). Even nurses could administer it [10]. ESCIM on the other hand preferred HFNC as the mode of oxygen delivery for the first-line therapy in COVID-19 patients with acute hypoxemic respiratory failure over NIV or CPAP. Nevertheless, the latter could be used under close monitoring if the respiratory conditions worsened [9].

In a study from China, 63% of patients suffering from COVID-19 infection with severe acute respiratory failure were treated with HFNC as first-line therapy, and 33% were treated with NIV. Thus, HFNC was the most common ventilation support [11].

Risk of infection from aerosolisation

The controversy is whether the benefits of using such interventions are more than the potential risks of aerosolisation of the virus, which could be the source of hospital-acquired infection. This concern is quite valid as personal protective equipment for medical staff is in short supply, even in the very developed nations.

It was observed that the majority of patients in Chinese hospitals with limited resources were receiving respiratory support through a nasal catheter or oxygen mask in general wards or emergency departments. The rates of nosocomial infection with COVID-19 had been estimated at around 40% [12].

Alhazzani W et al., perceived that, although Nasal Intermittent Positive Pressure Ventilation (NIPPV)/CPAP is known as an aerosolising procedure with increased risk of disease transmission, it was the same for HFNC as with CPAP [9].

Protection from aerosols by helmet devices

Helmets are the devices which consist of plastic bells covering the entire head and face of the patient attached to a rubber collar neck seal. It has come up as a mode of oxygen delivery with the hope of reducing the risk of nosocomial infection which is considered as a risk associated with NIV or HFNC.

Countries like Italy have employed it in an effort to limit aerosolisation. The Italian helmet is more advanced than that available elsewhere. It has a virus filter incorporated in it to prevent aerosol formation. It is more user friendly, with extra ports for medical staff to use [13]. Although ESICM guidelines describe them as an option to reduce exhaled air dispersion, but do not recommend regarding the use of helmet NIV compared with the mask as their safety or efficacy in COVID-19 is not sure [9].

Peculiarity of COVID-19 manifestation

Many patients with COVID-19 have blood oxygen levels so low that they may generally not be expected to survive. However, these patients are not gasping for air, there is no compensatory tachycardia, and their brains show no signs arising from a lack of oxygen [14]. It is the blood levels of oxygen, which for decades have driven the physicians in decision-making about breathing support for patients with pneumonia and acute respiratory distress. It might be misleading them in COVID-19 patient care. Thus, more patients could receive simpler, non-invasive respiratory support, to begin with or even for the duration of the illness [14,15]. That would also help relieve a shortage of ventilators, which is so critical that states are finding it hard to procure them, and some hospitals are taking the largely untested step of using a single ventilator for many patients.

This does not mean that ventilators are not necessary for the COVID-19 crisis, or that hospitals are wrong to fear about the crisis of ventilators. However, as more is learnt about treating COVID-19 and old doctrine about blood oxygen and the need for ventilators are questioned, simpler and more widely available devices might be substituted.

The outcome of intubated patients with COVID-19 infection

According to a report from Wuhan, 30 of the 37 critically ill COVID-19 patients who were given ventilatory support, died within a month [2]. A study in Seattle, USA concluded that just one out of seven mechanically ventilated patients older than 70 years survived and only 36% of the patients on invasive ventilation younger than 70 could survive [16]. According to another study conducted on 1,300 critically ill COVID-19 patients from Italy and published in JAMA, 88% were intubated and mechanically ventilated and only 11% received NIV. Twenty five percent died in the ICU, 58% remained in ICU until the study period and 16% had been discharged [17]. Older patients who survive have the risk of respiratory and permanent cognitive impairment from intubation and prolonged heavy sedation.

In a small study, at two hospitals in China, it was found by the physicians who treated COVID-19, that the majority of patients needed just a nasal cannula [11]. Among the 41% who needed ventilatory support, none was put on a ventilator right away. Instead, they received NIV; their blood oxygen levels had significant improvement after an hour or two. In due course, two out of seven needed intubation. It was concluded that Bilevel Positive Airway Pressure (BiPAP) is more comfortable, just as good as and as safe for COVID-19 patients as earlier use of a ventilator. A subjective experience from Italy also suggests that they were able to support a number of patients using these non-invasive methods [18].

Similarity with altitude sickness pneumonia

The possible reason for near-hypoxic levels of blood oxygen in COVID-19 patients in absence of the usual gasping and other signs of impairment might be the low blood carbon dioxide levels. That means lungs are continuing the task of carbon dioxide removal inspite of difficulty in oxygen absorption. That is suggestive of altitude sickness more than pneumonia [14].

Dissociation between relatively well-preserved lung mechanics with the severity of hypoxia

The existing clinical approach to patients with COVID-19 is that applied for severe ARDS which consists of high Positive End Expiratory Pressure (PEEP) and prone positioning. However, these patients fulfil the Berlin Criteria of ARDS which is an atypical form of ARDS [19]. A study on 16 patients showed the compliance of respiratory system to be 50.2±14.3 mL/cm H_2O with a shunt fraction of 0.50±0.11. Such a high lung compliance indicates well-preserved lung gas volume. This discrepancy is hard to see in ARDS. Severe hypoxia in compliant lungs indicate the loss of regulation lung perfusion and hypoximic vasoconstriction [20].

The pathological picture of lungs in COVID-19 unlike others with ARDS

In the most severe consequences of COVID-19 ARDSs, immune cells invade the lungs and the alveoli are filled with a gummy yellow fluid which limits the transfer of oxygen from lungs to the blood even when the patient is mechanically ventilated and receives oxygenation [14]. When oxygen cannot cross into the blood from the lungs, more significant force may prove harmful. High oxygen concentration impairs the lung's air sacs, while high pressure to force in more oxygen traumatises the lungs. Such patients need gentle ventilation, against increasing the pressure even though the blood oxygen levels remain low [15].

Autopsy findings of the lungs in COVID-19 patients

In a study on the autopsy findings in four patients, the parenchyma of both the lungs was diffusely edematous and firm as seen in ARDS. Nevertheless, regions of dark-colored haemorrhage with focal demarcation could be notably identified throughout the peripheral parenchyma in the lungs of all but one of the decedents. On cut sections, these haemorrhagic areas showed frank haemorrhage. In sections of the peripheral parenchyma, in some cases, small, firm thrombi were present. Histologic examination showed bilateral diffuse alveolar damage of the lungs with a comparatively mild-to-moderate lymphocytic infiltrate, composed of a mixture of CD4+ and CD8+ lymphocytes. Foci of haemorrhage were present in all but one case. The alveolar capillaries were quite thickened, with surrounding oedema, and fibrin thrombi were present within the capillaries and small vessels. Based on these findings, the effective therapy for these patients should target the microangiopathic and thrombotic effects of the virus, and a maladaptive immune response to viral infection besides targeting the viral pathogen [21].

The Heme theory

A study of conserved domain analysis, homology modeling, and molecular docking was used to compare the biological roles of specific proteins of the novel coronavirus. The result showed that COVID-19 virus could attack the beta chain of haemoglobin, dissociates heme, removing iron converting it to porphyrin [22]. The virus structural protein sticks to heme displaces oxygen, which releases iron-free ion, leading to toxicity and inflammation of alveolar macrophages, that results in bilateral CT scan changes as it is a systemic response [23].

There is no exchange of oxygen and carbon dioxide, resulting in lung inflammation and the ground glass appearance as seen on X-rays in COVID-19. This is neither pneumonia nor typical ARDS and hence the invasive ventilation does not seem to be the correct solution. The emergency intubation and mechanical ventilation may actually harm the patient and cause damage from its complications such as tracheal scarring and stiff lung [23].

The cause of desaturation is the failure of the blood to carry oxygen [24]. This may lead to multiorgan failure and mortality. The cause of lung damage seen on CT scans is the release of oxidative iron which in turn overcome the natural defenses against pulmonary oxidative stress and causes what is known as Cytokine storm [22,23]. This is just similar to carbon monoxide (CO) poisoning in which CO binds with the haemoglobin such that no gas exchange takes place. Ventilation does not reverse this cause, which is blood organ failure [23].

Intubation criteria

In cases such as cardiopulmonary arrest or a lost or jeopardised airway, the decision to intubate may be obvious and require little consideration. However, it can be a challenge to decide when to intubate and put a patient for invasive ventilation in COVID-19 patients with acute hypoxaemic respiratory failure. The Chinese Society of Anaesthesiology Task Force on Airway Management published the recommendation to proceed with endotracheal intubation for patients showing no improvement in respiratory distress, tachypnea (respiratory rate greater than 30 per minute), and poor oxygenation (PaO_2 to FIO_2 ratio less than 150 mmHg) after two hours of high-flow oxygen therapy or NIV [24]. The common intubation strategies in COVID-19 patients in Wuhan are thorough preparation, reasonable preoxygenation, modified rapid sequence induction and a videolaryngoscope for fast intubation.

These are empirical criteria with no strong supporting evidence. The concerns among the treating physicians in Wuhan during pandemic was that most patients were intubated for rescue rather than supporting them when their oxygenation was gradually declining and oxygen debt was increasing. A report showed that among the 22 ICU patients intubated, 19 (86%) of them died [25]. Many physician believe that the delay in the decision to intubate COVID-19 patients adversely affects the outcome. However there is no evidence that early intubation could decrease the mortality. It can also be looked the other way out. Is mechanical ventilation harming the patient by traumatising their lungs leading to increased mortality? Is the requirement of these patients different?

Silent hypoxia and preparedness for ventilation

Timely and not premature intubation is important in decision-making. Based on the experience of patient care in COVID-19 in Wuhan, liberal criteria were added for preparedness to intubate. It included room air oxygen saturation less than 93% and PaO_2 to FiO_2 ratio less than 300 mm Hg. This intended to avoid unprepared emergent intubation which is associated with the risks like increased morbidity and cross-infection. Besides, it is observed that some patients with good degree of hypoxia are relatively asymptomatic, referred to as 'silent hypoxia' in Wuhan [26,27]. Silent hypoxia may account for the quick deterioration in patients, thus giving a false sense of security when the oxygen debt has actually increased.

At present, there is no evidence or guideline to manage invasive mechanical ventilation in critically ill COVID-19 patients. Hence, guidelines established for patients with ARDS, with suitable modifications based on experiences in Wuhan has been adopted [28,29]. This is based on the recent reports which claim that 67% of the ICU patients developed ARDS.

As per ARDS lung-protective ventilation guidelines: 1) a tidal volume less than or equal to 6 mL/kg predicted body weight; 2) a respiratory rate less than or equal to 35 breaths/min; 3) a plateau airway pressure less than or equal to 30 cm H_2O; and 4) a PEEP greater than or equal to 5 cm H_2O is preferred [30,31]. The tidal volume can be started at 8 mL/kg to be lowered with an ultimate goal of 6 mL/kg. Some believe that, till the plateau pressure can be maintained ≤30 cm H_2O, it may be safe to ventilate the patient with tidal volumes more than 6 mL/kg predicted body weight [32]. In determining the precise tidal volume for an individual patient, the patient's plateau pressure, selected PEEP, thoraco-abdominal compliance, and breathing effort play role [28]. A driving pressure (plateau pressure minus PEEP) below 12 to 15 cm H_2O through tidal volume and PEEP adjustments in patients who are not spontaneously breathing are advantageous [33]. This approach is based upon several randomised trials and meta-analyses that have reported improved mortality from low tidal volume ventilation in patients with ARDS [34,35].

Desirable mode of ventilation

No mode of ventilation can be considered to be better than the other [36]. The high-frequency oscillatory ventilation proposed by Ramsey CD et al., as an alternative for viral-induced lung injury should best be avoided due to risk of aerosol generation [37-40]. Pressure-regulated volume control ventilation. although popular in perioperative settings lack evidence for benefits in outcomes and hence not preferred in ICUs. During pressure regulated volume control ventilation, in patients with ARDS or acute lung injury, the tidal volume may surpass the lung-protective ventilation goal [41].

Role of prone ventilation

For patients with COVID-19 that fail to achieve adequate oxygenation with low tidal volume ventilation, prone ventilation is the preferred next step. For its application, the suggested criteria are the ratio of partial arterial pressure of oxygen and fraction of inspired oxygen (PaO_2: FiO_2) ratio <150 mmHg, a FiO_2 ≥0.6, and PEEP ≥5 cm H_2O; excessively high airway pressures; or refractory hypoxemia, although some experts use a higher PaO_2:FiO_2 ratio. The reason for good response to prone ventilation may be due to preserved lung compliance in this population compared with patients who develop ARDS from other causes. Guidelines recommend early stage prone positioning and not a final desperate attempt, if it is considered as part of the treatment [28,29,42]. There is evidence that the early application of prone position in prolonged ventilation decreases 28- and 90-days mortality in patients with severe ARDS [43].

Lung recruitment

Lung recruitment manoeuvres open collapsed alveoli by transiently elevating the airway pressure during mechanical ventilation. This may improve oxygenation and shorten the length of hospital stay in ARDS. However it has no evidence of decreasing the mortality [44]. It can incite cough due to irritation of airway and may generate aerosol [45].

Newer Treatment Modalities

Hyperbaric oxygen therapy

With 100% oxygen at more than one atmospheric pressure for about 90 minutes twice a day for 5 days can help functioning hemoglobin to carry adequate oxygen to the organs so as to keep them alive [23]. COVID-19 patients should receive hyperbaric oxygen therapy as early as possible. Conscious, alert and compliant patients must be kept on maximum oxygen.

Blood transfusions or plasmapheresis

Blood transfusion with packed fresh red blood cells to patients after plasmapheresis may ameliorate the cytokine storm. Plasmapheresis and Blood transfusions give symptomatic relief [23].

Thrombolytic therapy

In a non-peer reviewed retrospective cohort study from China, it was found that LMWH improves the coagulation dysfunction of COVID-19 patients and has anti-inflammatory effects by decreasing IL-6 and increasing the percentage of lymphocytes. It is expected that LMWH can be a therapeutic agent in COVID-19 treatment [46].

Adjunct therapies

Proper sedation and analgesia drugs like dexmedetomidine, remifentanil and propofol should be considered in COVID-19 patients having respiratory overdrive. The evidence of the outcome about the muscle relaxant is controversial [47,48]. A recent meta-analysis found the role of muscle relaxant in improving oxygenation after 48 hours without any benefit in reducing mortality in moderate to severe ARDS patients. [49]. Still muscle relaxation should be considered in cases of breathing overdrive, patient-ventilator dyssynchrony, and to achieve the targeted tidal volume and plateau pressure. Fluid management in COVID-19 patients with severe lung disease requires a conservative approach in the absence of tissue hypoperfusion [28]. Disconnection of ventilatory circuits should be avoided to prevent loss of PEEP and atelectasis. Inline closed suction for endotracheal tube should be used and the tube should be clamped before disconnecting the breathing circuit.

Role of Extracorporeal Membrane Oxygenation (ECMO)

More than 40 COVID-19 critically ill patients have been treated using ECMO in Hospitals in Wuhan. The outcomes of these patients are not known [50]. The outcomes of these patients are not known. The WHO suggests ECMO as a rescue strategy, to be used in the failure of prone ventilation and the other evidence-based treatment modalities [4]. Also, ECMO is not universally available. ECMO can interfere with the interpretation of the laboratory results also by reducing the lymphocyte count and raise the interleukin-6 level [51].

Extubation criteria

Patients often remain infectious when ready for extubation, and because extubation is frequently associated with a little coughing, it is considered an aerosol-generating procedure. Extubation should follow the standard practice of performing spontaneous breathing trials but by using closed systems and not using a T-piece. A higher degree of readiness in patients with COVID-19 is preferred to reduce the risk of reintubation following extubation. To perform extubation, an airborne isolation room should be used. More care should be taken during extubation by keeping the inline suction catheter engaged during cuff deflation.

CONCLUSION(S)

It is the need of the time to relook at our ventilation strategy and investigate other modes of ventilation which may prove to be better, taking into consideration the poor outcome of the present strategy. The change in the treatment strategy in patients critically affected with COVID-19 is seriously warranted. Researches are required on other probabilities and new treatment guidelines specifically for this pandemic are urgently mandated.

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