Prone Position

29

Claude Guérin

Prone position has been used for almost 50 years from now (Fig. 29.1) and has received further appraisal with the COVID-19 pandemic. Indeed, the rate of use of prone position jumped from 10 to 30% in the classic Acute Respiratory Distress Syndrome (ARDS) [1, 2] to more than 70% in the COVID-19-related ARDS [3]. This finding was observed when the level of evidence was the same during the two periods. This chapter will cover the rationale, the timing, some practical issues, and the clinical results, including those observed during the COVID-19 pandemic, of using prone position.

29.1 Rationale

From achieving a better oxygenation in intubated ARDS patients with severe hypoxemia the rationale to indicate prone position has embedded the prevention of ventilator-induced lung injury (VILI). Furthermore, the fact that prone position preserves and can even improve cardiac output has been recently emphasized.

29.1.1 Effects on Oxygenation

The mechanisms by which oxygenation improves, sometimes dramatically, following proning, are important to take in consideration. Oxygenation improvement with

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G. Bellani (ed.), *Mechanical Ventilation from Pathophysiology to Clinical Evidence*, https://doi.org/10.1007/978-3-030-93401-9_29

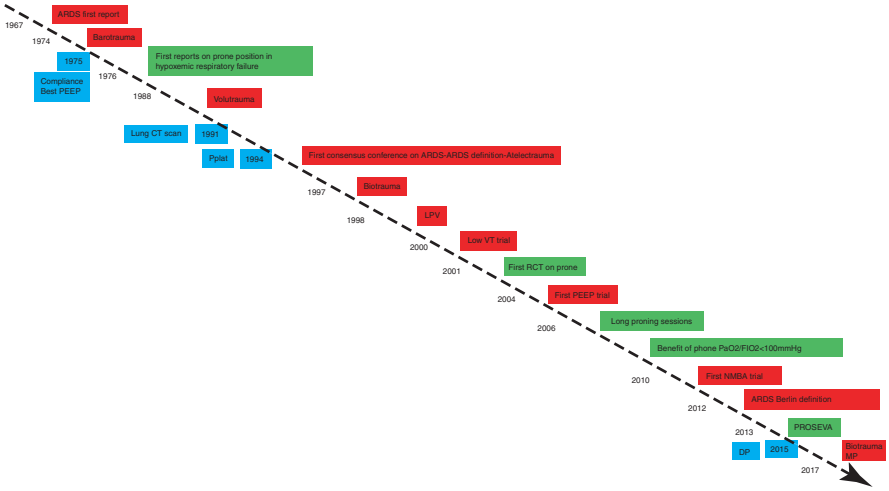

Fig. 29.1 Schematic drawing over time (not scaled) of some of the main steps in the acute respiratory distress syndrome (ARDS) management. Red boxes highlighted the mechanical ventilation, blue boxes the physiological monitoring and green boxes the prone position. *Pplat* plateau pressure, *LPV* lung protective ventilation, *PEEP* positive end-expiratory pressure, *DP* driving pressure, *RCT* randomized controlled trial, *VT* tidal volume, *NMBA* neuromuscular blockade agent, *MP* mechanical power

proning results from a reduction in intra-pulmonary shunt and a better ventilation-to-perfusion matching. The basic and typical scenario involves an increase in lung ventilation in the spinal, nondependent, parts of the lung, which continue to receive most of the pulmonary blood flow (at least in non-COVID-19 ARDS). Indeed, prone position promotes lung recruitment (lung tissue which gets aerated) in the dorsal lung regions, but does not significantly redistribute the pulmonary blood blow away from them. A scenario like this should also result in lower $PaCO_2$. Prone position enhances the beneficial effect on oxygenation of inhaled nitric oxide.

29.1.2 VILI Prevention

As the oxygenation goal should target modest objectives and the fact the VILI prevention came in as the main goal in delivering mechanical ventilation in ARDS, the central role of better oxygenation was less prominent, yet prone position still kept up the deal. Suggested by a landmark CT scan study that measured the lung gas-to-tissue ratio [4], the overall lung stress (i.e., the trans-pulmonary pressure) and strain (and its surrogate the driving pressure) is reduced in prone and, as importantly, its distribution throughout the lung is made more homogeneous [5] (Fig. 29.2). That means that the tidal volume is associated with a lower risk of over distending the baby lung, everything else being equal. For a given tidal volume, positive

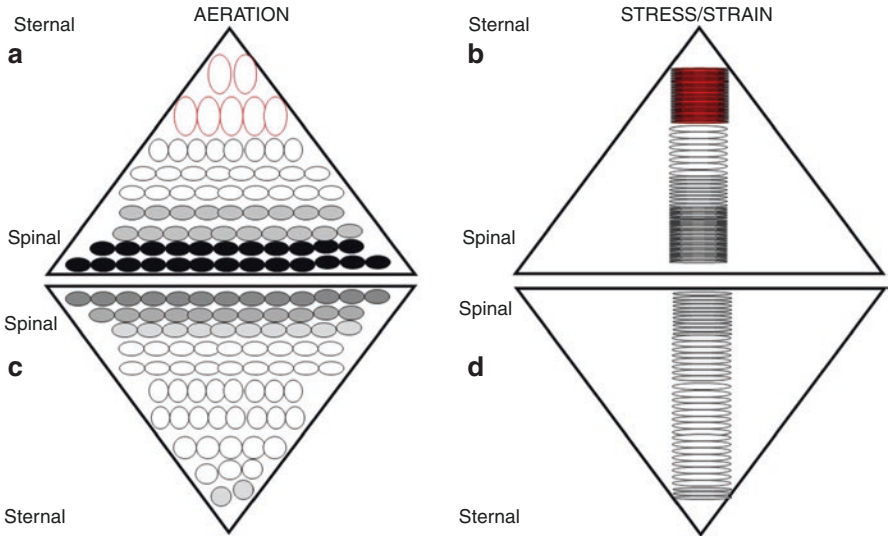

Fig. 29.2 Schematic drawing of the distribution of lung aeration and lung stress/strain in an ARDS lung in supine (**a**, **b**) and in prone position (**c**, **d**). The black ellipses are consolidated lung regions that do not experience stress because they are not ventilated. The gray ellipses are partially aerated lung regions. Those partially aerated lung regions that are close to the consolidated ones have a very high stress while those which are more distant have a lower stress but higher than normal. The white ellipses are normally aerated lung regions, i.e., the baby lung, with quite normal stress. Finally the white ellipses surrounded in red are overdistended lung regions and share a high stress. When turned to prone position there is both a lung recruitment and a reduction of overdistension. The overall lung stress/strain is reduced and its distribution is made more homogeneous across the lung

end-expiratory pressure (PEEP) does not significantly change the distribution of strain [5]. Proning increases the chest wall elastance from the supine at 0° inclination of the body [6]. Therefore, the change in respiratory system elastance may not reflect the change in lung elastance. For the lung elastance to decrease in prone, and then heralding lung recruitment, its reduction should be higher that the increase in chest wall elastance making the elastance of the respiratory system possibly unchanged. An increase in chest wall elastance, as it reduces lung overdistension, may also protect the lung [7].

29.1.3 Hemodynamics Effects

Proning can unload the right ventricle as a result of lowering pulmonary vascular resistance, via better gas exchange and increase in end-expiratory lung volume. More recently it has been shown that prone position can increase the cardiac output, in particular in preload-dependent patients in supine position [8].

29.2 Timing of Proning Application

29.2.1 PaO_2/F_IO_2 Threshold to Initiate Proning in ARDS

Stemming from an individual meta-analysis of four multicenter trials, the benefit of proning was suggested in ARDS patients with a PaO_2/F_IO_2 ratio < 100 mmHg at the time of randomization [9] (Table 29.1). This threshold was confirmed by experts [10]. However, a trial performed afterwards in moderate-to-severe ARDS patients included at PaO_2/F_IO_2 < 150 mmHg demonstrated a significant reduction in mortality up to 90 days after inclusion [11] (Table 29.1).

29.2.2 When to Start Proning

The PROSEVA trial [11] mandated a 12–24 h stabilization period before including the patients and, once included, the patient in the prone group were to be proned within the next 1 h. This aimed to proning the patient early after having made every effort to confirm the ARDS. At the same time, patients with an immediate indication of proning for extremely severe hypoxemia or those with a rapid improvement were not included. However, an early proning after ARDS recognition, stabilization and confirmation was efficient and safe. In the COVID-19 pandemic an early use of prone, i.e., within the 2 days after intubation, was associated with a better outcome as compared to a later proning in a large observational database [12]. The prone position-induced lung recruitment in the dorsal lung regions was significantly greater when pigs were proned early (day 1 after ARDS) than late (day 2) [13].

Table 29.1 Five large randomized controlled trials comparing prone to supine position in acute respiratory distress syndrome

First author	Italy	France	Spain	Italy	France and Spain
N patients (SP/PP)	152/152	378/413	60/76	174/168	229/237
% of ARDS (SP/PP)	93.3/94.7	28/33.9	100/100	100/100	100/100
PaO_2/FIO_2 (mmHg)	127	150	147	113	100
Tidal volume (mL/kg)	10.3 MBW	8 MBW	8.4 PBW	8 PBW	6.1 PBW
PEEP (cmH_2O)	10	8	12	10	10
PP hours per session	7	8	17	18	17
Mortality (SP/PP) (%)	25/21.1	31.5/32.4	58/43	32.8/31	32.8/16

Definition of abbreviations. *SP* supine position, *PP* prone position, *ARDS* acute respiratory distress syndrome, *PEEP* positive end-expiratory pressure, *MBW* measured body weight, *PBW* predicted body weight

29.2.3 When to Stop Proning

The timing to stop proning is as crucial as its initiation. In the PROSEVA trial [11] predetermined criteria based on oxygenation, PEEP and F_IO_2 were a priori defined in supine position. So, the definition of responders to prone in terms of oxygenation was defined by comparing supine pre-prone to supine post-prone, and not by considering the oxygenation change during the proning session. That means that proning was continued even though these criteria were not met, i.e., whether or not the patient exhibited an excellent oxygenation response or no change at all. A safety guard was that proning was stopped when oxygenation deteriorated by more than 20% over two consecutive sessions. This strategy aimed at setting the benefit of prone primarily from VILI prevention rather than oxygenation improvement. This issue is probably very important and led to some confusion in the literature, but also in practice. In the classic ARDS, there were no solid data showing that responders (in terms of oxygenation improvement) to prone did better than the nonresponders. A post-hoc analysis of the PROSEVA trial found no correlation between patient outcome and early or late response to prone in terms of PaO_2 or $PaCO_2$ [14] in line with a previous study by others [15]. However, in COVID-19 ARDS two observational studies suggested a significant association between oxygenation response and patient outcome [16, 17].

29.2.4 Duration of Proning Sessions

The three last trials done in Spain, Italy, and France used prolonged proning cycles, very much greater than 12 consecutive hours [18]. The rationale for long sessions is to minimize the occurrence of changing position for practical issues, having in mind nevertheless that changing position is a component of the proning treatment. Another rationale is more physiological: assuming that proning attenuates VILI, the longer the prone is applied the higher the likelihood of less VILI during mechanical ventilation. Extended use of proning in COVID-19 has been found feasible and effective [19].

29.3 Practical Issues

29.3.1 Patient Installation

In the large majority of the cases the use of patient's own bed and mattress and 3–4 caregivers with a mandatory one at the patient's head to control the artificial airway allows to make it. The COVID-19 with the large amount of patients who were proned, the prevalence of obese patients who were proned and the use of prone under ECMO challenged the nursing team and the devices as well. Exosquelettons attached at both the patient and the caregiver have been used to facilitate the procedure and increase its safety, and to reduce the injury to the caregivers [20, 21].

29.3.2 Support of Abdomen

Whether or not the abdomen should be supported is not definitely answered. A non-supported abdomen is recommended during late pregnancy together with the fetus heart rate monitoring.

29.3.3 Sedation and Neuromuscular Blockade During Prone Position

Most of the ARDS patients in prone position receive continuous intravenous both sedation and neuromuscular blockade [22]. The use of a minimal sedation with no neuromuscular blockade in ARDS even in prone position is a current hot topic but there is no published study on sedation in proned ARDS patients with or without neuromuscular blockade.

29.3.4 Setting the Ventilator in Prone Position

Resulting from better oxygenation the common ventilator setting change is a reduction in FIO_2 in prone. The frequent question about how to set PEEP in prone is still open. In the PROSEVA trial [11], PEEP was driven by a PEEP-F_IO_2 table and was reduced in prone, making the prone a-PEEP-sparing strategy. This may have contributed to 2 days with cardiovascular organ dysfunction less than in the supine group. Two other considerations would argue for higher PEEP in prone, one is the increase in chest wall elastance in prone and the other the lung recruitment. Indeed, if prone had induced lung recruitment, when the patient went back to supine higher PEEP should be set according to the "open the lung and keep it open" concept. Guiding PEEP setting by using esophageal pressure would be an attractive strategy as the relevance of esophageal pressure would be better in prone than in supine assuming that compression of the sensor by the gravity and the weight of lung, mediastinum and heart would be less. However, for a given end-expiratory transpulmonary target and as compared to the same baseline PEEP, the use of esophageal pressure did not result in a significant change in PEEP in prone as compared to supine [23]. However, it allowed to titrate the PEEP level at the individual patient level.

29.3.5 Contraindications

The single remaining absolute contraindication to proning in ARDS is an unstable spine fracture [18]. The followings are relative contraindications to be discussed on a case-by-case basis evaluating the risk-to-benefit ratio: shock, elevated intracranial pressure, surgical or medical abdominal problem. Obesity, even morbid, is not a

contra-indication as obese patients should benefit from proning given the important closing volume that should be relieved in prone, together with a judicious PEEP selection. As a matter of fact pregnancy is not a contra-indication to prone position as discussed above.

29.4 Clinical Evidence

29.4.1 Effects of Survival in Intubated Patients with Classic ARDS

As mentioned, several trials comparing supine to prone position did not find any significant outcome benefit but an individual meta-analysis resulted in the first positive signal favoring the use of proning in the most hypoxemic patients [18]. Then, the PROSEVA trial was the first one to demonstrate a significant outcome improvement with prone position, and, hence what is evidence-based is the prone position in ARDS patients with PaO_2/F_IO_2 ratio < 150 mmHg. This threshold received a conditional recommendation by experts [10] and a strong recommendation by others in the classic ARDS [24]. It was also recommended during the COVID-19 pandemic [25].

29.4.2 Findings in the COVID-19

The studies on pathophysiology of COVID-19-related ARDS pointed out two main findings: (1) a discrepancy between hypoxemia severity and preserved lung aeration reflected by better compliance of the respiratory system than in classic ARDS, (2) an involvement of the pulmonary circulation (microthrombi in the lung capillaries, impairment of hypoxic pulmonary vasoconstriction) making the redistribution of pulmonary blood blow with PEEP and also with prone position different from and the dead space higher than in the classic ARDS. However, the management of COVID-19 ARDS was recommended not to be different from the classic ARDS, including the use of prone position, which, as previously mentioned, exploded. Another trait was the massive use of prone position in awake non-intubated patients with severe COVID-19 pneumonia, not only in the intensive care unit (ICU) but also in the emergency room and in the ward. The goal was to spare the rare ICU resources, of utmost importance for the most severe patients. By doing so, the clinicians expected an improvement in oxygenation that would allow to buy time and to avoid intubation. This strategy was particularly used in developed countries, which experienced oxygen shortage. The risk was to delay intubation. Several trials have been conducted testing whether prone position, against supine, can avoid intubation and reduce mortality in awake non-intubated patients with a severe COVID-19 pneumonia. We are waiting for the final results of them. It should be mentioned that prone position in awake patients might be lung protective if it can reduce the patients' inspiratory effort and hence the trans-pulmonary pressure.

29.5 Conclusions

Prone position should be used in ARDS patients with a PaO_2/FIO_2 ratio < 150 mmHg if there is no contraindication. The COVID-19 clearly showed that the clinicians adopted this strategy even though the level of evidence was the same as before the pandemic. It remains to establish if this infatuation will continue when the pandemic is over.

Further studies are required to demonstrate if prone position can improve outcome in ARDS patients with PaO_2/F_IO_2 > 150 mmHg (a trial is in preparation in France), if prone position should be selected in responders, which requires a standardization of the response to prone, and if awake prone position has a role also outside COVID-19.

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Veno-Venous ECMO and $ECCO_2R$

30

Marco Giani, Christophe Guervilly, and Giuseppe Foti

30.1 Pathophysiology of Severe Respiratory Failure: Pulmonary Shunt and Alveolar Dead Space

Patients suffering from the most severe form acute respiratory distress syndrome (ARDS) present with life-threatening hypoxemia and/or respiratory acidosis. The ARDS lung shows complex histopathological alterations, including alveolar flooding, alveolar collapse and microvascular thrombosis [1]. These alterations result in shunt and dead space, which lie at the two opposite limits of the ventilation–perfusion relationship. Shunt occurs in alveolar-capillary units which are perfused but not ventilated, and is responsible for hypoxemia refractory to increased inspiratory oxygen (FiO_2) fraction.

In the presence of shunt, the ventilated regions are relatively underperfused. This, in adjunct to the microvascular thrombosis determines the increase of alveolar dead space, which result in the requirement of high minute ventilation to remove carbon dioxide (CO_2) from blood, due to the "waste" of mechanical ventilation in alveoli which are not perfused.

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G. Bellani (ed.), *Mechanical Ventilation from Pathophysiology to Clinical Evidence*, https://doi.org/10.1007/978-3-030-93401-9_30

30.2 Why Extracorporeal Gas Exchange?

Since more that 40 years, veno-venous extracorporeal membrane oxygenation (V-V ECMO) has been described as an effective rescue therapy to replace the gas exchange function of the failing lung [2, 3]. The rationale of extracorporeal gas exchange relies on providing oxygenation, CO_2 removal and to drastically decrease the ventilation of the native lungs. In a way, V-V ECMO is a "symptomatic" treatment that buys time for the lung to heal.

V-V ECMO may be used either as a rescue therapy for hypoxemia [2], or to decrease ventilatory load by the extracorporeal removal of CO_2 ($ECCO_2R$) [4–6]. To achieve the first goal, a high-flow veno-venous extracorporeal support (i.e., 3–6 L/min of blood flow) is required to provide adequate oxygenation. Contrarily, $ECCO_2R$ requires only a low extracorporeal blood flow (i.e., 500–1500 mL/min) due to higher solubility and diffusion through the membrane lung of CO_2 as compared with O_2 [7]. Eventually, this may correct or prevent respiratory acidosis, thus reducing the ventilatory burden. This divergence is secondary to the different physiology of O_2 and CO_2 exchange. Oxygenation mainly depends on the extracorporeal blood flow [8], whereas CO_2 transfer mainly depends on the sweep gas flow rate set at the membrane lung (ML) [9, 10].

As described above, high inspiratory O_2 fraction do not correct hypoxemia in the presence of elevated pulmonary shunt. V-V ECMO allows to increase the mixed venous O_2 content, so that the "shunted" blood becomes oxygenated. V-V ECMO is therefore proposed when severe hypoxemia is life-threatening despite low tidal-low volume ventilation, use of moderate to high positive end expiratory pressure (PEEP), continuous neuromuscular blockers infusion and at least one trial of prone positioning [11].

On the other hand, the indication for $ECCO_2R$ deserves more discussion. The more severe is the compromise of the lung function, the higher airway pressure and minute ventilation are required to maintain viable oxygen and carbon dioxide levels. Furthermore, the lung pathological lead to a decrease of the lung compliance, thus requiring higher ventilatory pressures. This high ventilation burden may worsen the lung inflammation (i.e., ventilator induced lung injury, VILI), leading to a vicious circle. Moreover, the simultaneous presence of hypoxic pulmonary vasoconstriction, hypercapnia, and high ventilatory pressures determine an increase pulmonary resistances and pulmonary arterial pressure (i.e., right ventricular afterload), eventually leading to right ventricular dysfunction or failure [12].

The extracorporeal removal of carbon dioxide allow to reduce the ventilatory load down to near-apneic ventilation, which in the experimental model [13] allowed to decreases histologic lung injury and fibroproliferation. Mechanical ventilation during ECMO is discussed in detail in Chap. 31. Briefly, wide variability exists among ECMO centers on how ventilatory setting is modified after the start of extracorporeal gas exchange [14]. In general, tidal volume is usually lowered to 3–6 mL/kg (calculated on ideal body weight) to achieve a plateau pressure below 25 cmH_2O and driving pressure below 12–15 cmH_2O. In addition, to further decrease the ventilation burden, many centers reduce respiratory rate down to 10–15 breaths per minute. Figure 30.1 shows the reduction of ventilation achieved in the first 20 min after the ECMO start in 36 ARDS patients at our center (unpublished data).

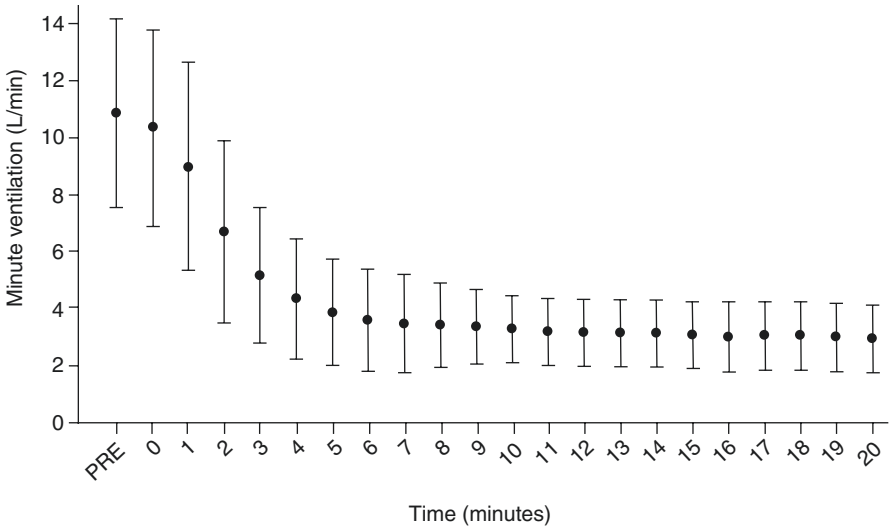

Fig. 30.1 Minute ventilation before and after the ECMO start. Points represent mean values; error bars display standard deviation. *L/min* liters per minute. *$P < 0.05$ vs. step PRE

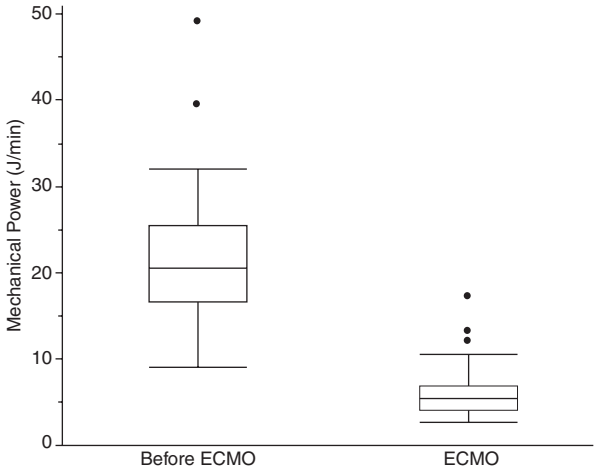

Fig. 30.2 Mechanical power before and after the ECMO start. *ECMO* extracorporeal membrane oxygenation

This reduction of minute ventilation was achieved by reducing the tidal volume from 5.6 ± 1.8 to 4.5 ± 2 mL/kg ($P < 0.001$) and the respiratory rate from 30 ± 5 to 10 ± 2 breaths per minute ($P < 0.001$). The reduction of tidal volume led to a decrease of driving pressure of 4 cmH_2O (from 14 ± 3 to 10 ± 3).

Accordingly, the mechanical power, which represents the amount of total energy transmitted by the ventilator to the damaged lungs, is dramatically reduced after start of ECMO, as shown in Fig. 30.2 (66 ARDS V-V ECMO patients at ASST Monza, unpublished data).

As a common clinical experience, the start of V-V ECMO is followed by a significant improvement of hemodynamics. The normalization of arterial O_2 and CO_2 levels, together with the decrease of intra-thoracic pressures, determines a reduction of pulmonary resistances and right ventricle unloading [15], thus reducing the risk of developing acute cor pulmonale, which is observed in up to 22% of severe ARDS patients and is strongly associated with mortality [16].

30.3 "Full" V-V ECMO Versus Low-Flow $ECCO_2R$

Typically, in very severe ARDS patients requiring extracorporeal gas exchange high-flow veno-venous ECMO is the technique of choice. Severe hypoxemia defined by PaO_2/FiO_2 below 50–80 mmHg (at 100% FiO_2) and severe respiratory acidosis (pH <7.25) are the main inclusion criteria used in clinical trials on extracorporeal support [2, 17–19]. However, Gattinoni et al. challenged the idea that a very low arterial oxygen tension determines tissue hypoxia, and postulated that almost all severe ARDS patient might be managed with low-flow systems. Indeed, patients with an arterial O_2 tension lower than 60 mmHg do not seem to suffer from any organ damage [10]. Actually, the greatest benefit of ECMO in the EOLIA trial [17] was found in the group of patients who presented with a degree of respiratory acidosis which prevented protective ventilation (24% mortality in the ECMO group vs. 55% in the control group). This finding may suggest that the benefit from ECMO probably relies more on VILI prevention than on the improvement of arterial O_2.

When the extracorporeal gas exchange is only required to decrease the mechanical ventilation load, a less invasive $ECCO_2R$ technique may be a reasonable option. However, defining a ventilatory burden cutoff which mandates the extracorporeal CO_2 removal may prove challenging. Actually, a recent trial on $ECCO_2R$ and ultraprotective lung ventilation—the Supernova study [20]—, used an oxygenation index and not ventilatory load as an inclusion criterion. This study only reported a slight decrease of plateau pressure using low or intermediate blood flow by two different devices.

The $ECCO_2R$ system (cannula size, pump and membrane surface) limits the maximum blood flow achievable, becoming useless in case of life-threatening hypoxemia. Ultraprotective ventilatory strategies (i.e., tidal volume reduction below 6 mL/kg) aim at VILI reduction in critical ARDS patients. However, this often results in lung de-recruitment and consequently in a worsening of hypoxia [21].

Indeed, in a study of $ECCO_2R$ safety, prone positioning and conversion to high-flow V-V ECMO were required as rescue therapies for life-threating hypoxemia in 2 and 4 out of 15 patients, respectively [22]. Besides, due to modulation of the respiratory quotient by the membrane lung, $ECCO_2R$ could expose patients to paradoxical hypoxemia [23, 24].

In the past, our group has proposed and validated a mathematical model of oxygenation during V-V ECMO [8], with a high accuracy and predictive power. Through this model, we retrospectively analyzed data of 76 patients treated with high-flow V-V ECMO at our institution. Among these patients, a blood flow reduction down

to the $ECCO_2R$ range (i.e., 1 L/min) would have determined a severe desaturation (i.e., a peripheral oxygen saturation below 85%) in 30 patients (39%), despite 100% of O_2 inspiratory fraction at the ventilator [unpublished data]. Due to the retrospective, preliminary and in silico nature of these data, further research is warranted to determine the safety and feasibility of a pure $ECCO_2R$ technique versus a high-flow V-V ECMO in severe ARDS patients.

As explained above, an extracorporeal blood flow of 500–1500 mL/min is required to remove a significant fraction of the total CO_2 production (VCO_2). Experimental techniques were developed to improve the extracorporeal CO_2 extraction of the membrane lung, with the aim of extracting up to half of VCO_2 from a very low blood flow, such as the one used for renal replacement techniques (150–300 mL/min). This would allow to use small dual-lumen catheters (e.g., 12–14 French) and, hypothetically, regional citrate anticoagulation.

Blood acidification has been proposed as an experimental technique to increase the carbon dioxide removal capability of the membrane lung [25]. Acidification converts bicarbonates into carbon dioxide, increasing the carbon dioxide transfer [26, 27]. More recently, respiratory electrodialysis has been described as a new experimental technique to efficiently performs $ECCO_2R$ [28, 29]. When compared to conventional $ECCO_2R$, respiratory electrodialysis almost doubled the ML CO_2 removal and halved minute ventilation. Due to the very preliminary nature of these experimental findings, further research is warranted in this field.

30.4 Evidence for Extracorporeal Gas Exchange in ARDS Patients

As mentioned, V-V ECMO is an indisputable life-saving therapy for refractory hypoxemia and a strong physiological rationale supports its use when high plateau pressures and/or tidal volumes are required. However, it is unclear how to define the oxygenation and ventilation load cutoffs which mandates the start of the V-V extracorporeal support.

Recently, two important studies have changed the evidence on V-V ECMO use.

About 10 years ago, the CESAR trial [18] clearly showed that the most severe ARDS patients should be transferred to an ECMO-capable center to significantly improve survival without severe disability. Even if only 75% of the patients received ECMO, it's highly likely that the use of ECMO had an impact on the survival benefit.

The more recent EOLIA trial [17] randomly assigned 249 patients with severe ARDS to receive early V-V ECMO or conventional tidal volume (Vt) and pressure limited ventilation (including late ECMO as rescue therapy). Despite inconclusive survival results (35% and 46% mortality in ECMO and control group, respectively, $P = 0.09$), the high percentage of sicker patients that crossed over from the conventional treatment group to the ECMO group for rescue therapy (28%) endorsed the use of V-V ECMO in life-threatening hypoxemia. Moreover, per-protocol and Bayesian post hoc analysis provided more favorable interpretation of the study

results [30, 31]. Thus, an individual patient data meta-analysis [30] of EOLIA and CESAR trials found a significant decrease in 90-day mortality in patients supported by ECMO compared with conventional management.

The combined use of $ECCO_2R$ and mechanical ventilation has proved to be feasible when compared to mechanical ventilation (MV) alone [7, 20, 22]. However, the benefit of $ECCO_2R$ need to counterbalance the risks of the technique. The recently published REST trial [21] aimed to establish whether $ECCO_2R$ and ultraprotective ventilation may improve all-cause mortality in comparison with standard of care. The study was stopped prematurely due to futility and feasibility issues. Ninety-day mortality rate was 41.5% in the experimental group (lower tidal volume ventilation + $ECCO_2R$) vs. 39.5% in the standard care group ($P = 0.68$). However, there were fewer ventilator-free days and more serious adverse events in the extracorporeal carbon dioxide removal group. Adverse events in the extracorporeal carbon dioxide removal group included intracranial hemorrage, which occurred in 9 patients (4.5% vs. 0% in the control group), and bleeding at other sites (3.0% vs. 0.5%). The study had some relevant limitations, including that the tidal volume target (3 mL/kg) in the experimental arm was not achieved. However, based on these findings, $ECCO_2R$ cannot yet be recommended as a strategy to improve ARDS patients' outcome.

30.5 Outcome of ARDS Patients Treated with V-V ECMO

The Extracorporeal Life Support Organization (ELSO) collects and publishes on a regular basis the number of ECMO runs and their outcome. Overall, the reported hospital survival rate of adult patients treated with V-V ECMO is 59% [32]. Over the last 10 years, the number of ECMO runs has almost tripled [32], and the recent SARS-CoV-2 pandemic led to a further rise of V-V ECMO use worldwide. After early reports from China of very high mortality rates of COVID-19 patients treated with ECMO [33], large observational studies showed satisfactory outcomes in this population. A large observational study from the Extracorporeal Life Support Organization (ELSO) registry [34] included 1035 COVID-19 patients and reported a 90-day mortality of 37%. Later reports [35–37] which included patients from the second COVID wave in fall 2020 showed a trend toward increased mortality (48–60%). This finding was only partly explained by patient characteristics at baseline. The authors hypothesize that failure of prolonged noninvasive ventilation strategies before intubation and increased lung damage may have influenced this worse outcome [36]. This underlines how, in the context of acute respiratory distress, V-V ECMO should only be considered as a bridge-to-recovery therapy, and should not be indicated when lung damage is deemed irreversible.

30.6 Should the Number of ECMO Centers Be Increased?

In the last decade the number of ECMO centers has increased steadily [32]. It might be tempting to think that every hospital/ICU should develop the ECMO capability, to be able to face any severe respiratory (or cardiac) failure refractory to

conventional therapies. However, providing ECMO requires a multidisciplinary team (i.e., physicians, nurses, perfusionists) with specific skills that are difficult to develop in a short time and require a high case volume to be maintained. Several studies showed that a major determinant of the outcome of ECMO patients is the center case volume [38, 39]. For this reason, a hub and spoke model seems able to provide the best result s [39]. 24/7 mobile ECMO teams are available in many ECMO centers and allow a safe patient retrieval with good outcomes. The CESAR trial [18] showed unequivocally that centralization of patients with severe but potentially reversible respiratory failure to an ECMO-capable center significantly improves survival. Peripheral "spoke" hospital must develop the delicate skill of early identification and management of ARDS patients at risk at deterioration and should consult ECMO centers timely, as prolonged mechanical ventilation (especially if not protective) has proved to be an independent predictor of poor outcome [39].

30.7 Conclusions

In a nutshell, V-V ECMO provides oxygenation and allow a more protective ventilation strategy [14, 40]. Considering its strong rationale and the results of recent randomized trials [30], its application in experienced ECMO centers should be considered for the most severe ARDS patients when other therapies (i.e., prone positioning) fail. However, defining the appropriate level of lung rest, the setting of mechanical ventilation and the role of assisted breathing during extracorporeal support still need further investigation.

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Mechanical Ventilation Setting During ECMO

31

Luigi Camporota and Eddy Fan

31.1 Introduction

31.1.1 Mechanical Ventilation Strategy in ARDS

In patients with acute respiratory distress syndrome (ARDS), mechanical ventilation is instituted to support gas exchange and the work of breathing, while the patient receives treatment from the underlying disease. It is now clear, however that the mechanical forces generated by the ventilator can damage the small and inhomogeneous diseased lung through pathophysiological mechanisms known as

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G. Bellani (ed.), *Mechanical Ventilation from Pathophysiology to Clinical Evidence*, https://doi.org/10.1007/978-3-030-93401-9_31

ventilator-induced lung injury (VILI). These mechanisms are also the factors that contribute to the development of extra pulmonary organ failure [1, 2].

Based on the appreciation of VILI, over the last 50 years the aim of mechanical ventilation has gradually shifted from focussing on achieving near-normal arterial oxygen and carbon dioxide tension (PaO_2 and $PaCO_2$) levels regardless of the cost in terms of airway pressures and tidal volumes, to the goal of minimising the intensity of mechanical energy delivered to the lungs (mechanical power). In this context, particular attention is now placed to the setting of a respiratory rate as low as possible (based on $PaCO_2$) [3], the use of moderate positive end-expiratory pressure (PEEP) with the avoidance of routine use of recruitment manoeuvres (RM) [2, 4], and tidal volumes which are in proportion to the resting lung volume. This latter concept is reflected in the measure of driving pressure, which represents the ratio between tidal volume delivered and compliance of the respiratory system [5].

31.1.2 Mechanical Ventilation Strategy in Severe ARDS Receiving ECMO

The association between the different components of the mechanical power [6] and outcome is even more relevant for patients with very severe ARDS who receive extracorporeal membrane oxygenation (ECMO) [1], given that the very low lung volume and greater heterogeneity makes the lung parenchyma more vulnerable to mechanical stress and strain—and therefore VILI.

Several studies have also demonstrated the value of a lung protective ventilation and ECMO in patients with ARDS [7]. The evidence available so far seems to show that ventilating patients with lower driving pressure (tidal volumes) and respiratory rate once on ECMO is feasible [8–12] and leads to improved outcomes [13, 14].

In this chapter, we will review some of the evidence related to mechanical ventilation during ECMO and some practical recommendations.

31.1.3 Effects of ECMO on Gas Exchange and Interactions with Native Lung Function

Venovenous ("respiratory") ECMO allows deoxygenated blood drained from a central vein to be reinfused—fully oxygenated and decarboxylated—into the vena cava or the right atrium at sufficient flows (3–7 L/min) to achieve oxygen delivery able to satisfy metabolic demands.

In patients with ARDS not on ECMO, the arterial oxygen content (CaO_2) depends on the shunt fraction of the native lung, and on the oxygen content of the mixed venous blood:

$$CaO_2 = CcO_2 \times \left(1 - \frac{Q_s}{Q_t}\right) + \left(CvO_2 \times \frac{Q_s}{Q_t}\right) \quad (31.1)$$

where, $1 - (Q_s/Q_t)$ is the portion of the cardiac output going through the ventilated lung parenchyma, and Q_s/Q_t is the portion of the cardiac output perfusing non-ventilated lung areas.

In patients fully dependent on ECMO (i.e. with no residual native lung function) the CaO_2—in its simplest form, without accounting for recirculation (see below)—is:

$$CaO_2 = C_{post-oxy}O_2 \times ECBF + CvO_2 \times (CO - ECBF) \tag{31.2}$$

This formula is analogous to Eq. (31.1) where ECMO blood flow is noted as ECBF and CO is the cardiac output of the patient, CvO_2 is the content of oxygen in the venous blood and $C_{post\text{-}oxy}O_2$ content of the blood exiting the oxygenator.

By rearranging Eq. (31.2):

$$CaO_2 = \left(\frac{ECBF}{CO}\right) \times C_{post-oxy}O_2 + \left[1 - \left(\frac{ECBF}{CO}\right)\right] \times CvO_2 \tag{31.3}$$

Using this formula, the oxygen content is expressed in terms of the ratio between the ECBF and the cardiac output—in a similar way as the shunt equation of the native lung.

It becomes clear that oxygen content depends not only on the ECMO blood flow and the content of oxygen in the venous blood, but also on the ratio between ECBF and the patient's cardiac output. To understand this concept, we have to consider how the venous return, equal to the patient cardiac output, is "split" into two components: (1) one part—equal to the ECBF—will pass through the oxygenator and therefore will return to the right atrium fully saturated with oxygen ($S_{post\text{-}oxy} = 100\%$; $P_{post\text{-}oxy}O_2 \sim 60–70$ kPa or 450–525 mmHg); (2) the second part of the venous return—which is equal to the amount of flow that exceeds the ECBF (i.e. CO − ECBF) will have the saturation of the venous blood. Therefore, the mixed venous blood of the patient (the oxygenation of the blood in the pulmonary artery) will be a mixed "weighed average" of the two in a proportion that will depend on: the ratio between ECBF and CO; the venous oxygenation and the functioning of the membrane (i.e. the ability to fully oxygenate the venous blood).

31.1.4 Interaction Between the Native and the Artificial Lung

Form the principles discussed above, is clear that unless the ECBF is exactly equal (or greater—if we consider recirculation) than the cardiac output, the patient arterial saturation will be less than 100%, and often in the range of 85–92%. In this context, the management of the native lung through appropriate ventilation can be relevant to maintain a certain degree of native lung function. So, it is relevant to reflect that once a patient is placed on ECMO, the native lung function may deteriorate because of two main physiological phenomena:

1. Abolition of hypoxic vasoconstriction—(from hyper-oxygenation of the mixed venous blood) with an increase in the physiological shunt of the native lung,
2. Reduction in alveolar oxygen tension resulting from the CO_2 removed by the membrane lung—and a reduction of the alveolar CO_2 (demonstrated by the reduction in the end tidal CO_2). The reduction of the alveolar CO_2 is responsible for the reduction in the respiratory quotient of the natural lung and a progressive fall in the alveolar PO_2 based on the alveolar gas equation:

$$PAO_2 = \left[FiO_2 - P_{atm-H_2O} \right] - \left(\frac{PaCO_2 \times VO_2}{VCO_{2NL}} \right) \quad (31.4)$$

Where VO_2 is the oxygen consumption and VCO_{2NL} is the amount of CO_2 removed by the native lung per minute. It is important to note that an ultra-protective strategy of ventilation (severe hypoventilation with normocapnia) can lead to reabsorption atelectasis, and a reduction in inspiratory pressure can cause significant reduction in end-expiratory lung volume, and lung collapse due to compression atelectasis. All these conditions are avoidable using an adequate level of PEEP.

Along with the hemodynamic changes which follow ECMO initiation, these physiological mechanisms and changes in ventilator settings contribute to an increase in shunt fraction and a worsening in the gas exchange of the native lung (Fig. 31.1).

31.1.5 Mechanical Ventilation on ECMO: General Principles

The settings used to ventilate patients with severe ARDS on ECMO are highly variable across different international ECMO centres, and there no universally accepted consensus on the optimal strategy. Although the majority of the centres reports adopting a "lung rest" strategy with low tidal volumes [15], there is large variation in terms of PEEP setting and titration and use of recruitment manoeuvres [16] and less than one-third of centres have an explicit mechanical ventilation protocol for ECMO patients [16]. This variation in practice reflects the lack of robust evidence from randomised trials (RCT) on one hand, and the variation in background, expertise, and case-mix within each ECMO centre on the other.

However, it appears logical that the primary focus of mechanical ventilation during ECMO should be that of averting VILI, while promoting lung rest and healing [7]. Therefore, mechanical ventilation should maximise lung protection, while gas exchange is supported by ECMO.

The "standard" ventilation settings used in the CESAR study [17] were the following: FiO_2 reduced to 0.3 (or the lowest possible); tidal volume of 2–4 mL/kg of predicted body weight to limit the plateau pressure to 20–25 cmH_2O; PEEP—initially maintained to defend mean airway pressure then gradually reduced to 10 cmH_2O, giving a driving pressure of 10 cmH_2O. Respiratory rate was maintained

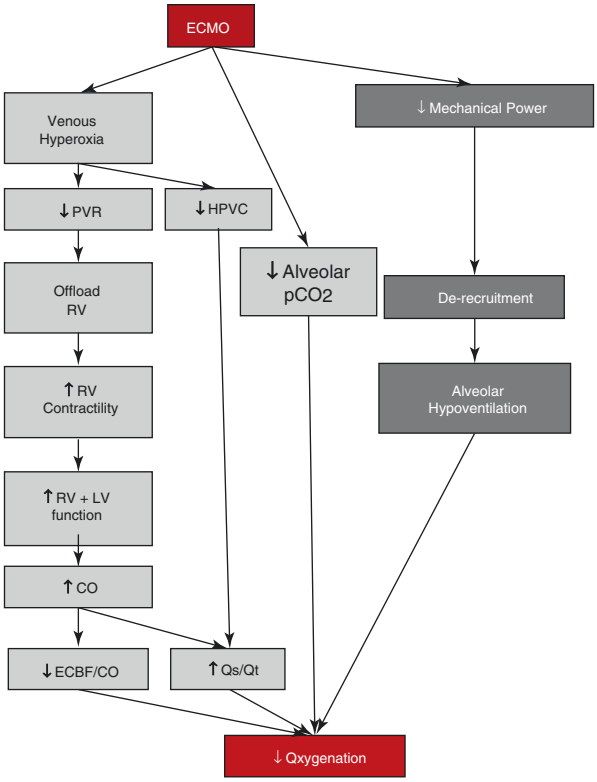

Fig. 31.1 Pathophysiological changes that may affect arterial oxygenation after ECMO initiation. VV-ECMO increases venous oxygenation and allows a reduction of mechanical power. ECMO produces venous hyperoxia which in turn reduces pulmonary vascular resistance and hypoxic pulmonary vasoconstriction. This improves right ventricular function, cardiac output and increase shunt (Q_s/Q_t). The cardiac output (CO) improves and reduce the ration between extracorporeal blood flow (ECBF) and cardiac output. All these changes can result in a lower arterial oxygen tension

at 10 breaths/min. A similar strategy was used in the more recent EOLIA trial [18], but the respiratory rate was permitted to range between 10 and 30 breaths/min.

Although data from RCTs are more limited in patients supported by ECMO, the evidence in the management of ARDS accumulated over the last 20 years can offer some guiding principles that can be safely extrapolated to patients on ECMO.

If we consider the single guiding principle that the determinant of VILI—by definition—is the total energy delivered to the lung by the ventilator (in the case of controlled ventilation), it is clear that the best way to reduce VILI is to minimise each individual components of the mechanical power equation: respiratory rate, driving pressure (through tidal volume), inspiratory flow, and PEEP [6, 19] (Fig. 31.2).

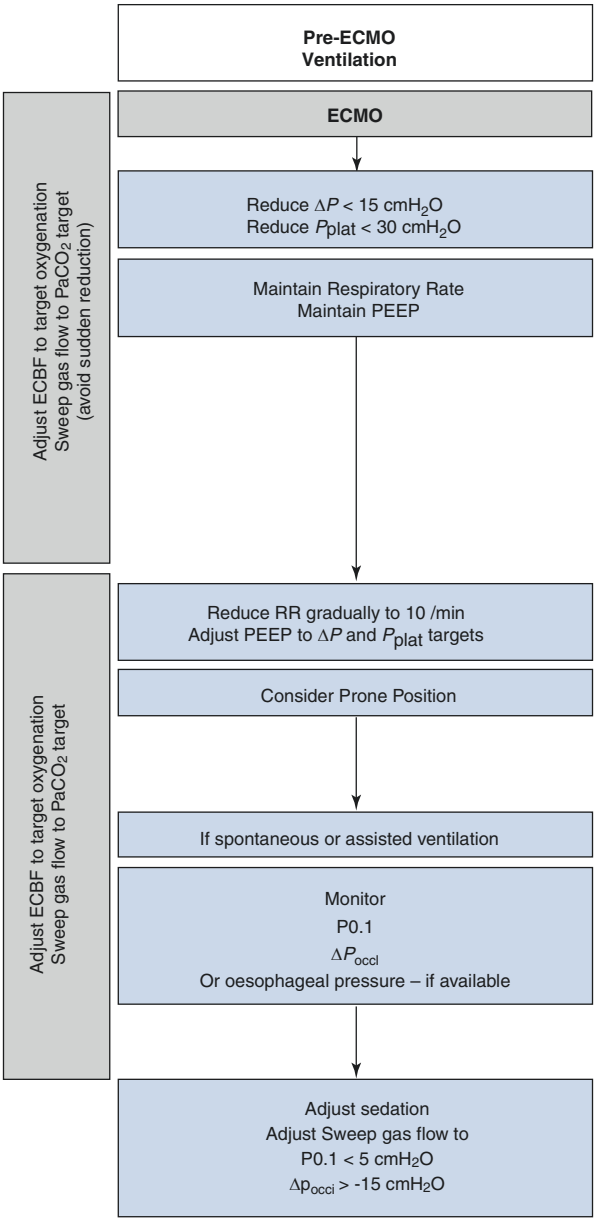

Fig. 31.2 Mechanical ventilation during ECMO: steps and targets

31.1.6 Mechanical Ventilation Setting on ECMO

31.1.6.1 Tidal Volume

Although there is still debate on what is the optimal tidal volume (V_T) referenced to predicted body weight (6 vs. 4 vs. 3 mL/kg), there is growing evidence supported by strong physiological principles that the determinant of volutrauma is lung *strain*—measured as the ratio between tidal volume and the resting lung volume (functional residual capacity—FRC).

In the absence of bedside measures of FRC, the relationship between FRC (the volume of the lung that can be ventilated, or "baby lung") and compliance of the respiratory system (C_{RS}) can be used to make approximation on the level of strain (Eq. 31.5) and therefore make clinical decisions regarding setting the most appropriate tidal volume whether V_T is appropriate for the size of FRC.

$$\text{Strain} = \frac{V_T}{\text{FRC}};\ \text{FRC} \propto C_{RS} \rightarrow \text{Strain} \approx \frac{V_T}{C_{RS}} \tag{31.5}$$

$$\text{Strain} = \frac{V_T}{\dfrac{V_T}{P_{plateau} - \text{PEEP}}} = P_{plateau} - \text{PEEP} \tag{31.6}$$

Indeed, if FRC is substituted for C_{RS} in the strain equation (Eqs. 31.5 and 31.6), one can see how driving pressure (plateau pressure minus PEEP) represents lung strain. Therefore, driving pressure can be used to set tidal volume regardless of the severity of ARDS [3, 20]. ECMO makes it possible to reduce driving pressure below the threshold of 14 cmH_2O, beyond which the risk of mortality increases [3, 5].

A multicentre, prospective cohort study of patients undergoing ECMO for ARDS during a 1-year period in 23 international ICUs showed that after ECMO initiation V_T was decreased from 6.4 ± 2.0 to 3.7 ± 2.0 mL/kg PBW, reducing the driving pressure from 20 ± 7 to 14 ± 4 cmH_2O and—with a simultaneous reduction in respiratory rate—mechanical power was markedly reduced from 26.1 ± 12.7 to 6.6 ± 4.8 J/min [8]. Similar reductions were achieved in the EOLIA trial [18] and in a multicentre observational study [11]. A reduction in tidal volume and driving pressure is strongly associated with mortality in ECMO patients, with a 6% increase in the risk of in-hospital mortality for each additional cmH_2O of driving pressure (hazard ratio 1.06; 95% CI 1.03–1.1) [12].

31.1.6.2 Respiratory Rate

Respiratory rate is probably the most underappreciated determinant of VILI. In patients with ARDS not on ECMO, respiratory rate is often increased to compensate for the low tidal volumes and control hypercapnia. The removal of CO_2 via the membrane lung allows the reduction in respiratory rate even to very low levels. This strategy can decrease inflammation and lung injury [21, 22]. Based on currently available data, it is recommended that respiratory rate on ECMO is set as low as possible—using the CESAR protocol [17] ta 10/min, or in the range of 4–15/min as recommended by ELSO [23].

31.1.6.3 PEEP

Recommendations regarding PEEP setting during ECMO are more variable and may depend on lung recruitability and mean airway pressure pre-ECMO [24]. While very low PEEP levels may cause progressive de-recruitment, atelectasis formation and progressive lung consolidation and fibrosis, very high PEEP levels can contribute to static volutrauma, increased lung stress and strain, haemodynamic compromise and ECMO cannula access insufficiency. Therefore, PEEP levels between 10 and 15 cmH_2O are a reasonable compromise, provided that plateau pressure and driving pressure remain within safe ranges.

31.1.7 Additional Considerations

31.1.7.1 Prone Position

The use of prone position in ECMO is possible and observational data suggests it is associated with an improvement in outcome [25, 26]—although it may be associated with longer ECMO duration [26]. While definitive evidence is awaited, prone position in ECMO seems a useful additional strategy to protect the lung and minimise de-recruitment post-ECMO. Important precautions need to be considered to avoid pressure areas or occlusion/kinking of cannulae which will interfere and interrupt extracorporeal blood flow.

31.1.7.2 Respiratory Effort

One potentially problematic issue related to the ventilation of patients on ECMO is the transition between mandatory ventilation and spontaneous/assisted ventilation. Patients on ECMO may have high respiratory drive and inspiratory effort despite a relatively normal gas exchange mainly due to the high elastance which stimulates respiratory drive and effort, leading to hunger and distress. These symptoms may not be improved by tracheostomy, particularly during the early stages of the disease [27], and may be associated with complications if the patients is fully ECMO dependent or coagulopathic [28]. The increased respiratory effort can cause large increases in pleural pressure, resulting in an uncontrolled increase in local transpulmonary pressure, with lung injury and barotrauma—a process named patient self-inflicted lung injury (P-SILI) [29].

Clinicians should be aware of this possibility and monitor inspiratory efforts using measures such as P0.1, occlusion pressure (P_{occ}) [30] or using more invasive methods such as oesophageal pressure or the electrical activity of the diaphragm (Eadi). An occlusion pressure can be easily performed using and end-expiratory hold manoeuvre. The occlusion pressure is the difference between PEEP and the most negative airway pressure deflection during the first breathe after the occlusion. Ideally, patients should be managed so that they can maintain a P0.1 < 4–5 cmH_2O and an occlusion pressure >−15 cmH_2O [31].

31.2 Conclusion

The general principle of ventilation during ECMO is to maximise lung protection while gas exchange is maintained through the extracorporeal membrane lung. Careful attention and monitoring of driving pressures, respiratory rate and PEEP selection is essential during mandatory ventilation, while monitoring of respiratory effort and drive can reduce the risk of patient self-inflicted lung injury.

Declaration of Interests The authors declare that they have no conflict of interests.

Funding None.

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