

Mechanical ventilation and respiratory monitoring during extracorporeal membrane oxygenation for respiratory support

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Abstract: Over the past decade, the use of veno-venous extracorporeal membrane oxygenation (VV-ECMO) for respiratory support has widely expanded as a treatment strategy for patients with acute respiratory distress syndrome (ARDS). Despite considerable attention has been given to the indications, the timing and the management of patients undergoing ECMO for refractory respiratory hypoxemic failure, little is known regarding the management of mechanical ventilation (MV) in this group of patients. ECMO enables to minimize ventilatory induced lung injury (VILI) and it has been successfully used as rescue therapy in patients with ARDS when conventional ventilator strategies have failed. However, literature is lacking regarding the best strategies and MV settings, including positive end expiratory pressure (PEEP), tidal volume (VT), respiratory rate (RR) and plateau pressure (PPLAT). The aim of this review is to summarize current evidence, the rationale and provide recommendations about the best ventilator strategy to adopt in patients with ARDS undergoing VV-ECMO support.

Keywords: Mechanical ventilation (MV); extracorporeal membrane oxygenation (ECMO); acute respiratory distress syndrome (ARDS); positive end expiratory pressure (PEEP)

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Introduction

Extracorporeal membrane oxygenation (ECMO) is an extracorporeal technique able to provide temporary gas exchange support in patients with respiratory failure refractory to conventional treatment (1). ECMO is able to support gas exchanges in patients with refractory hypoxia, and one of its main indications is in patients with acute respiratory distress syndrome (ARDS) (2).

The first successful use of ECMO was reported in 1972 in a patient with post-traumatic ARDS (3) and since then, technological improvements facilitated a wider expansion of the technique along with decreased complications and improved outcomes (4).

Over the last decade, literature has widely focused

on the indications, timing, complications and the effects on outcome (5-9). Mechanical ventilation (MV) and the ventilator management of the native lung play a central role during ECMO. Nevertheless, surprisingly, this aspect has received little attention (10-16). Most studies report only ventilator setting and respiratory mechanics data before ECMO; few studies report also data regarding the first day of ECMO (*Table 1*); and very few studies extend the description of ventilator parameters beyond the first day. For these reasons, it is very difficult to recognize and reproduce specific ventilator approaches; there are not enough data to compare different studies, and not enough data supporting a specific ventilatory approach. Even less information are available on how respiratory monitoring is

Table 1 Setting of PEEP, V_T , respiratory rate and FiO_2 before and 24 hours after VV-ECMO

Study	Type of study	N	PEEP (cmH ₂ O)		TV/PBW (mL/kg) or TV (mL)		RR (bpm)		FiO ₂	
			Pre ECMO	During ECMO	Pre ECMO	During ECMO	Pre ECMO	During ECMO	Pre ECMO	During ECMO
Combes <i>et al.</i> (6)	Multi-center randomized trial	124	11.7 [3.9]	11.2 [3.9]	6.0 [1.3]	3.4	30.7 [3.4]	23	NR	NR
Bein <i>et al.</i> (17)	Multicenter randomized trial [av ECCO ₂ -R]	40	16.1 [3]	NR	5.9 [1.2]	3	22.4 [3]	10–25	0.62 [0.2]	NR
CESAR trial (5)	Multicenter randomized trial	68	13.7 [9.6]	10–15	NR	NR	NR	10	NR	0.3
Brogan <i>et al.</i> (18)	ELSO registry report	600	12 [10–17]	10 [8–14]	NR	NR	20 [15.25]	10	NR	0.5 [0.4–0.51]
Schmidt <i>et al.</i> (15)	Retrospective analysis of a multicenter registry	168	13.6 [4.0]	12.7 [2.9]	6.3 [1.5]	3.9 [1.5]	22 [18–30]	15 [10–25]	NR	NR
Serpa Neto <i>et al.</i> (10)	Individual patient data meta-analysis of observational studies	545	13.7 [4.0]	12.9 [3.4]	6.0 [1.9]	4.0 [1.7]	21.9 [7.9]	17.8 [8]	0.90 [0.17]	0.69 [0.24]
Pham <i>et al.</i> (8)	Retrospective multicenter cohort analysis	123	13 [4]	13 [4]	6.7 [1.6]	3.9 [1.4]	27 [6]	19 [8]	NR	NR
Patroniti <i>et al.</i> (19)	Retrospective multicenter cohort analysis	60	16 [14–19]	16 [14–19]	6.2 [4.7–7.7]	4.6 [3–6.3]	25 [22–28]	10 [8–12]	1 [1–1]	0.6 [0.4–0.8]
Marhong <i>et al.</i> (13)	Systematic review	2,042	14 [12.3–16.1]	12 [9.2–14]	6.1 [5.9–6.6]	3.9 [3–5]	NR	NR	0.99 [0.89–1]	0.4 [0.3–0.5]
Frenckner <i>et al.</i> (11)	Single center observational study	38	13 [0–20]	NR	610 [280–950]	NR	NR	10	> 0.9	0.4
Holzgraefe <i>et al.</i> (20)	Single center observational study	13	17 [15–20]	<5 (from chart)	545 [408–617]	<200 (from chart)	NR	NR	1	0.6 [0.46–0.63]
Kipping <i>et al.</i> (21)	Retrospective single center analysis	18	18 [14.5–24.5]	18 [16–24.5]	5.4 [3.2–7]	3.2 [2.4–4.7]	NR	NR	NR	NR
Bonacchi <i>et al.</i> (22)	Randomized single center analysis	30	13.2 [3.5]	10–15	NR	NR	NR	4–10	0.99 [0.07]	≤0.5

Data are expressed as mean [standard deviation] or median [interquartile range]. Italic data are predefined protocol targets. PEEP, positive end expiratory pressure; TV, tidal volume; RR, respiratory rate; FiO_2 , fraction of inspired oxygen; NR, not reported.

accomplished.

The aim of this review is to describe the pathophysiological principles of MV during ECMO for respiratory failure in patients with ARDS and to report on applied ventilatory strategies and respiratory monitoring on the basis of the current evidence and available literature. As the veno-venous (VV-ECMO) configuration is the most frequently used for ECMO respiratory support (23) this review will be confined to the use of MV during VV-ECMO.

Conventional ventilatory management of ARDS patients and indications to ECMO

ARDS is defined as a life threatening condition characterized by refractory hypoxemia (2).

Despite several advances in intensive care management over the last decades, mortality and morbidity associated with ARDS is still high, with a mortality rate of 34–58% (24–29), and a large amount of survivors harboring permanent physical and neuropsychological impairment with a consequent dramatic loss of productive life-years (29,30).

MV is a mainstay element in the management of patients with respiratory failure as it provides adequate gas exchange while buying time for the lung to heal. However, a growing body of evidence has highlighted that, even though necessary, MV *per se* could activate inflammation and further worsen lung damage leading to the so-called ventilator-induced lung injury (VILI) (31). VILI is caused by different mechanisms (32,33) which include the application of pressure (stress, barotrauma) (34,35), the distension of the lung (strain, volotrauma) (36,37), the shear force associated to cyclical alveoli opening and closing (atelectrauma) (33), trigger of lung inflammation (biotrauma) (38,39), and oxygen lung toxicity by use of high fraction of inspired oxygen (40,41).

Current approach to MV of ARDS patients aims to provide adequate gas exchange, while minimizing VILI.

Key elements of protective MV are the use of volume and pressure limited ventilation which have shown to be have a benefit on patients' outcome (42,43). Adjunctive therapies that have shown benefit on mortality in most severe ARDS patients are prone positioning (44,45) and neuromuscular blockade (46,47). In patients with more severe impairment of gas exchange permissive hypercapnia, high levels of PEEP (48), and recruitment maneuvers (RMs) (49) are variably and sometimes forcedly applied.

Indication to respiratory ECMO

In the management of acute respiratory failure and ARDS, use of ECMO has two main indications:

- (I) As a rescue therapy in the most severe cases where hypoxia is refractory to conventional treatment. This has been the main ECMO indication for ARDS patients since from its earlier use (50,51). In the era of protective ventilatory strategy, two randomized controlled trials have investigated the efficacy of VV-ECMO as a rescue therapy in ARDS patients with refractory hypoxia (5,6).

Results from the CESAR trial (5) suggest that transferring adult patients with severe ARDS to a center with an ECMO-based protocol can have a considerable benefit on patients' mortality at 6 months compared with patients allocated to conventional management. However, this trial did not allocate patients of the treatment arm to a standardized ventilatory protocols and fewer patients in the control group received protective MV undermining the results of the study.

More recently, the EOLIA study (6) showed a trend toward improved 60-day mortality in patients undergoing ECMO as rescue therapy compared to conventional mechanical therapy (relative risk 0.76; 95% confidence interval: 0.55–1.04; P=0.09). Differently from the CESAR trial, the ventilatory strategy in both the ECMO and the control group were well codified, and the control group received the possible best ventilatory management available. Interpretation of the results of the study and the consequences for the future of ECMO are under discussion, but certainly will not stop the wide spreading use of ECMO as a rescue therapy.

- (II) VV-ECMO can be also taken in consideration to manage and further prevent ventilator-associated lung injury (VILI) in patients with ARDS in which oxygenation is not dramatically impaired. In these less severe forms of ARDS, in which respiratory system compliance is markedly reduced and the achievement of a sufficient V_T determinates extremely high P_{PLAT} , ECMO and extracorporeal carbon dioxide removal (ECCO₂R) have been proposed as a means of minimizing airway pressures while maintaining adequate ventilation (17,52–54). Only one prospective

randomized trial, by Bein *et al.* (17), has investigated the efficacy of ECCO₂R in ARDS patients. A pumpless arteriovenous extracorporeal system providing CO₂ removal allowed to lower V_T down to 3 mL/kg in the treatment group against traditional 6 mL/kg in the control group. While there were no significant differences between the two groups, a post hoc analysis found a significant improvement in ventilator free days in the subgroup of more severe patients (with PaO₂/FiO₂ <150 mmHg).

Pathophysiology of gas exchanges during ECMO

During VV-ECMO the artificial oxygenator and the native lung are in series. Venous blood is diverted from the venous compartment towards the artificial oxygenator, which provides blood oxygenation and removal of CO₂. The blood is then returned to the patient (1).

Gas transfer exchange through the membrane depends on different factors: the intrinsic performance and characteristics of the membrane, the membrane surface area, and the oxygen and carbon dioxide pressure gradient between the flow and the blood.

The CO₂ content of blood is high; 500 mL of venous blood contains around 250 mL/min, which is approximately the entire minute CO₂ production, thus allowing CO₂ removal even with relatively low ECMO blood flow (BF). The sweep gas flow reduces the partial pressure of CO₂ inside the hollow fibers and therefore increases the partial pressure gradient between gas and blood. The sweep gas flow ventilating the artificial lung is then the main determinant of the amount of CO₂ removed.

Removal of CO₂ through the ML enables to reduce the respiratory minute volume through reduction of both tidal volume (i.e., indirectly the P_{PLAT}), and/or RR, thus maximizing the possibility of protective ventilation (see *Figure 1*). It also allows to reduce dynamic hyperinflation and uncontrolled hypercapnia during status asthmaticus (55) or chronic obstructive pulmonary disease (COPD) (56) or as a bridge to lung transplant (57).

On the other hand, oxygen solubility in plasma is minimal (0.003 mL/mmHg per 100 mL of blood) and the oxygen content in the blood is limited by hemoglobin concentration and saturation. Blood leaves the peripheral tissues with a low content of oxygen. The ECMO circuit withdraws part of the venous blood towards the membrane lung, and the blood returning to the right heart is the

result of both well oxygenated extracorporeal blood and deoxygenated venous return. The direct effect of VV-ECMO on oxygenation is increasing of the mixed venous saturation of the blood returning to the patient lung. The amount of delivered oxygen is directly related to the amount of ECMO BF relative to total patient cardiac output, and inversely related to the oxygen saturation of drained BF. As a result for the ventilator setting, oxygenation support provided by ECMO may allow reduction of ventilator FiO₂ and airway pressures (PEEP and indirectly P_{PLAT}) (see *Figure 1*).

Ventilatory strategies during vv-ECMO

It is important to understand that there is a complex interaction between patient, extracorporeal circuit and ventilator.

Artificial lung and native lung both participate to gas exchange. The amount of ECMO BF, and then choice of ECMO equipment and cannula size, depends on the residual gas exchange function of the native lung, which ultimately depend on the ventilator setting we choose. Conversely, the degree of native lung rest we may achieve in terms of minute ventilation and airway pressure will depend on the efficiency of ECMO in delivering oxygen and removing CO₂.

Rational of ventilator setting during vv-ECMO for minimizing VILI

As the main objective of ECMO support, after assuring adequate oxygenation, is the prevention of VILI, it is crucial to understand how changes in the ventilator setting relate to mechanisms of VILI.

For instance, reduction of V_T and PEEP has important effects on alveolar stress, strain, and shear stress. Alveolar strain, which represents the amount of alveolar distension from a resting volume, is one of the main mechanisms, responsible for volutrauma (36,37). In patients with ARDS undergoing ECMO this is a dramatic concern as these patients have very small area of normally aerated alveoli that receiving most of V_T undergo to extreme strains. Assuming functional residual capacity as the resting volume of the lung, during MV the total strain may be separated in two components (36). The static strain, which is related to the lung volume consequent to the application of PEEP, and the dynamic strain which is directly related to V_T.

Airway pressures relevant for lung stress are P_{PLAT} (which

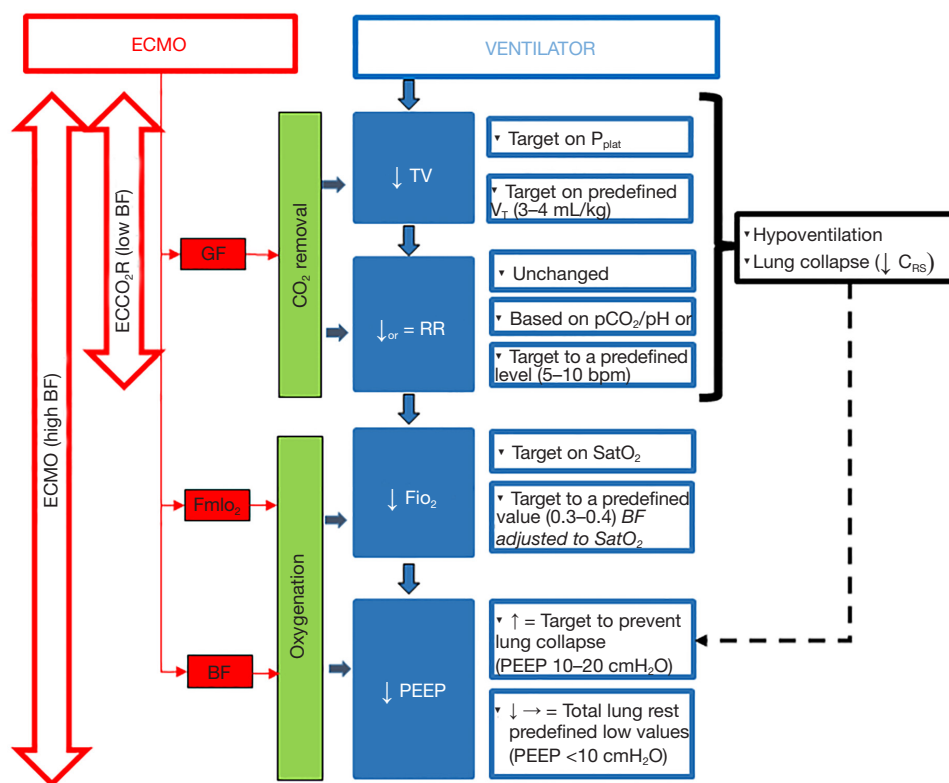


Figure 1 A flow chart of ventilator settings after ECMO starting. Sequence of setting changes follow literature common procedure. Tidal volume (V_T) is decrease targeting a safe plateau airway pressure or targeting a predefined V_T value (ultra-protective ventilation). After adjusting V_T , respiratory rate (RR) may be changed according to PaCO_2/pH or target to a fixed low level (5–10 bpm). Decrease of V_T and RR are allowed by CO_2 removal mainly modulated by acting on sweep gas flow (GF). This is feasible both with ECMO or ECCO₂R. When high ECMO blood flows (BF) are used, oxygenation is supported, and FiO_2 may be decreased. PEEP may either be decreased if a total lung rest strategy is used, or may be set to avoid derecruitment associated to low V_T ventilation (black dotted line). ↓, decrease; ↑, increase. ECMO, extracorporeal membrane oxygenation.

is directly related to total lung strain) and driving pressure (which is directly related to dynamic strain) (37).

Finally, we should not forget atelectrauma associated to cyclical alveoli opening and closing. This is important considering that ventilator settings leading to lower degree of baro and/or volotrauma may lead to worst atelectrauma.

Terminology for ventilator strategies during ECMO

After initiation of ECMO, different ventilator approaches are possible depending on how V_T , RR, PEEP and FiO_2 are set.

Expressions like “lung rest” (1,14-16) or “ultra-protective ventilation” (53,54) are variably and sometimes interchangeably used when referring to protective

ventilatory strategies. However, such expressions are generic and imprecise and do not refers to specific ventilator settings. As a general orientation, the term “ultra-protective ventilation” (54) has been more often utilized when referring to strategies mainly characterized by decrease of V_T , accompanied or not by a decrease in RR, as for example with ECCO₂R. The term “lung rest” is more indefinite, and even more imprecise, as it his utilize indifferently to describe a low V_T ventilation with or without a decrease in PEEP and mean airway pressure (1,14-16). To indicate a strategy combining ultra-protective ventilation with low level of PEEP, some authors have proposed the expression “total lung rest” (14-16,58).

In a recent international survey conducted among Extracorporeal Life Support Oxygenation (ELSO) registry centers by Marhong *et al.* (12), when asked about primary

goal in setting MV during ECMO, the respondents could choose between four possibility: “lung rest (i.e., avoid ventilator associated lung injury)”, “alveolar recruitment (i.e., opening the lung)”, “varies greatly depending on most responsible intensivist/physician”, and “others”. Not surprisingly, 77% of centers declared lung rest was their primary goal (12). However, the way the question was placed, opposing the concept of lung opening to that of VILI prevention, assume that alveolar recruitment does not play a role in lung protection. Moreover, it does not consider the possibility, widely seen in the clinical practice, of decreasing minute ventilation while setting a level of PEEP sufficient to avoid derecruitment.

MV protocols: international guidelines, recommendations, single center and randomized controlled trials

ELSO guidelines for respiratory failure (59) suggest to target ventilator management to use $\text{FiO}_2 < 0.4$, and $P_{\text{PLAT}} < 25 \text{ cmH}_2\text{O}$. It is recognized the possibility total consolidation of the lung, and use of “some inflation pressure as high pressures are decreased” is suggested to avoid lung collapse. For the first 24 hours, moderate to heavy sedation and pressure controlled ventilation with PEEP 15 and peak airway pressure of $25 \text{ cmH}_2\text{O}$ is suggested along with a RR of 5 bpm. However, there are no specific limits to the level of PEEP provided that negative hemodynamics effects are avoided. After 24–48 hours, lower levels of pressure (PEEP 10 and peak airway pressure of $20 \text{ cmH}_2\text{O}$) are recommended, and use of light sedation promoting some spontaneous breathing is suggested. It is important to remind that ELSO guidelines simply describe useful and safe practice and are not intended to define a standard of care. However, few points deserve some discussion. First, in spite of the attention given in the literature, there is no specific recommendation about V_T setting, and P_{PLAT} and RR are the only recommended ventilator targets. Second, the step decrease in PEEP down to $10 \text{ cmH}_2\text{O}$ recognizes the danger of too fast decrease in PEEP after ECMO starting. At the same time, however, there is little attention to the need of individualize how fast to reach specific ventilatory targets according to before-ECMO ventilator conditions: especially PEEP, minute ventilation requirements, alveolar recruitability and PEEP response, presence of alveolar plasma leakage and lung infection. Finally, in spite of the important consequences that MV management during ECMO may

have on respiratory mechanics and lung function, there is no indication on respiratory monitoring to target ventilator setting and follow its effects.

Review articles, position papers, and expert point of view recognize some of the above points. In particular the role of PEEP in avoiding alveolar derecruitment associate to ultra-protective ventilation and its potential contribution in protecting from VILI is widely recognized (1,14,16,58).

Surprisingly, in the survey by Marhong *et al.* (12) only 27% of centers declared of having a MV protocol during VV-ECMO. Likely, this may in part be explained with the fact that in clinical practice there is a wide inter-patient variability and ventilator setting needs to be individualized making protocols difficult to define and apply.

In the CESAR trial, ECMO system was designed to provide high BF capabilities ($>5 \text{ L/min}$) and full substitution of pulmonary gas exchange. Ventilator setting was targeted to peak inspiratory pressure of $20 \text{ cmH}_2\text{O}$, using PEEP of $10 \text{ cmH}_2\text{O}$, RR of 10 bpm, and FiO_2 of 30% (5). Unfortunately, no data are reported on ventilator parameters and time to reach the above targets after ECMO initiation.

In the EOLIA trial V_T was targeted to limit P_{PLAT} below $24 \text{ cmH}_2\text{O}$ in conjunction with a PEEP of at least $10 \text{ cmH}_2\text{O}$ and FIO_2 of 0.3–0.5 (6). The published study and the available data supplement provide a full report of ventilator parameters, including important respiratory mechanics variables such as respiratory system compliance (Crs), before and during ECMO. This is extremely important as no other study provide such extensive information.

MV practice from prospective and retrospective observational studies

Data retrieved from observational studies are the main source of information on center clinical practices (Table 1) (5,6,8,10,11,13,15,17–19,21,22,57). However, the lack of a standardization in reporting data, and the apparent lack in the use and report of monitoring variables that would be useful to interpret and compare different practices, make these data of scarce utility. Nevertheless, a common trend in clinical practice is recognizable, and supported by physiological background, it is possible to build an indicative flow chart that may guide through different ventilator strategies (see Figure 1).

With no exception, pressure controlled is the preferred mode of ventilation. A common trend after starting ECMO

for refractory hypoxia is the decrease of V_T and FiO_2 with or without decrease in RR. In case of ECCO₂R indications, FiO_2 is left unchanged. Setting of PEEP depends on the ventilatory strategy (total lung rest *vs.* prevention of alveolar derecruitment).

Setting of V_T

When asked about V_T setting, 81% of adult centers declare V_T setting lower than 6 mL/kg (34% below 4 mL/kg). This corresponds to what reported in most studies (Table 1). The decrease in V_T results in decrease in both P_{PLAT} and driving pressure. Theoretically, a full high flow ECMO may provide enough CO₂ removal to virtually eliminate the need for any ventilation and exploit a total rest lung strategy. Nevertheless, no study has explored this possibility. The studies by Serpa Neto *et al.* (10) and Schmidt *et al.* (15) are the most detailed font of information. Serpa Neto *et al.* collected individual data of 545 pts from nine studies. V_T was decreased in the first 24 hour after ECMO from 6 to 4 mL/kg. This determined a decrease in P_{PLAT} and driving pressure of almost 5 cmH₂O. The only respiratory parameter associated with survival was driving pressure before ECMO.

Schmidt *et al.* collected data, retrospectively, from three expert centers (2 Australians and 1 French) (15). V_T was decreased from 6.3 ± 1.5 to 3.9 ± 1.6 . P_{PLAT} and driving pressure decrease by around 5 cmH₂O in average.

It must be recognized that, in most reports, V_T is not target directly, but rather it is the result of targeting a safe level of P_{PLAT} . This strategy is also supported by recent observation by Pham *et al.* showing that a high P_{PLAT} on the first day of VV-ECMO for acute respiratory failure was significantly associated with mortality (8). However, in the last years, following the concept of ultra-protective ventilation, some studies have explored the possibility of directly setting a target low V_T (3–4 mL/kg). Bein *et al.* have first investigated the feasibility of ventilating with 3 mL/kg (17). More recently, different authors have explored the possibility of lowering V_T to 4 mL/kg using ECMO systems able to run at BFs as low as 300–400 mL/min (54). It is important to remember that this strategy has been proposed and explored in less severe ARDS patients in whom oxygenation is not severely impaired.

RR

Published data show, in the average, a moderate decrease

in RR. Two different trends may be observed. Some center target low levels of RR (5–10 bpm) as suggested in ELSO guidelines, probably considering RR an important contributor of VILI. Other centers decrease RR moderately probably to avoid hypocapnia that may result from the CO₂ removal efficiency of ECMO. It is worth notice that RR data are often not reported.

Decrease of V_T and RR are achievable with all ECMO indication and systems (high BF ECMO and ECCO₂R).

FiO_2

In case of high BF ECMO providing sufficient oxygenation support also FiO_2 and PEEP may be decreased. As for RR, also reduction of FiO_2 shows a wide inter-center variability. Except for few centers aiming to levels as low as 0.3 since from the very beginning of ECMO, in most centers FiO_2 is reduced more progressively. This difference, likely reflects a different strategy on the native lung. If a total lung rest strategies is employed there is no usefulness in administering high level of FiO_2 .

PEEP

Differently from V_T , declared practice about PEEP setting after ECMO initiation show higher variability, with 47% of centers aiming to PEEP lower than 10 cmH₂O (12). This data contrasts with what reported by most studies showing average PEEP values above 10 cmH₂O. This reflects the fact that, while there is a common general agreement on the role of lowering V_T , RR and FiO_2 to maximize protection from VILI, setting of PEEP is still a matter of great debate. The role of PEEP in VILI is multifactorial and controversial. On one side, increase of PEEP determines an increase in static strain, and, if no alveolar recruitment is present, even overdistention with increase in P_{PLAT} and driving pressure. In addition, inappropriate high levels of PEEP have hemodynamic detrimental effects secondary to decreased of venous return and increase of right heart afterload. On the other side, depending on the amount of associate alveolar recruitment, increase of PEEP may be associated with a decrease in driving and P_{PLAT} and dynamic strain. Moreover, PEEP may stabilize alveoli and protect from atelectrauma. These considerations are even more important during VV-ECMO, where the use of very low V_T and RR causes alveolar instability and lung collapse. As a consequence, respiratory system compliance decrease, the expected decrease in driving pressure is dumped, and

mechanism of atelectrauma exacerbated. In this context, there are convincing evidences that PEEP may play an important protective role (15). The decrease in V_T results in a decrease in dynamic strain, P_{PLAT} and driving pressure which are considered the most important determinant of VILI.

In an experimental study on 20 animals, Protti *et al.* showed that at equal level of injurious total strain, combination of high static and low dynamic strain (i.e., high PEEP and low V_T) was associated with less VILI compared to application of low static and high dynamic strain. They concluded that VILI was prevalently associated with dynamic strain, and that static strain may also play a protective role (36).

In the study by Schmidt *et al.* higher PEEP level in the first 24 hours after ECMO were associated with better survival (15).

When analyzing available data about PEEP setting during ECMO, few points deserve particular attention to avoid over interpretation.

First, published data show a very moderate decrease in the average PEEP (around 1–2 cmH₂O) in the first 24 hours of ECMO. This marginal change in the average PEEP across the studies hides a wide interpatient variability in individual PEEP settings. It is likely that PEEP may be decreased or increased in the same center on different patients depending on the individual patient response.

Second, as evident from *Table 1*, there is a wide range variability in the average PEEP even before ECMO (from 12 to 18 cmH₂O), reflecting the center by center differences in PEEP criteria before ECMO. Theoretically, larger alveolar collapse and more detrimental effects on the native lung are expected after bigger and faster reduction in PEEP. This may explain why in studies where high PEEP levels are present before ECMO, there are no changes in PEEP in the first 24 hours of ECMO.

Third, independently from any other ventilator parameter PEEP level is the main determinant of residual native lung function. At low PEEP level, native lung contribution may become minimal and patient oxygenation totally dependent on ECMO. In this condition, any ECMO related complication might put the patient at risk of life.

Finally, extensive lung collapse may lead with time to extreme pulmonary vasoconstriction, refractory pulmonary hypertension, and right heart failure that may require conversion from VV to VA-ECMO.

The historical ECMO center of Karolinska Institute is the unique ECMO center, from available published data, really

adopting a total lung rest strategy (11,20). The report by Holzgrafe *et al.* on their ECMO experience in patient with H1N1 is particularly useful, since it allows to appreciate several aspects of a total lung resting approach (20). First, PEEP was decreased from a median of 17 cmH₂O down to 5 cmH₂O during ECMO. During ECMO, the contribution of native lung was minimal, and in spite of the high ECMO BF, at maximal oxygen supply arterial oxygen saturation was around 85%. This is a very crucial point, because it reflects an intrinsic limitation of VV-ECMO in providing oxygenation when native lung residual contribution to oxygenation is minimal. Finally, in 4 of 13 patients, VV-ECMO had to be switch to VA-ECMO because pulmonary hypertension and right heart failure. This high rate of conversion from VV-ECMO to VA-ECMO is not reported in any other study and likely reflects the negative effects of a low PEEP-total lung rest strategy on pulmonary circulation and right heart function.

Respiratory monitoring during VV-ECMO

To date very little data exist on respiratory monitoring during VV-ECMO. This is disappointingly as very simple measurements may have a great utility in managing MV during ECMO. Respiratory monitoring during ECMO has three main goals: monitor the function of native lung, guide ventilator setting, monitor possible complications.

Monitor of gas exchange

Traditional blood gas analysis is essential to drive ECMO setting in providing adequate gas exchange. However, it may not be used to assess the native lung function, as the both PaO₂ and PaCO₂ will depend on the relative contribution of native and membrane lung. Thus, classical indices of oxygenation such as PaO₂/FiO₂ have little value during VV-ECMO. Given the relatively low V_T and minute ventilation capnography may be of limited utility. Still some important information may be derived if daily changes are strictly monitor (60). On the oxygenation side, an interesting approach is to monitor on daily basis the effect of administering FiO₂ of 1 on the ventilator side. When the lung function is impaired and the contribution of native lung is low, setting FiO₂ to 1 will have minimal or no effects on PaO₂. However, as the lung function will improve the administration of a high FiO₂ will result in bigger and bigger increase in PaO₂. On the same basis, end tidal-CO₂ (ETCO₂) may be very low during VV-ECMO. However,

as the lung function will improve $ETCO_2$ will increase prompting the need to decrease sweep gas on the ECMO side (60).

Monitor of respiratory mechanics

ECMO per se has no direct influence on respiratory mechanics, and the classical simple monitoring variables are still valid during ECMO. V_T , P_{PLAT} , driving pressure, and respiratory system compliance should be strictly and frequently measure as these variables are important not only to guide in the ventilator setting, but also to assess the effect of ventilator changes on lung function. In particular, assess of alveolar recruitment/derecruitment and/or overdistension are crucial. Hemodynamic monitoring is of course also important. Pulmonary arterial pressure and right heart function should be strictly monitored, especially when high PEEP levels or, at the opposite, a total lung rest strategy are used. In this context, echocardiography is essential. With femorofemoral cannulation approach, use of Pulmonary Artery Catheter is feasible and a continuous monitor of pulmonary arterial pressure and intrapulmonary shunt are possible (60).

Advanced respiratory monitoring

In the last years, new promising monitor tools have been proposed.

Given the difficulties in obtain frequent thoracic computed tomographic assessment during ECMO, less invasive imaging tools have recently been tested. Franchineau *et al.* have recently assessed the possibility of titrating PEEP level during ECMO by electrical impedance tomography (EIT) (61). Fifteen patients underwent to a decremental PEEP trial from 20 to 0 cmH_2O . EIT derived parameters were used to quantify at each PEEP level the degree of collapse and overdistention. They found a wide variability in the optimal PEEP level and concluded on the need of individualization of ventilator setting during ECMO.

P_{PLAT} and driving airway pressure are a measure of the stress applied to all respiratory system. Depending on chest wall compliance, the amount of airway pressure effectively applied to the lung is unknown unless transpulmonary pressure is measured (62–64). Grasso *et al.* assessed the possibility of identify patients requiring ECMO by measuring transpulmonary pressure in 14 patients with severe ARDS referred for ECMO (65). In seven cases,

the transpulmonary pressure was lower than 25 cmH_2O (considered a safe level). In these patients PEEP was raised from 17.9 ± 1.2 to 22.3 ± 1.4 cmH_2O to obtain a target transpulmonary pressure of 25 cmH_2O . As the oxygenation improved, these patients were successfully managed without ECMO. On other seven patients, transpulmonary pressure was higher than 25 cmH_2O and all patients received ECMO.

Conclusions and recommendations

MV during ECMO plays an important role on patients' complications and outcome and often the lack of standardized protocols has influenced the results of outcomes of patients undergoing ECMO support.

The optimal ventilator strategy during ECMO is still debated, with great variability among the centers. Obtaining lung protective ventilation appears to be feasible with extracorporeal support but the optimal targets and the timing to achieve and maintain these parameters are not clear. A number of ventilator strategies may potentially be used to avoid VILI. Based on available data the most reasonable approach is reduction of V_T to safe level of P_{PLAT} , reduction of RR to moderate levels (10–15 bpm) and maintain moderate respiratory levels of PEEP targeted in preventing alveolar derecruitment and avoiding overdistention. To guide on this process respiratory monitoring is essential. While advanced tools, such EIT and transpulmonary pressure are promising, classical respiratory mechanics variables such plateau and driving airway pressure, and respiratory system compliance are easily implementable and may allow frequent assessment.

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Footnote

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