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Ventilatory Management Strategies For Acute Respiratory Distress Syndrome (Ards) Due To Covid-19 Disease

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Abstract

Acute Respiratory Distress Syndrome (ARDS) is a life-threatening diffuse inflammatory condition in the lungs and result in the oxygen treatment-refractory hypoxemic respiratory failure. ARDS is not a disease and is the result or complication of an underlying disease. COVID-19 pneumonia-related ARDS is a specific condition with unique phenotypes. Although patients had very severe hypoxemia in the early stages of respiratory distress due to COVID-19 disease, there was relatively well-preserved lung compliance. This phenotype is named as "atypical ARDS" or "ARDS type L". In advanced stage, some patients (20-30%) can return to a clinical picture more characteristic of typical ARDS progressively. This phenotype is called "typical ARDS" or "ARDS type H". Different types of ARDS that develop due to COVID-19 pneumonia require different ventilation strategies, depending on the underlying pathophysiology. In patients with early-stage atypical ARDS phenotype higher TVs and lower PEEP may be preferred, as opposed to the lung protective mechanical ventilator strategy. Nowadays, in the typical ARDS phenotype, the lung protective ventilation strategy used in classical ARDS is widely preferred. Refractory patients (a small number of patients) need to additional applications which are including prone ventilation and exorcoral membrane oxygenation (ECMO).

Keywords: COVID-19 disease, ARDS, Ventilatory management strategies, Prone ventilation, ECMO

Introduction

Acute Respiratory Distress Syndrome (ARDS) is a life-threatening acute diffuse inflammatory condition in the lungs. ARDS is result in the oxygen treatment-refractory hypoxemic respiratory failure[1]. ARDS is not a disease and is the result or complication of an underlying disease. In ARDS, hypoxemia occurs as a result of different mechanisms. Alveolar edema and collapse resulting from diffuse alveolar damage (DAD), which is considered the morphological hallmark of the lung in ARDS, decreases lung volumes and results in a decrease in compliance[2]. Disruptions in the resulting intrapulmonary shunt and ventilation/perfusion (VA/Q) ratio cause hypoxemia. In addition, surfactant deficiency, the loss of hypoxic pulmonary vasoconstriction and impaired regulation of pulmonary blood flow also contribute to the development of hypoxemia. DAD may be due to pulmonary or extra-pulmonary causes. Pulmonary ARDS is a direct insult to the lung affecting alveolar epithelium whilst extra-pulmonary ARDS is an indirect lung injury caused by inflammatory mediators acting on the vascular endothelium[3]. Pulmonary ARDS is noticeably more common than extra-pulmonary ARDS, and its most common cause is pneumonia (about 60% of cases)[4]. Extra-pulmonary ARDS is more common amongst postoperative and trauma patients.

In ARDS due to COVID-19 pneumonia, thrombosis and associated ischemic events are very common[5,6]. COVID-19 is a systemic disease that mainly causes damage to the vascular endothelium. The disproportionate endothelial injury plays a major role in the deterioration of pulmonary vasoregulation, the deterioration in the VA / Q ratio (possibly the primary cause of severe hypoxemia at the beginning) and thrombogenesis. COVID-19 has a highly activated coagulation cascade that goes through diffuse micro and macro thrombosis in the lung and other organs and very high D-dimer levels are associated with badly results. Most deaths from ARDS due to COVID-19 pneumonia have evidence of a thrombotic disseminated intravascular coagulation (DIC)[7].

The current definition of ARDS is the Berlin defination at the international American-European Consensus Conference in 2012 (Table 1). The Berlin definition, ARDS is classified according to the degree of hypoxemia. Treatments and ventilator management strategies have also been proposed according to the degree of hypoxemia. In the LUNG SAFE study performed using Berlin criteria in 2014 among 459 intensive care units (ICUs) in 50 countries patients with ARDS represented 10% of all ICU admissions and 23% of all intubated patients in ICU were due to ARDS[4]. Among them, 30% had mild, 47% had moderate and 23% had severe ARDS. It was also stated that 59% of these ARDS developed due to pneumonia, 14% to aspiration, 16% to sepsis and 7.5% to non-cardiogenic shock. ARDS develops in 42% of patients presenting with COVID-19 pneumonia and 61-81% of those who require hospitalization in the ICU[8].

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Table 1. ARDS Berlin Diagnostic Criteria

Timing	New or increased respiratory symptoms starting within a week
Chest Radiography	Bilateral diffuse infiltrations: completely effusion, atelectasis, no lobar collapse or nodule
Cause of Edema	Clinical findings should not be explained by the presence of heart failure or fluid load. If there is no risk factor, echocardiography should be performed to exclude hydrostatic edema.
Oxygenation	
Mild	When PEEP ≥5 cmH2O: 300 ≥ PaO2/FiO2 > 200
Moderate	When PEEP ≥5 cmH2O: 200 ≥ PaO2/FiO2 > 100
Severe	When PEEP ≥5 cmH2O: PaO2/FiO2 ≤ 100

Even though it can meet the Berlin criteria, COVID-19 pneumonia-related ARDS is a specific condition with unique phenotypes[9]. Although patients had very severe hypoxemia in the early stages of respiratory distress due to COVID-19 pneumonia, there was a relatively well-preserved lung compliance[10,11]. The median respiratory system compliance is usually around 50 ml/cmH_2O. In the early stage, ground-glass pattern on chest tomography (CT) suggesting interstitial involvement rather than alveolar edema and generally peripheral involvement are noteworthy. Many of these patients do not appear overtly dyspneic. This phenotype is named as "atypical ARDS" or "ARDS type L", which has low lung elastance (relatively high compliance) and high lung gas volume, thus low response to the application of extrinsic positive end-expiratory pressure (PEEP)[9,12,13]. High PEEP administration does not improve oxygenation, as severe hypoxemia primarily results from deterioration in the VA / Q ratio rather than alveolar collapse. For many patients, the disease may stabilize at this stage without worsening or progressing. In advanced stage, some patients (20-30%) can return to a clinical picture more characteristic of typical ARDS progressively, depending on disease severity and host's response or suboptimal management. This phenotype is called "typical ARDS" or "ARDS type H". At this stage, there are widespread consolidations in chest CT, high lung elastance (low compliance), low lung gas volume and high response to to the application of extrinsic PEEP. However, it should be kept in mind that intermediate forms can be found in which the features of these two types with different pathophysiology may coincide[9,12,13].

Regardless of the condition that causes ARDS, most severe ARDSs require invasive mechanical ventilation. Unlike spontaneous breathing, invasive mechanical ventilation delivers positive pressure throughout the breathing cycle. If the lung-protective mechanical ventilator strategy is not followed (eg. tidal volume (TV): >12ml/kg and PEEP: about 5cmH2O), invasive mechanical ventilation itself can worsen existing lung damage. It is known that ventilation with 6 ml/kg TV significantly reduces mortality (9%) compared to ventilation with 12 ml/kg TV[1,14]. Therefore, it should be aimed to prevent the occurrence of ventilator induced lung injury (VILI) in mechanical ventilation application. VILI consists of many different components such as volutrauma, barotrauma, atelectrauma and biotrauma. The most important is volutrauma. Atelectotrauma is caused by repeatedly opening and closing small airways and alveoli over the breathing cycles. Biotrauma is a general biological response that results in cytokine release due to the effect of stress and strain at the cellular level. The cellular toxicity of oxygen is another component of VILI[14].

It is not clear whether different types of ARDS that develop due to COVID-19 pneumonia require different ventilation strategies. The key treatment strategy is to maintain oxygenation[9,12,13]. Different ventilation strategies are required, depending on the underlying pathophysiology (Table 2). In patients with early-stage atypical ARDS phenotype with good lung compliance, higher TVs (7-8 mL/kg ideal body weight) and lower PEEP (8-10 cmH_2O) may be preferred, as opposed to the lung protective mechanical ventilator strategy. Today, in the typical ARDS phenotype associated with COVID-19, the lung protective ventilation strategy used in classical ARDS is widely preferred[9,15]. In this section, ARDS, which develops due to COVID-19 pneumonia, will refer to lung protective low tidal volume ventilation (LTVV), which is the basic mechanical ventilation strategy.

LOW TIDAL VOLUME VENTILATION (LTVV)

As with all ARDS patients, the recommended mechanical ventilation strategy in patients with COVID-19 pneumonia that develops ARDS and needs a ventilator is lung protective mechanical ventilation which low TV, optimal PEEP and plateau pressure (Pplat) are monitored tightly. The main purpose is to adjust the ventilator settings in a way that ensures sufficient gas exchange without causing VILI (by maintaining Pplat <30 cmH_2O and driving pressure <14 cmH_2O). The most common practice is to target at least 55 mmHg for partial arterial oxygen pressure (PaO_2) and at least 88% for arterial oxygen saturation (SaO_2). More conservative oxygenation strategies that target SpO_2 with pulse oximeter between 88-92% may also be possible in patients undergoing mechanical ventilation[16].

Table 2. Ventilation Strategies in ARDS Associated with COVID-19 Pneumonia[9]

Time Period	Purpose	Respiratory Support Options
Before Intubation	• Ensuring adequate gas exchange • To prevent P-SILI formation	- Oxygen therapy - CPAP, NIMV, HFNC - Keep in pron position - Ensure inspiratory effort is not severe
Mechanical Ventilation	• Preventing increased lung damage • Preventing VILI	- Minimize TV, breathing frequency and PEEP - Make settings to ensure proper gas exchange - Adjust the fluid balance - Reduce tissue oxygen consumption - Keep in mind the need for ECMO
After Intubation	• Minimizing pulmonary stress • Preventing VILI	**Atypical ARDS**: - Use lower PEEP (<10 cmH_2O) - Use more liberal TV (7-9 ml/kg) when needed - Reduce tissue oxygen consumption - Keep in mind the prone positioning
	• To reduce and distribute pulmonary and vascular stresses equally • Optimizing oxygen • Preventing VILI	**Typical ARDS**: - Use higher PEEP (<15 cmH_2O) - Use low TV (5-7 ml/kg)ü - Reduce tissue oxygen consumption - Prone positioning
Weaning	• Preventing return to VILI or lung damage	- Make the transition carefully - Avoid sudden changes - Perform spontaneous breathing trial at the end of the weaning process

ARDS: *Acute Respiratory Distress Syndrome*, P-SILI: *Patient Self-Induced Lung Injury*, VILI: *Ventilator-Induced Lung Injury*, CPAP: *Continious Positive Airway Pressure*, NIMV: *Non-Invasive Mechanical Ventilation*, HFNC: *High Flow Nasal Cannula*, TV: *Tidal Volume*, PEEP: *Positive End Expiratory Pressure*, ECMO: *Extracorporeal Membrane Oxygenation*

In patients with ARDS with COVID-19 pneumonia, LTVV ≤6 mL/kg should be targeted according to the ideal body weight. Initially, tidal volume 6 mL/kg with volume limited assist control mode should be preferred and Pplat should be ≤30 cmH_2O. PEEP adjustment should be made according to the inspired oxygen fraction (FiO_2), keeping PaO_2 in the range of 55 to 80 mmHg or keeping SaO_2 in the range of 88% to 95% (Table 3). In situations such as severe hypercapnia or patient-ventilator dyssynchronies, there may be a need to change this ventilation strategy. LTVV reduces the development of VILI which can cause additional lung injury and mortality in patients with ARDS.

TV, Pplat and compliance values, which are standard variables in mechanical ventilator management, are used in patients with ARDS. Driving pressure is also used in the management of severe or refractory cases with a lung that has the flexibility to benefit from high PEEP values. Lung protective ventilation strategies are associated with limited driving pressure (driving pressure = Pplat measured with ventilator-applied PEEP or TV/respiratory system compliance).

Application and Adjustment

When starting LTVV, typically volume or pressure limited assist control mode selection, TV and breathing frequency adjustments, and PEEP and FiO_2 levels are adjusted. Worldwide volume-limited assist control ventilation is most commonly used mode of ventilation in ICU[17]. Pressure limited mode is also a viable option as long as a consistent and stable TV is provided in accordance with the LTVV strategy. There are no clinical data demonstrating a difference in outcomes between these two modes[18]. In most patients with ARDS, pressure limited mode provides good patient tolerance and stable airway pressure, while volume limited mode provides a stable TV. The main advantage of volume limited mode in

Table 3. FiO_2 and PEEP Combinations

FiO_2	0,3	0,4	0,5	0,6	0,7	0,8	0,9	1,0
PEEP*	5	5-8	8-10	10	10-14	14	14-18	18-24

* The initial PEEP value should be set at the lowest value shown in the table according to FiO_2.

terms of respiratory mechanics is that it allows continuous monitoring of Pplat pressure. Regardless of whether volume limited or pressure limited ventilation mode is selected, fully supported control modes (eg. assist control) are preferred over partial assisted control modes (eg. synchronous intermittent mandatory ventilation [SIMV]).

The initial TV should be adjusted to 6 mL/kg based on predicted body weight and to meet the minute ventilation needs of the patient, provided that the initial respiratory rate is ≤35 breaths/min (usually 14-25 breaths/min). The reason for setting the respiratory rate relatively high (by increasing the minute ventilation) is to prevent the occurrence of respiratory acidosis, which can be caused by low TV. However, there is some experimental evidence that mild respiratory acidosis can protect the lungs[19]. In the next 1 to 4 hours, the patient's clinical response, gas exchange, and Pplat can be used to adjust the TV and breathing rate as needed. TV adjustments should be made to ensure that lung-protective ventilation is properly applied and to evaluate the response in real time before taking arterial blood gases. Simultaneous adjustments are typically made to adapt the clinic, gas exchange and Pplat parameters. Pplat target should be ≤30 cmH_2O and TV should be adjusted according to Pplat. If Pplat ≤30cmH_2O and TV is 6 mL/kg according to ideal body weight, no further adjustment is required. If Pplat >30 cmH_2O, it can be planned to decrease up to 4 mL/kg with decreases of 1 mL/kg on TV. The breathing frequency should be increased to ensure proper minute ventilation at any decrease in TV. In cases where patient-ventilator dyssynchronies, Pplat <25 cmH_2O and TV <6 mL/kg, Pplat should be increased between 25 and 30 mmH_2O or TV to 6 mL/kg in 1 mL/kg increments. If dyssynchronization is serious, the TV can be increased up to 8 mL/kg. TV and breathing frequency adjustment can also be made depending on gas exchange. LTVV can trigger respiratory acidosis. However, although there is no consensus on the upper or lower limit, the pH value should be kept above 7.2. TV can be increased when the pH reduces below 7.15-7.20[20].

While adjusting PEEP, it should be aimed to provide the highest compliance and lowest alveolar dead space, thus increasing the gas volume of the lung. The purpose of PEEP in patients with ARDS is to maintain and maximize alveolar ventilation. Thus, oxygenation is improved and oxygen toxicity is prevented. However, the response to PEEP may differ according to the origin of ARDS (pulmonary vs. extra-pulmonary), the timing (early vs. late) and the localization of infiltrates (diffuse vs. lobar)[21]. Thus, a personalized approach is best, adjusting PEEP for each patient to optimize his/her alveolar recruitment. Indeed, whwn increasing PEEP reduces the driving pressure it indicates recruitment and is associated with improved survival[16]. Optimal PEEP was found to be between 11-16 cmH_2O in moderate to severe ARDS[22]. In typical ARDS developing due to COVID-19 pneumonia, it may be beneficial to increase PEEP gradually up to 14-15 cmH_2O pressure. However, at this stage, a decrease in mixed venous oxygen saturation (SvO_2) is a sign that cardiac output is decreasing, indicating that higher PEEP levels will no longer be beneficial[13].

Efficacy and Side Effects

Many studies have shown that early administration of LTVV improves mortality and other clinical outcomes in patients with ARDS[1,23]. LTVV is generally well tolerated; however, there are potential side effects. Hypercapnic respiratory acidosis is an expected and generally well tolerated side effect of LTVV. LTVV can cause permissive hypercapnia as a ventilation strategy that allows alveolar hypoventilation to minimize complications from alveolar overstress and provide a low alveolar pressure. The degree of hypercapnia can be minimized by setting the highest respiratory rate that will not cause auto-PEEP. The LTVV strategy itself can also cause auto-PEEP. Increased breathing frequency to maintain minute ventilation during LTVV can create auto-PEEP by reducing the respiratory cycle time and therefore the time required for expiratory. When auto-PEEP is suspected, the clinician should estimate the contribution of auto-PEEP to all PEEP and manage the strategy accordingly.

LTVV may also cause an increase in the need for sedation and use of neuromuscular blocker agents and related side effects associated with sedation. When the TV falls below 7 mL/kg according to the ideal weight, the patient's effort to breathe increases and can create patient-ventilator dyssynchronies. With double triggering, higher TVs are created that can negatively affect the benefits of LTVV. If the patient's severe inspiratory effort is not brought under control, it may worsen the existing lung injury by raising the transpulmonary pressure, which is called the patient's self-induced lung injury (P-SILI)[24]. The use of sedation and neuromuscular blocking agent increases the patient's mechanical ventilation tolerance. It allows the respiratory muscles to rest, thereby reducing oxygen consumption by these muscles. As a result, oxygenation is improved, lung and systemic inflammation are reduced and survival is improved[25]. Although LTVV may require an increase in the need for sedation, the need for increased sedation is not continuous. Double examination is a form of dyssynchronization that can occur despite deep sedation. Double triggering can be corrected by providing a slightly higher TV (7-8 mL/kg, predicted body weight) or additional sedation as long as Pplat <30 cmH_2O remains.

Patients with Recovery Findings

The majority of patients with ARDS show improvement with LTVV. In these patients, FiO2 and PEEP should be

gradually decreased and partial assist or spontaneous modes should be attempted according to tolerance. Because the immobility of the diaphragm in controlled modes can quickly lead to marked muscle atrophy and reduced contraction force[26]. Airway pressure release ventilation (APRV) is a ventilation mode that combines invers ratio ventilation with pressure control ventilation that allows spontaneous breaths. Since the two valves of the ventilator are continuous, it is possible to maintain spontaneous breaths at any stage of the breathing cycle. Sustaining spontaneous breaths in APRV mode has been shown to improve respiratory functions and reduce time to stay in mechanical ventilation by reducing sedation requirements[27]. Pressure-support ventilation (PSV) is a spontaneous mode often used during the weaning period. The best time to switch from assist-controlled modes to PSV is unknown, but switching to PSV should be considered when most respiratory cycles are triggered by the patient and the underlying disease is under control. Another support mode for spontaneous breathing is a neurally adjusted ventilator-assisted (NAVA) mode that triggers assisted breaths through a diaphragmatic EMG inserted into a special naso-gastric catheter and reduces patient-ventilator dyssynchrony[28].

Treatment for COVID-19 or secondary developing disease should be optimized, and sedation and vasopressor support should be reduced as much as possible. The time of weaning from the ventilator is completely patient-based; it does not seem possible to give an exact time. This period can extend from 24-48 hours to days or even weeks.

Patients Without Recovery Signs

Patient-ventilator dyssynchrony, high alveolar pressure (Pplat ≥30 cmH_2O) hypoxemia progression ocur in patients with LTVV intolerance. It does not matter if intolerance or deterioration occurs immediately after ventilation or after a short recovery period. In both cases, the management strategy is similar. Unexpected airway pressure changes in patients with volume-limited ventilation or unexpected TV changes in patients with pressure-controlled ventilation require investigation of causes that may lead to acute changes in compliance (eg. pneumothorax, endotracheal tube obstruction).

Choosing an Option

In case of failure of the LTVV response, the underlying causes should be determined and corrected. Supportive moves such as treatment of the current disease, management of fluid therapy, consideration of alternative diagnoses, and complications of ARDS or mechanical ventilation should be made. If dissynchronization is present, it should be corrected. It can also be planned to continue LTVV by making alternative adjustments such as switching to pressure-controlled or vice versa while volume-controlled or increasing the inspiratory-expiration rate. These regulations depend on factors such as the severity of ARDS, its complications, and the patient's comorbidity. All these options should be individualized for each patient. Switching from volume-limited to pressure-limited mode or increasing inspiratory flow rates is an appropriate approach in patients with air hunger. In patients with subsegmental atelectasis causing oxygenation disruption, it is beneficial to prolong the inspiration time by decreasing flow rates in volume-limited modes and increasing the inspiratory time in pressure-limited modes.

Supportive Measures

Pulmonary edema may occur in patients with ARDS due to increased vascular permeability. This problem may require discontinuation or reduction of fluid therapy or diuresis. In cases where the fluid status is unclear, measurement techniques that reflect the fluid status may need to be used. There may be complications with conditions such as pneumothorax, ventilator-associated pneumonia, and pulmonary tromboembolism in ARDS. It is a useful approach to exclude these situations before terminating LTVV and before resorting to other ventilation strategies.

Patient-ventilator dyssynchronies occurs in about 25% of patients who undergo mechanical ventilation[29,30]. Patient-ventilator dyssynchrony may cause increased breathing effort, and in some cases, auto-PEEP and decreased gas exchange may lead to prolonged stay in mechanical ventilation, increased sedation / neuromuscular blockage requirement, and barotrauma[29,30]. Patient-related factors (eg. respiratory drive, timing, compliance, resistance to airflow) and ventilator-related factors (respiratory rate, inspiratory flow rate / shape, trigger sensitivity) are affect synchronization. Ineffective triggering or double triggering are the most common examples of dissynchronization[29,31]. It becomes evident in cases where minute ventilation requirement increases, such as metabolic acidosis or high dead space breathing in ARDS. The approach to patient-ventilator dyssynchrony is done by evaluating flow-time, pressure-time and pressure-volume curves. In the management of dyssynchronization, firstly, sedation should be increased as much as possible, and trigger changes and small changes should be made in the inspiratory flow. Double triggering is a second exhalation of the ventilator by the patient before completing the first exhalation. This causes the formation of harmful high TVs[27]. It is often caused by the adjustment of a tidal volume that is too low to meet the needs of the patient during LTVV or by keeping the inspiratory time short. In this case, the inspiratory time can be kept longer by selecting the decreas-

ing flow form, reducing the flow rate or adding an inspiratory pause[31]. Ineffective triggering occurs when the patient's respiratory effort fails to trigger the ventilator. Ineffective triggering can also contribute to auto-PEEP formation. Ineffective triggering can be corrected by reducing the trigger sensitivity. Flow dissenronization is the failure of the ventilator flow to meet patient needs and can be corrected by increasing the flow or by changing the ventilator mode.

Alternative Settings and Modes in LTVV

Alternative modes may sometimes be required for patients who are unable to tolerate volume-limited LTVV (eg. Pplat ≤30 cmH_2O failure, ventilator synchronization disorder). Pressure limited modes (pressure regulated-volume controlled ventilation and pressure support modes, APRV, volume targeted pressure controlled ventilation) or NAVA are alternative modes. Generally, it is preferred to apply alternative modes for a short time. Close monitoring of ventilator waveforms, airway pressures, tidal volumes, and gas exchange assessment is important in evaluating the response. If success can be achieved, it is an appropriate approach to continue with the same mode.

In some patients, increasing the inspiratory-expiration rate (I:E) by prolonging the inspiratory time may increase oxygenation by creating more time for gas exchange in the lung. When the inspiratory time exceeds the expiratory time, this is known as inverse rate ventilation (IRV). Despite the improvement in oxygenation, prolongation of inspiratory time or IRV has not been shown to clinically improve outcomes in ARDS[32].

REFRACTORY PATIENTS

A small number of patients with ARDS pose a special challenge due to the lack of adequate gas exchange without exposure to refractory hypoxemia (PaO_2/FiO_2<150) and/or high alveolar pressure (Pplat >30 cmH_2O) despite LTVV and other supportive measures specific to ARDS. These patients have a high risk of mortality.

Additional applications in these patients include prone ventilation, ventilator strategies that maximize alveolar flexibility (eg. high PEEP administration, open lung ventilation strategies, and recruitment maneuvers), pharmacotherapies (eg. neuromuscular blockers, pulmonary vasodilators) and exorcoral membrane oxygenation (ECMO). These applications do not have a clear advantage over each other; however, a meta-analysis showed that only prone position and ECMO were associated with a decrease in mortality rates[33]. In practice, the vast majority of clinicians prefer prone position application firstly, and ECMO is applied if there is no success.

Prone Ventilation

The prone position is to place the patients face down and maintain mechanical ventilation treatment in this position for a long period of time. Indications of prone position are resistant hypoxemia despite positive end-expiratory pressure (PEEP) >10 cmH_2O and FiO_2 >60% with protective MV application and/or difficulty to maintain MV (When VT 4-6 mL/kg is given according to ideal body weight, plateau pressure (Pplato) >30 cmH2O and pH <7.15 (respiratory acidosis)); and/or are moderate or severe ARDS patients with right ventricular dysfunction on echocardiography due to hypoxia and hypercapnia[34]. In severe ARDS, it is recommended to start the prone position in the early period (within 36 hours) following ventilation in the supine position for 12-24 hours[35]. Contraindications and complications of the prone position are shown in Table 4.

Due to prone position, the reduction of the pleural pressure gradient from the dependent lung areas to the non-dependent lung areas and the appropriate displacement of the lungs in the thoracic cavity are provided and as a result, the aeration and tension of the lungs becomes more homogeneous. In the light of all these factors, better oxygenation is achieved in ARDS cases due to prone position. Prone position may provide an increase in carbon dioxide clearance as a result of the regulation of oxygenation in ARDS along with opening of atelectatic alveoli and increased number of ventilated alveoli despite the minute ventilation does not increase[34,36]. Mechanism to improve oxygenation of the prone position:

- Opening of the atelectatic dorsal lung areas
- Improvement of ventilation perfusion rate
- Homogeneous distribution of lung elastance to all lung areas
- Increased chest wall elastance
- Decrease in the amount of alveolar shunt
- Functional residual capacity increase
- Mobilization of secretions

In addition, a homogeneous lung ventilation is provided and ventilator-associated lung damage is reduced as a result of ventilation of dependent lung areas, recruitment of alveoli and reduction of hyperinflation in non-dependent lung areas in ARDS cases due to prone position[34,36].

Improvement of oxygenation with the prone position may also improve V/Q mismatch by reversing inadequate hypoxic pulmonary vasoconstriction. Finally, while the improvement of oxygenation prevents the progression of dyspnea, reconstruction of lung tissue with prone position

Table 4. Prone position: Contraindications and Complications[34]

Contraindications	Relative Contraindications
• Shock (e.g. permanent mean arterial pressure <65 mmHg)	• Current Deep Vein Thrombosis <2 days
• Acute bleeding (e.g. hemorrhagic shock, massive hemoptysis)	• Chest tube with air leak
• Multiple fractures or trauma (e.g. femur, pelvis, facial bone fractures)	• Major abdominal surgery
• Spine instability	• Clinical conditions that reduce life expectancy
• Pregnancy	• Severe burns
• Increased intracranial pressure> 30 mmHg or Cerebral perfusion pressure <60 mmHg	• Lung transplant recipient
• Tracheal surgery or sternotomy within 2 weeks	• Having a pacemaker

Complications

- Nerve compression (e.g. Brachial plexus injury)
- Venous stasis (e.g. facial edema)
- Dislocation of the endotracheal tube
- Pressure sores
- Removal of vascular catheters or drainage tubes
- Retinal damage
- Vomiting
- Temporary arrhythmias

changes lung stress-strain relationship and intra-thoracic forces, slows the formation of lung edema and slows the progression of the disease from the L-phenotype to the H-phenotype[13]. It can be used to prevent the high rate of hospitalization of COVID-19 patients to ICUs and to improve the oxygenation and prevent their transfer to ICUs in awake patients[37].

The optimal duration of the prone position is unknown. In a randomized study (PROSEVA) demonstrating the benefit of prone position on mortality in severe ARDS, the average time in the prone position was 17 hours per day with an average of four sessions per patient[35]. Usually, a response is noted in the first hour of the first attempt, but longer times (e.g. 12 to 18 hours) are required to provide a meaningful response.

If prone ventilation fails (e.g., if the patient has no change in gas exchange, or in case of deterioration in lung mechanics, gas exchange, or cardiovascular system), the patient should be turned into the supine position and alternative strategies (e.g. extracorporeal membran oxygenation) should be focused on to improve oxygenation.

Extracorporeal membran oxygenation (ECMO)

ECMO is the life support system that directs the venous blood of the patient to the artificial gas exchanger (oxygenator), thereby ensuring oxygenation and removal of CO_2 and return of blood to the venous or arterial system of the patient again. Veno-arterial ECMO (VA ECMO) performs both heart and lung functions, while venous-venous ECMO (VV ECMO) performs lung functions only and can be used in respiratory failure[38]. The use of ECMO support has increased in recent years, the patient should have a specified indication and no contraindications to consider this treatment option. Patients who do not respond to optimum conventional MV may be candidates for ECMO in institutions with appropriate resources (equipment and staff). The ECMO mode used in COVID-19 patients is usually VV ECMO. In this section we will focus more on VV ECMO.

Indications for VV ECMO can be listed as follows[38]:

1. For any reason (primary or secondary) in hypoxemic respiratory failure, ECMO should be considered when the mortality risk is 50% or more, and it should be started when the mortality risk is 80% or more.
   - Mortality risk ≥ %50: When FiO_2: 0.9, PaO_2/FiO_2 <150 and/or Murray score = 2-3 or age adjusted oxy-

genation index (AOI) >60 or Plateau Pressure Score (APPS) = 5-7
- Mortality risk ≥ %80: If FiO_2: 0.9, PaO_2/FiO_2 <100 and/or Murray score = 3-4 or AOI >80 or APPS = 8-9 despite optimal treatment for at least 6 hours

2. CO_2 retention despite high plateau pressures (>35 cm-H_2O)
3. Serious air leak syndromes
4. A patient who is in the lung transplant list, requiring intubation
5. Sudden cardiac or respiratory collapse (e.g. pulmonary embolism)
6. Hypercapnic respiratory failure with arterial pH <7.20

There is no strict contraindication for ECMO support, as each patient should be evaluated individually for gain and loss. However, despite ECMO, there are situations that are associated with a poor result and can be considered as a relative contraindication[38]:

1. MV requirement for 7 days or more (FiO_2 >0.9, p plateau >30 cmH_2O). Many centers think that the duration of ventilation is not a contraindication.
2. Major pharmacological immunosuppression (absolute neutrophil count < 400/mm^3)
3. Recent or progressive central nervous system (CNS) bleeding
4. Irreversible major CNS damage or terminal malignancy
5. Although advanced age is not a contraindication; increasing risks with increasing age should not be ignored

ECMO components (Cannulas, Pumps, Oxygenators)

Cannulas: Although the use of a negative pressure chamber is ideal for any invasive procedure in COVID-19 patients, this may not be possible most of the time. The Centers for Disease Control and Prevention (CDC) and other organizations state that surgeons, anesthesiologists and other clinicians who participate in the cannulation and initiation of ECMO should wear ideal personal protective equipment (PPE). The main differences between the VA and VV ECMO circuits are the cannula types and the location of the vessels in which they are located. Drainage cannulas are larger in diameter (22-31 Fr), multi-holed and long; while it is sufficient to select the return cannula with a small diameter (15-22 Fr). By using two separate cannulas for VV ECMO, neck-femoral region or right-left femoral region can be selected, while right internal jugular vein cannulation with a double lumen cannula can also be performed. Recently, double lumen cannula is preferred. In this type of cannulation, drainage is provided from the superior and inferior vena cava, while the return is towards the tricuspid valve in the atrium. Therefore, this system appears to be more advantageous because it provides more oxygen to the pulmonary arteries, reduces recirculation, requires only a single cannula to be inserted and facilitates rehabilitation and individual mobilization in patients requiring long-term ECMO[39].

Pumps: For ECMO units, there are two types of pumps: roles and centrifugal. Today, centrifugal pumps for ECMO systems have almost become a standard. The smaller centrifugal pumps deliver blood from the center of the vortex to the periphery with a magnetically driven impeller rotating up to 10,000 rpm in a conical cavity. When using a centrifugal pump, venous blood is taken independently of gravity and the patient's height relative to the pump does not affect the rotation. The blood flow depends on the pump's rotation rate per minute (rpm), front and afterload. Since high pressure gradient is not possible in centrifugal pumps, they do not cause significant embolism or tube rupture. Excessive negative pressure at the pump inlet can cause cavitation and hemolysis, but the degree of hemolysis is much lower compared to roller pumps[40].

Oxygenators (Membrane Lung, ML): The blood exiting the pump enters the oxygenator, the most important part of the ECMO system. ECMO oxygenators serve as artificial lungs to replace both oxygen (to blood) and carbon dioxide (from blood) instead of the patient's natural lungs. The basic principle in ECMO is the transport of oxygen from a semipermeable membrane to the blood. The membrane placed distal to the pump should have a high permeability for the passage of gases and have a resistant structure that prevents the passage of liquid from the blood to the gas phase. Membranes of different shapes consisting of hollow fiber tubes are used. As the sweep gas passes through the fiber cavity, effective gas exchange is achieved by passing from outside of fiber as opposite current to the blood. Modern membrane oxygenators are coated with "biocompatible-thrombus resistant polymers" that limit inflammation and thrombus formation. In the long-term use of membranes, when there is fluid accumulation in the fiber lumen and coagulation on the faces of the fibers in contact with blood; short-term sweep gas flow may need to be increased to ensure pore opening[41].

Anticoagulation during ECMO

Inflammation that develops as a result of blood contact with the non-biological ECMO circuit triggers coagulation. Immune-dysregulation, endothelial dysfunction and depletion of coagulation factors occur. Also, hypercoagulability is common in COVID-19 patients. Even though ECMO circuit and membranes are coated with heparin, systemic anticoagulation is required to prevent thromboembolic complications in ECMO treatment. One of the biggest problems during ECMO treatment is to reach and maintain therapeutic anticoagulation levels. Hemorrhagic and thromboembolic complications are major complications of ECMO therapy and are the most common causes of death. In ELSO study, it was reported that %20 of patients receiving ECMO support

had thrombotic complications[42]. In thrombotic complications, the most common cause is the lack of proper anticoagulation. The optimum hemostatic values and anticoagulant drugs used during ECMO are shown in Table 5 and Table 6.

Weaning from ECMO

Weaning from ECMO is a complex process, requires organized approach and a good ventilator management with comprehensive knowledge of ECMO physiology. Weaning is initiated when the underlying disease in the lungs is successfully treated and lung functions are recovered, improvements begin on the chest X-ray, FiO_2 < 0.45, PEEP < 10 cmH_2O or peak inspiratory pressure (PIP) <27 cmH_2O. If the ventilator settings still allow applying lung-protective ventilation strategies and CO_2 excretion is initiated by the natural lung then the ECMO blood flow is changed to adjust the pH value. According to blood gas controls, ECMO blood flow is gradually decreased to 1.5 L/min. The effectiveness of natural lung in removing CO2 is evaluated by taking blood gas before and after ML. When PCO_2 difference (pre and post ML) is less than 0.2-0.4 kPa (1.5-3.0 mmHg) the patient is considered as "balanced". This means that ML neither adds CO_2 to the patient's blood nor removes CO_2 from blood. CO_2 produced by the patient is completely cleared by the patient's own lungs. If arterial SaO_2 is sufficient, weaning from ECMO may be considered. FiO_2 is set to 0.35-0.50, the sweep gas is turned off. If turning off process is well-tolerated, sweep gas can be kept turned off for hours or all night long. If the ECMO weaning attempt fails, the sweep gas is switched on and the next day a weaning attempt is planned again. If blood gas maintains stabile and patient develops no tachypnea or dyspnea, the decision to wean from ECMO can be made. In patients receiving VV ECMO for respiratory support, the duration of support usually does not exceed 10 days[43].

Table 5. Optimum homeostatic values in ECMO patients

Parameters	**Recommended values**
Activated clotting time (ACT) (seconds)	180-220
International normalized ratio (INR)	1.3-1.5
R time in thromboelastography (seconds)	16-25
Maximum clot frequency in FibTEM (mm)	>10
Fibrinogen (mg/dL)	>100
Anti-thrombin activity (%)	70-80
Platelet count (mm3)	>80.000 (bleeding patient/high risk)
	>45.000 (no bleeding/low risk)
D-dimers **(µg/L)**	<300

Table 6. Anticoagulant agents used in ECMO treatment

Drug	**Advantages**	**Disadvantages**
Unfractionated Heparin (UFH)	Its mechanism and the drug itself are well known. Easy to antagonize (Protamine). Easy to monitor (aPTT/ACT).	Its effect is variable, it is not linear. It may cause HIT.
Low Molecular Weight Heparin (LMWH)	Easy to administer. Low risk for HIT induction.	It can accumulate in renal failure. Partially antagonizable. Not easy to monitor (anti-Xa levels).
Direct Thrombin Inhibitor (DTI)	Independent of AT levels. Good dose response. Doesn't induce HIT.	Has no antagonist. Coagulation inhibition is less in stasis areas. May have a ceiling effect on aPTT. May interact with INR measurement.
Antiplatelet agents	Inhibits coagulation at the initiation point. May reduce platelet consumption	Anticoagulant effect is not enough. Not enough evidence.

ACT: *Activated coagulation time*, aPTT: *Activated partial thromboplastin time*, AT: *Antithrombin*, HIT: *Heparin-induced thrombocytopenia*, INR: *International standardized ratio*

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