The use of extracorporeal life support systems in patients with acute respiratory insufficiency

The Use of Extracorporeal Life Support Systems in Patients with Acute Respiratory Insufficiency

Mirko Belliato

Maastricht University
Maastricht UMC+
Hart+Vaat Centrum

THE USE OF EXTRACORPOREAL LIFE SUPPORT SYSTEMS IN PATIENTS WITH ACUTE RESPIRATORY INSUFFICIENCY

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Mirko Belliato

Cardio-Thoracic Department
Heart & Vascular Centre
Maastricht University Medical Centre (MUMC+)
Maastricht University
Maastricht, The Netherlands

Supervisors:

Prof. dr. R. Lorusso

Prof. dr. J. G. Maessen

Assessment Committee

Prof. dr. N.K.A. Walther van Mook (Chair)

Prof. dr. A.W. Danilo Gavilanes-Jimenez

Prof. dr. Giacomo Grasselli, University of Milan (Italy)

Prof. dr. Thomas Mueller, University Hospital Regensburg (Germany)

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Chapter 1.

General Introduction

Acute respiratory distress syndrome (ARDS) is the most severe form of acute lung injury and is characterized by critical hypoxemia and diffuse alveolar damage [1-3]. This syndrome can be caused by direct injury to the lungs, as in the case of pneumonia, or it can have indirect causes, such as sepsis or pancreatitis. In ARDS, severe hypoxemia (i.e., PaO2 to fraction of inspired oxygen [FiO2] ratio lower than 200 mm Hg) develops acutely as gas exchange is compromised by noncardiogenic pulmonary edema resulting from increased permeability of the capillary endothelium. Diffuse alveolar edema is a defining feature of ARDS, appearing as bilateral infiltrates on chest radiography and significantly reducing lung compliance [4]. Acute respiratory distress syndrome occurs frequently, with an estimated annual incidence of 150 000 cases in the Unites States. This syndrome is a common cause of admission to the intensive care unit because of respiratory failure requiring treatment with mechanical ventilation, and despite advances in treatment, ARDS is associated with a very high mortality rate of up to 58% of all cases [5]. Significant research efforts have been directed at reducing the morbidity and mortality rates associated with ARDS; however, no effective pharmacological therapies have been found. Conventional treatment of ARDS continues to be supportive, involving methods to optimize oxygenation and allow time for the underlying disease process to improve and lung tissue to recover. In fact, the only strategy that has improved survival rates in patients with ARDS is the use of supportive mechanical ventilation with low tidal volume ventilation of no more than 6 mL/kg of ideal body weight [6]. Other factors of importance in treatment with mechanical ventilation include the use of

adequate positive end-expiratory pressure (PEEP) and limiting peak plateau airway pressures to less than 30 cm H2O to limit further barotrauma and alveolar shearing [7]. Despite the use of lung-protective ventilation, lung injury may still persist or even progress in some patients, worsening hypoxemia, which often leads to the need for increased oxygen concentrations, increased positive pressure ventilation settings, and subsequent increased peak airway pressures, all resulting in further trauma to the alveoli. Several non-ventilatory strategies, including inhaled nitric oxide, prone positioning, and corticosteroid therapy, to improve oxygenation in ARDS have also been tested in recent decades. Although implementation of these strategies has shown transient improvements in oxygenation, the research has shown no demonstrated survival benefits associated with their use [8]. One additional intervention has been examined in patients with ARDS with hypoxemia that is refractory to conventional ventilatory management. Extracorporeal membrane oxygenation (ECMO) therapy, also called extracorporeal life support (ECLS), has been implemented in patients with severe ARDS when a fragile balance exists between the ability to maintain adequate oxygenation to support tissue perfusion and the ability to use ventilatory strategies that will protect the injured lungs from further damage [9-12] Patients with ARDS provide a challenging situation to physicians and advanced practice nurses involved in managing their care. Early implementation of conventional ventilatory management is crucial to minimize further deterioration in lung function. However, knowing that the underlying lung injury often continues to worsen despite optimal medical management, clinicians must be aware

of other available strategies that may provide support for their patients and improve overall outcomes. With advancement in technology and the 2009 outbreak of influenza A (H1N1) infections resulting in many ARDS cases, the use of ECMO therapy for refractory hypoxemia in patients with ARDS has increased [13,14]. ECMO is defined according to the Extracorporeal Life Support Organization (ELSO), ECMO is "the use of mechanical devices to temporarily support heart or lung functions during cardiopulmonary failure, leading to organ recovery or replacement."[15] Treatment with ECMO is indicated for patients with severe heart or lung failure who are at a high mortality risk despite optimal conventional therapy. During ECMO therapy, blood is circulated away from the patient's body by a mechanical pump; oxygen and carbon dioxide are exchanged in an oxygenator; blood is then pumped back into the body. Via the use of large cannulae, ECMO can be configured as veno-venous (V-V) or veno-arterial (V-A), depending on the need for pulmonary or cardiopulmonary support. In both methods, blood is typically removed from the inferior and/or superior vena cava. The return location of the oxygenated blood determines V-V versus V-A ECMO support. Percutaneous cannulation is possible for both methods in up to 90% of adults. In V-V ECMO therapy, oxygenated blood is returned to the right atrium. This method relies on the patient's adequately functioning heart to circulate the newly oxygenated blood but allows the lungs to rest without the need for high oxygen concentrations or ventilation pressures that might worsen the underlying cause of ARDS. This type of therapy is the most used method to treat patients with ARDS, supplied patients show no evidence of cardiac compromise [16]. Veno-venous ECMO therapy may be

done using 2 cannulation sites. In this approach, blood is typically removed from the inferior vena cava via femoral vein cannulation, and oxygenated blood is reinfused into the right atrium, most commonly via the right internal jugular vein. Veno-venous ECMO therapy also may be performed via a single-access site using a dual lumen cannula that is inserted into the right internal jugular vein. This carefully placed cannula allows deoxygenated blood to be removed through one lumen of the catheter via ports located in the superior and inferior vena cava, and the oxygenated blood is then returned to the right atrium via a second lumen of the same catheter. In V-A ECMO therapy, both the heart and lungs are supported by removing deoxygenated blood from the inferior vena cava and returning the oxygenated blood to the arterial system, usually in the distal aorta via the femoral artery. Hemodynamic support is then determined by adjusting the blood flow through the pump [17]. Note that as a result of the arterial cannulation, V-A ECMO therapy is associated with a greater risk of complications, including limb ischemia, systemic emboli, and increased left ventricular wall tension. A risk of maldistribution of oxygenated blood also is present because the return site from the ECMO is in the distal aorta [18]. The best way to measure cerebral oxygenation in this case is to monitor the arterial saturation of the blood from the right upper extremity, because the innominate artery is the last aortic arch vessel to receive blood from the ECMO circuit [19]. The ECMO circuit provides support by using a centrifugal blood pump to push blood through the oxygenator and back to the patient, while also augmenting venous outflow to the circuit. The speed of the pump, measured in rotations per minute, can be changed to adjust

blood flow through the circuit. The flow, measured in litters per minute, is variable and depends not only on the pump speed but also on the blood volume from the patient and the size of the venous outflow cannula. Gas exchange is controlled by an adjustable sweep flow. The sweep flow is delivered to the gas side of the oxygenator membrane to allow the exchange of oxygen and carbon dioxide with the patient's blood. The sweep controls the flow through the oxygenator and may be increased to improve gas exchange. The greater the sweep flow, the more carbon dioxide is eliminated. The fraction of delivered oxygen is selected from the blender on the ECMO circuit. To increase the amount of oxygen delivery, clinicians can increase the flow of blood through the pump by increasing the pump speed [20].

Management of patients with ARDS receiving ECMO therapy

Note that a team approach is essential to manage adult patients with ARDS being treated with ECMO support. Extracorporeal membrane oxygenation programs are best implemented in a tertiary-level intensive care unit with trained and experienced personnel who include, but are not limited to, critical care physicians, perfusionists, advanced practice clinicians, nurses, and cardio-surgeons. Close and continuous collaboration among team members is crucial to ensure best patient outcomes. In addition, ongoing quality assurance evaluation procedures and formal guidelines for starting and managing ECMO support should be available for review [21,22].

Supporting Lung Function and Gas Exchange

Once ECMO therapy is started, patients often stabilize quickly with improved oxygenation and gas exchange. Arterial blood gases should be checked often from site to monitor trends, and an adequate arterial oxygen saturation of >88% should be kept whenever possible. As previously mentioned, increasing the sweep flow will ease carbon dioxide removal [23,24]. The fraction of delivered oxygen can be adjusted on the circuit blender and increasing the pump speed to increase blood flow will help increase the amount of oxygen delivery to the patient. Because this gas exchange is now occurring thanks to the oxygenator, the lungs are no longer completely responsible for this function. Therefore, aggressive recruitment manoeuvres, high levels of PEEP, and high inflation pressures should be avoided to prevent further lung injury and to allow the lungs to rest. Ventilator settings that have been deemed acceptable at initiation of ECMO therapy include decelerating flow (pressure control), a respiratory frequency of 4 to 5 breaths per minute, moderate PEEP (e.g., 10 cm H_2O), and low inflation pressure (e.g., 10 cm H 2 O above PEEP or a peak inspiratory pressure of 20 cm H_2O) [25]. As patients improve, clinicians can consider reducing sedation and allowing spontaneous ventilation. The interaction between the ECMO circuit and the physicochemical properties of drugs may lead to significant changes in the PK of many important drugs, after altering the dosing requirements for patients on ECMO. An advanced understanding on this intricate interaction is critical to drug dosing in patients receiving ECMO, at least until more robust dosing guidelines become available. ECMO circuit, which includes the tubings and membrane

lung, introduces additional extracorporeal volume and increases the foreign surface that drugs can be trapped in and adsorbed on, especially the sedative ones. This results in an increase in distribution volume and subsequent decreases in plasma drug concentrations [26,27]. However, the adsorption phenomenon may decrease over time due to saturation of binding sites and it is imperative that dosing of drugs also reflects this situation; applying higher dosing continuously during ECMO to overcome this adsorption phenomenon may later lead to drug toxicity. Conversely, the circuit may serve as a reservoir and redistributes the sequestered drug back into the patient even after the drug administration stops, potentially leading to prolonged undesirable pharmacological effects. Sequestration of drugs can be influenced by the following circuit factors: membrane lung materials, polymetilpentene or polypropylene [28-30]; the plastic type of conduits and tubing [31]; the circuit age [31-33] and the composition of the priming solution used [34-36].

Forced diuresis is often necessary in patients with ARDS being treated with V-V ECMO therapy, and fluids are typically minimized. Continuous hemofiltration also may be implemented as needed to help a conservative fluid management strategy if pharmacological diuresis is inadequate [36].

There are three reported CRRT configurations for patients receiving ECMO: through an independent vascular access, an in-line connection of a haemofilter to an ECMO circuit, and a separate CRRT device connected to an ECMO circuit. As for the first method, the placement of a new large two-way venous catheter during ongoing ECMO treatment has potential

complications related to the site of cannulation (with considerable risk of bleeding in patients receiving anticoagulants),
and it may prevent the placement of an additional cannula that might be needed for the ECMO inflow line. The introduction of a haemofilter to the ECMO circuit after the blood pump is relatively simple and safe. The most relevant drawback of this approach is the inability to measure both the pressure in the haemofilter and the precise volume of the net-ultrafiltration delivered. [38,39] The third option is the direct connection of an external CRRT machine to an ECMO circuit, combining two independent parallel extracorporeal systems; this configuration enables the most precise measurements of pressure, blood flow, and net-ultrafiltration. Inlet and outlet CRRT lines can be connected in various locations on the ECMO circuit; however, a definitive guideline describing the best configuration is lacking in the nephrology research literature. Furthermore, technical challenges may arise from this CRRT-ECMO interaction, such as the management of the various types of pressure measured in the CRRT inlet and outlet lines, preceded by a very high blood flow volume to the ECMO circuit. A highly negative pressure obtained before the ECMO blood pump and the extremely positive pressure after it often fall in the alarm range of the inlet and outlet CRRT lines, causing repetitive interruptions of the CRRT session, impairing the treatment's efficacy and the filter's lifespan. [40,41] Other complications are the shaking, also known as "chatter," in the ECMO circuit catheters indicate excessive negative pressure because of low circulating blood volume in the system patient-circuit. This shaking may be amended by volume administration if hypovolemia is suspected. However,

because a conservative fluid-management strategy is often used in the setting of ARDS, temporarily decreasing the pump speed to stop the chatter rather than administering volume is a reasonable choice if the clinician suspects the patient is euvolemic [20,21]. This approach may require a temporary increasing the fraction of delivered oxygen on the blender and/or FiO_2 on the ventilator if the lower pump flow decreases oxygen saturation and for the reduced oxygen delivery due to the haemodilution. Lowering the pump speed also increases the risk for thrombosis, and anticoagulation strategies should be re-evaluated, so the chattering problem should be solved and fixed. One of the solutions could be the adding of a second drainage cannula, as describe in the most complex ECMO configurations [42], in which it could be applied an ECMO configuration with two different drainage cannulas, one in the femoral vein and one in the jugular vein. Moreover, if the inlet pressure (the pressure applied by the pump for blood reinfusion) is higher than 300 mmHg, it could be necessary a second inlet cannula, e.g. one into the femoral artery and a second one into the axillary/subclavian artery or in the contra-lateral femoral artery.

Aim of Thesis

The aim of this thesis is to enrich the management of patient under ECMO support for respiratory failure, e.g. severe ARDS, in terms of understanding the performance of patient's lungs and membrane lung efficiency, of optimization of ECMO functioning for minimizing the impact of ECMO, e.g. haemolysis, on the patients organ functions.

The main topic of the thesis is to deeply study the CO_2 elimination during ECMO run, for understanding the partial contribution given by the membrane lung and by the native patient's lungs [26]. I started with the assessing of a new type of volumetric capnometer for measuring the CO2 removal done by the ECMO instead the standard calculation [43], after that we studied the ventilation during ECMO support, particularly which is the impact of mechanical ventilation on the injured lungs [44-46] and we tried to define a new index for defining the lungs recovery, as to identify the right time for weaning starting. In second part we studied some major complication of ECMO as the haemolysis [47] and the brain injury, these to help the caregiver to prevent secondary damages to the organs, as acute kidney failure or neurological impairment [48].

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Chapter 2.

Mechanical Power during Veno-Venous Extracorporeal Membrane Oxygenation Initiation: A Pilot-Study

Mirko Belliato, Francesco Epis, Luca Cremascoli, Fiorenza Ferrari, Maria Giovanna Quattrone, Christoph Fisser, Maximilian Valentin Malfertheiner, Fabio Silvio Taccone, Matteo Di Nardo, Lars Mikael Broman and Roberto Lorusso

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Background

The complex interaction between mechanical ventilation (MV) and the native lung may promote ventilator-induced lung injury (VILI), especially in patients suffering from the acute respiratory distress syndrome (ARDS) [1], which would lead to gas exchange impairment and decreased respiratory system compliance [2]. The concept of lung protective ventilation has been developed and proven to reduce mortality in ARDS patients [3]. Low tidal volume (VT), low driving pressure (DP) [4,5], and high positive end-expiratory pressure (PEEP) are recommended to minimize the forces applied to the lungs and to avoid cyclic collapse and reopening of alveoli [6]. Nowadays, extracorporeal membrane oxygenation (ECMO) has become an effective and safe intervention in severe ARDS, with an increasing use in clinical practice [7,8]. In the absence of any standardized protocol, strategies to mitigate VILI during ECMO [9] rely on expert opinions [10]; nevertheless, it is generally accepted that reduced VILI would enhance lung recovery also in these patients [11,12]. To perform lung protective ventilation, it is necessary to understand how to reduce the forces applied by MV on lung tissue [13]. Stress and strain are difficult to measure in daily practice. As such, an available parameter which accounts for most of the potential causes of VILI has been recently introduced [14,15]: the so-called “mechanical power” (MP) represents the total energy delivered within a given time frame to the respiratory system, expressed in joules/minute (J/min) [16]. MP is the sum of the forces acting on the lung surface during MV, which are, according to the equation of motion: respiratory rate (RR), VT, respiratory system elastance, inspiratory-to-

expiratory time ratio, airway resistance, and PEEP [14,16]. MP has been suggested as a main determinant of VILI pathogenesis [17–19]. Additionally, it was independently associated with intensive care unit (ICU) mortality, ICU and hospital length of stay, and ventilator-free days in ARDS patients, even when low VT and low DP were applied [20]. In this study, we aimed to assess the changes in MV parameters after the initiation of VV ECMO in a cohort of ARDS patients. The primary aim of this pilot study was to describe and quantify the variation of MP resulting from the adjustment of MV settings. The second aim was to evaluate whether MP was associated with ICU mortality when analyzed during the initial phases of ECMO run.

Materials and Methods

Study Population

This multi-center, prospective, observational study was performed between December 2015 and June 2017 at three European ICUs experienced with ECMO: Foundation IRCCS San Matteo Hospital (Pavia, Italy), Universitätsklinikum Regensburg (Regensburg, Germany) and Hôpital Erasme (Brussels, Belgium). Institutional review boards of each center approved the study protocol. Eligible candidates were screened from local investigators. Informed consent was acquired retrospectively from every patient or a member of the family, as appropriate [21], according to local laws. Patients enrolled in this study had severe ARDS according to the Berlin Definition [22], unresponsive to maximal medical therapy. VV ECMO was employed according to Extracorporeal Life Support

Organization (ELSO) guidelines for adult respiratory failure [23]. Exclusion criteria were age < 18 years, mechanical ventilation 7 days before ECMO implementation, futility, extracorporeal support as bridge to lung transplantation and involvement in other interventional trials conflicting with the present study. Drop-out criteria were patient extubation during ECMO, relocation to another ICU, unpredicted situations that would not allow detailed evaluation and continuous monitoring (i.e., failing circuits). Patients study recruitment was completed within 12 h from ECMO initiation. Standard care was provided according to clinical practice.

Data Collection

We registered all data in an anonymous Excel file (Excel 2010, v14.0. Microsoft Corporation, Redmond,WA, USA). After study enrolment, patient demographic and anthropometric data, as well as diagnosis upon hospital and ICU admission, were collected. Sequential Organ Failure Assessment (SOFA) score [24] and Simplified Acute Physiology Score (SAPS) II [25] on ICU admission and Respiratory ECMO Survival Prediction RESP (RESP) score [26] before ECMO implementation were also recorded. MV settings [PEEP (cmH2O), plateau pressure (Pplat, cmH2O), peak respiratory pressure (Ppeak, cmH2O), DP (cmH2O), RR (breaths/min), VT adjusted to patient ideal body weight (VT/IBW, mL), inspired oxygen fraction (FiO2, ratio)] were recorded simultaneously, the first time within 12 h from the initiation of VV ECMO, then once a day during the entire ECMO length. Last reported MV settings before ECMO cannulation were also collected. Ppeak was considered equal to Pplat in pressure controlled MV modes. DP was directly computed as the difference between the reported values of Pplat

and PEEP [4]. VT/IBW was calculated according to the Devine formula [27]. VV ECMO run and ICU stay lengths were recorded, such as ECMO successful weaning and ICU mortality. Each MP record was calculated retrospectively from MV data, using an energy calculator, developed by Gattinoni et al. for this specific purpose [28]. We adopted a simplified formula derived from the extended equation [14], as follows:

$$Power_{rs} = 0.098 \times RR \times V_T \times \left(P_{peak} - \frac{1}{2}\Delta P \right) \quad (1)$$

MP values were obtained by filling in the software RR, VT and Ppeak. This mathematical simplification of the original mechanical power formula allows an easier computation of MP at bedside. As stated in the original paper [14], this formula is limited, as the extended one, by the assumption of a linear compliance of the respiratory system in the range of considered pressures and volumes.

Statistical Analysis

Statistical analysis was conducted with STATA [Stata Statistical Software: Release 14 (2015). StataCorp LP, College Station, TX, USA] and significance level was set at 0.05. Categorical data are expressed as counts and percentage; continuous data are presented as median (IQR, 25th-75th percentiles). Study patients were evaluated according to the ICU outcome (i.e., non-survivors vs. survivors). Baseline and clinical characteristics of the patients were compared among these groups using Fisher's exact test and Mann Whitney U-test, as appropriate. To estimate the MV variations after ECMO, the mean values of the first 48 h of ECMO run was considered for

each patient. Wilcoxon rank-sum test for paired data was used to test changes in MV parameters before and after ECMO initiation. The duration of ECMO therapy was divided into quartiles for each patient and the MV variables mean values of the first quartile were considered. As such, MV parameters were analyzed according to the ICU outcome, using theWilcoxon rank-sum test. Considering the first quartile of ECMO run, MV continuous variables were categorized according to the mean values of our sample. MP value was therefore categorized according to the threshold for risk of VILI from an experimental model (i.e., 12 J/min) [17]. Pearson's chi-square test was then used to analyze the correlation between MV parameters (including MP) and ICU mortality.

Results

Study Population

From a total of 151 patients undergoing VV ECMO during the study period, 35 patients were included in the final analysis. The most frequent diagnosis was primary ARDS from bacterial (n = 20, 57%) or viral pneumonia (n = 6, 17%). Other common diagnoses were secondary ARDS from abdominal sepsis (n = 3, 9%) and major trauma (n = 2, 6%). Among the remaining patients (n = 4, 11%), three developed a primary ARDS after fungal pneumonia, lung transplantation and chemotherapy, respectively, while the fourth patient developed ARDS secondary to major surgery. Median age of the study cohort was 53 (40–64) years; other demographic and

anthropometric baseline data among the study population are listed in Table 2.1.

	Study Population (n = 35)	ICU Non-Survivors (n = 11)	ICU Survivors (n = 24)	*p*-Value
Age [years; median value (25p–75p)]	**53** (40–64)	**53** (39–67)	**53** (42–62)	0.902
Male sex [n; %]	**24** (68)	**6** (54)	**18** (75)	0.233
Weight [kg; median value (25p–75p)]	**84** (70–110)	**75** (60–85)	**85** (77–118)	0.057
Height [cm; median value (25p–75p)]	**175** (169–180)	**171** (167–177)	**177** (169–180)	0.182
BMI [kg/m^2; median value (25p–75p)]	**27** (24–35)	**24** (21–29)	**28** (26–37)	0.145
SOFA score [n; median value (25p–75p)]	**12** (9–17)	**14** (11–18)	**12** (8–17)	0.228
SAPS II score [n; median value (25p–75p)]	**53** (42–68)	**68** (51–80)	**49** (37–60)	0.005
RESP score [n; median value (25p–75p)]	**−4** (−7–0)	**−6** (−9–−1)	**−3** (−7–0)	0.398
pre-ECMO MP [J/min; median value (25p–75p)]	**32.4** (29.3–36.6)	**31.1** (29.4–35.8)	**32.6** (23.6–38.2)	0.918
pre-ECMO PEEP [cmH_2O; median value (25p–75p)]	**14** (10–15)	**10** (8–12)	**15** (12–16)	0.032
pre-ECMO P_{plat} [cmH_2O; median value (25p–75p)]	**27** (21–33)	**30** (19–38)	**27** (21–31)	0.506
pre-ECMO P_{peak} [cmH_2O; median value (25p–75p)]	**33** (29–37)	**34** (30–38)	**33** (28–35)	0.604
pre-ECMO ΔP [cmH_2O; median value (25p–75p)]	**11** (7–23)	**22** (7–29)	**13** (7–13)	0.237
pre-ECMO RR [breaths/min; median value (25p–75p)]	**22** (20–30)	**25** (23–40)	**21** (18–27)	0.059
pre-ECMO V_T/IBW [mL/kg; median value (25p–75p)]	**5.5** (4.3–7.4)	**5.1** (4.1–6.9)	**5.9** (4.8–7.4)	0.441
pre-ECMO F_iO_2 [ratio; median value (25p–75p)]	**1.00** (0.80–1.00)	**1.00** (0.80–1.00)	**1.00** (0.80–1.00)	0.929
ICU stay length [days; median value (25p–75p)]	**20** (11–33)	**11** (5–15)	**28** (16–38)	0.009
VV ECMO run length [days; median value (25p–75p)]	**10** (4–15)	**4** (2–11)	**10** (5–16)	0.031

Table 2.1. *Study population baseline demographic and anthropometric characteristics, ICU admission prognostic scores, MV settings before VV ECMO initiation (pre-ECMO), ICU stay and ECMO run length. Variables comparison according to ICU mortality. [ICU intensive care unit, MV mechanical ventilation, VV ECMO veno-venous extracorporeal membrane oxygenation, BMI body mass index, SOFA sequential organ failure assessment, SAPS simplified acute physiology score, RESP respiratory ECMO survival prediction, MP mechanical power, PEEP positive end-expiratory pressure, Pplat plateau pressure, Ppeak peak pressure, DP driving pressure, RR respiratory rate, VT/IBW patient ideal body weight adjusted tidal volume, FiO2 lung inspiratory oxygen fraction].*

Prognostic scores on ICU admission and the mechanical ventilation settings before ECMO initiation are also reported in Table 2.1. Median length of ICU stay was 20 (11–33) days, while median duration of ECMO run was 10 (4–

15) days. ECMO weaning was successful in 28 patients (80%); the remaining seven patients died while on ECMO support. Four additional patients died due to complications during the ICU stay after successful ECMO removal; as such, overall ICU mortality was 32% (11/35 patients). Table2.1 reports the main differences between ICU non-survivors and survivors. SAPS II score [68 (51–80) vs. 49 (37–60), p = 0.005] and PEEP before ECMO [10 (8–12) vs. 15 (12–16), p = 0.03] were significantly different between these groups; ICU stay [11 (5–15) vs. 28 (16–38) days, p = 0.009] and duration of ECMO run [4 (2–11) vs. 10 (5–16) days, p = 0.031) were notably shorter in ICU non-survivors when compared to others.

MV Parameters before and after ECMO Initiation

Table 2.2 and Figure 1 show main differences in MV parameters before and after VV ECMO initiation. In particular, a significant reduction in MP [32.4 (29.3–36.6) vs. 8.2 (5.5–11.7) J/min, p < 0.001] was observed. Similarly Pplat [27 (21–33) vs. 21 (20–25) cmH2O, p = 0.012], Ppeak [33 (29–37) vs. 30 (21–32) cmH2O, p < 0.001], DP [11 (7–23) vs. 8 (7–10) cmH2O, p = 0.014], RR [22 (20–30) vs. 14 (10–17) breaths/min, p < 0.001], VT/IBW [5.5 (4.3–7.4) vs. 4.0 (2.8–5.4 mL/kg, p = 0.001] and FiO2 [1.0 (0.80–1.00) vs. 0.60 (0.40–0.80), p < 0.001] significantly decreased after ECMO initiation.

	pre-ECMO (n = 35)	ECMO (n = 35)	Δ%	*p*-Value
MP [J/min; median value (25p–75p)]	**32.4** (29.3–36.6)	**8.2** (5.5–11.7)	−74.7%	<0.001
PEEP [cmH_2O; median value (25p–75p)]	**14** (10–15)	**13** (10–16)	−7.1%	0.390
P_{plat} [cmH_2O; median value (25p–75p)]	**27** (21–33)	**21** (20–25)	−22.2%	0.012
P_{peak} [cmH_2O; median value (25p–75p)]	**33** (29–37)	**30** (21–32)	−9.1%	<0.001
ΔP [cmH_2O; median value (25p–75p)]	**11** (7–23)	**8** (7–10)	−27.3%	0.014
RR [breaths/min; median value (25p–75p)]	**22** (20–30)	**14** (10–17)	−36.4%	<0.001
V_T/IBW [mL/kg; median value (25p–75p)]	**5.5** (4.3–7.4)	**4.0** (2.8–5.4)	−27.3%	0.001
F_iO_2 [ratio; median value (25p–75p)]	**1.00** (0.80–1.00)	**0.60** (0.40–0.80)	−40.0%	<0.001

Table 2.2. Differences in MV parameters before (pre-ECMO) and during the first 48 h after VV ECMO initiation (ECMO). [MV mechanical ventilation, VV ECMO veno-venous extracorporeal membrane oxygenation, D% percentage variation, MP mechanical power, PEEP positive end-expiratory pressure, Pplat plateau pressure, Ppeak peak pressure, DP driving pressure, RR respiratory rate, VT/IBW patient ideal body weight adjusted tidal volume, FiO2 lung inspiratory oxygen fraction].

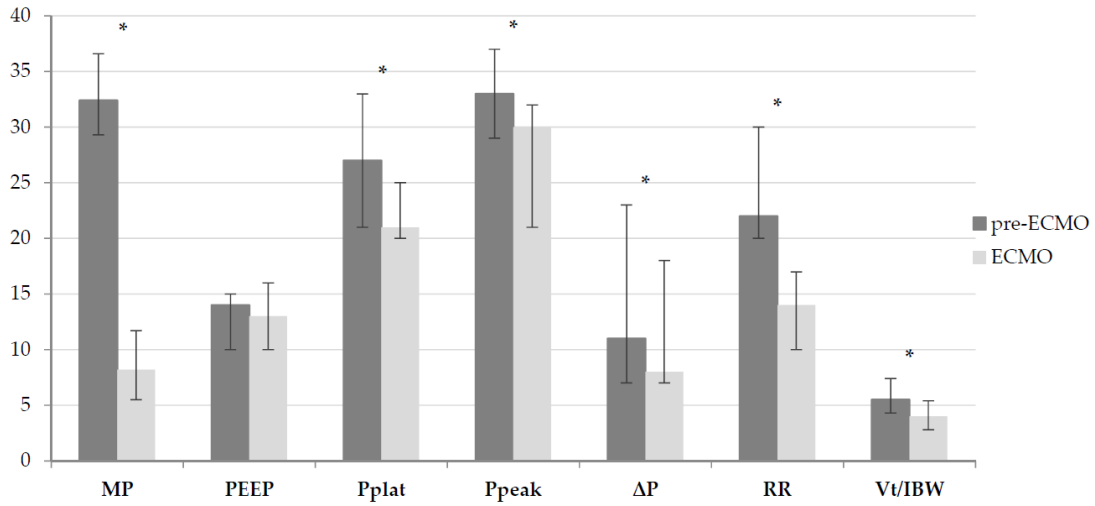

Figure 2.1. Differences in MV parameters before (pre-ECMO) and during the first 48 h after VV ECMO initiation (ECMO). [MV mechanical ventilation, VV ECMO veno-venous extracorporeal membrane oxygenation, MP mechanical power, PEEP positive end-expiratory pressure, Pplat plateau pressure, Ppeak peak pressure, DP driving pressure, RR respiratory rate, VT/IBW patient ideal body weight adjusted tidal volume].

MV Parameters during Early Phases of ECMO Run and ICU Mortality

As shown in Table 2.3, during the first quartile of ECMO run, RR [17 (15–25) vs. 13 (10–16) breaths/min, p = 0.003] was significantly higher in ICU non-survivors than survivors. Similarly, PEEP [10 (8–12) vs. 14 (11–16) cmH2O, p = 0.048] and VT/IBW [3.0 (2.0–4.0) vs. 4.0 (3.5–6.0) mL/kg, p = 0.028] were significantly lower in ICU non-survivors. Moreover, a RR greater than 15 breaths/min correlated to an increase in ICU mortality (p = 0.008, Table 2.4). No further differences in other MV variables values (including MP) were detected between these groups.

	Study Population (n = 35)	ICU Non-Survivors (n = 11)	ICU Survivors (n = 24)	*p*-Value
MP [J/min; median value (25p–75p)]	**8.0** (5.0–14.0)	**8.0** (5.0–20.0)	**8.0** (6.0–13.0)	0.530
PEEP [cmH_2O; median value (25p–75p)]	**12** (10–16)	**10** (8–12)	**14** (11–16)	0.048
$\mathbf{P_{plat}}$ [cmH_2O; median value (25p–75p)]	**22** (20–25)	**22** (19–29)	**22** (20–25)	0.880
$\mathbf{P_{peak}}$ [cmH_2O; median value (25p–75p)]	**26** (22–31)	**30** (24–34)	**26** (21–30)	0.174
ΔP [cmH_2O; median value (25p–75p)]	**10** (7–12)	**12** (7–15)	**9** (6–12)	0.229
RR [breaths/min; median value (25p–75p)]	**14** (10–17)	**17** (15–25)	**13** (10–16)	0.003
$\mathbf{V_T/IBW}$ [mL/kg; median value (25p–75p)]	**4.0** (3.0–5.0)	**3.0** (2.0–4.0)	**4.0** (3.5–6.0)	0.028
$\mathbf{F_iO_2}$ [ratio; median value (25p–75p)]	**0.55** (0.43–0.73)	**0.43** (0.40–0.73)	**0.57** (0.50–0.75)	0.345

***Table 2.3**. Comparison of MV parameters during the first quartile of VV ECMO length, according to the ICU mortality. [MV mechanical ventilation, VV ECMO veno-venous extracorporeal membrane oxygenation, ICU intensive care unit, MP mechanical power, PEEP positive end-expiratory pressure, Pplat plateau pressure, Ppeak peak pressure, DP driving pressure, RR respiratory rate, VT/IBW patient ideal body weight adjusted tidal volume, FiO2 lung inspiratory oxygen fraction].*

	Variable Categorization	Pearson's Chi-Square Test	*p*-Value
MP (J/min)	≤12; >12	0.475	0.491
PEEP (cmH_2O)	<12; ≥12	2.828	0.093
$\mathbf{P_{plat}}$ (cmH_2O)	≤23; >23	2.198	0.138
$\mathbf{P_{peak}}$ (cmH_2O)	≤27; >27	0.957	0.328
ΔP (cmH_2O)	<10; ≥10	1.247	0.264
RR (breaths/min)	<15; ≥15	7.098	0.008
$\mathbf{V_T/IBW}$ (mL/kg)	<4.5; ≥4.5	1.847	0.174
$\mathbf{F_iO_2}$ [ratio]	≤0.6; >0.6	0.088	0.766

Table 2.4. Association with ICU mortality, according to the categorization of MV parameters during the first quartile of VV ECMO run. [ICU intensive care unit, MV mechanical ventilation, VV ECMO venovenous extracorporeal membrane oxygenation, MP mechanical power, PEEP positive end-expiratory pressure, Pplat plateau pressure, Ppeak peak pressure, DP driving pressure, RR respiratory rate, VT/IBW patient ideal body weight adjusted tidal volume, FiO2 lung inspiratory oxygen fraction].

Discussion

In this pilot study, we evaluated MP and other MV parameters after VV ECMO initiation and its prognostic role in a selected ARDS population. We observed that an ultra-protective lung ventilation strategy was applied in these patients, with a consequent significant reduction in MP after ECMO initiation. Nevertheless, RR, PEEP, and VT/IBW, but not MP, were the MV variables that differed during the early phases of ECMO run between ICU non-survivors and survivors.

During ARDS, MV is grounded on minimizing VT, with a reduction in DP, and maintaining adequate level of PEEP [6]. Nowadays, it is possible to safely rely on VV ECMO support for both oxygenation and carbon dioxide clearance, limiting VILI and allowing the lungs to recover [7,12]. Despite lung-protective ventilation being relatively standardized in ARDS patients

without ECMO [29], there is no specific recommendation on how to manage native lung ventilation and respiratory workload during VV ECMO [30,31], which resulted into different strategies in clinical practice [3,32,33]. As for all ARDS patients, DP has been shown to be an important MV variable correlating with mortality in VV ECMO [34–36]; however, there are no large studies showing the effects of DP-individualized MV therapy in ECMO patients and lung recovery or patients' survival [37]. In the last years, the severity of VILI has been related to the MP, which represents the amount of energy transmitted during MV to the respiratory system per time unit [14]. Taking into account some potential limitations [15,38,39], MP might represent a useful tool to optimize MV and potentially limit VILI [16–19] during ECMO. In our multi-center observational study, the median pre-ECMO MP value of 32.4 J/min was particularly high considering the threshold (i.e., 17.0 J/min), which has been associated with an increased risk of mortality [20]. This is an interesting finding, since it reported the inadequacy of MV settings in severe ARDS patients failing to respond to conventional therapies [3,4]. After MV adjustments following ECMO initiation, the median MP value dropped significantly to 8.2 J/min, which is below the reported threshold (i.e., 12 J/min) which was associated with an increased risk of VILI in experimental models [17]. This reduction in MP is consistent with results from an international study from experienced ECMO centers [37]. Considering MV settings, our results showed that ultra-protective ventilation strategy [32], with significant reductions in VT/IBW (from 5.5 to 4.0 mL/kg), Pplat (from 27 to 21 cmH2O), DP (from 11 to 8 cmH2O) and RR (from 22 to 14 breaths/min) was feasible in all patients

after ECMO initiation. However, lung ventilation parameters were also within the "protective" ranges before ECMO initiation [3], with levels of PEEP (from 14 to 13 cmH2O) indicating the maintenance of an "open lung" strategy [40,41], even during ECMO. These findings suggest the importance of MP monitoring at the bedside, as lung stress may occur even within acceptable ranges of VT, Pplat, and PEEP and might prompt an earlier use of extra-corporeal therapies to reduce the occurrence of VILI. Whether high PEEP levels, which are relevant to avoid alveolar de-recruitment during ECMO [10,42], can also influence patients' outcome remains to be demonstrated; also, individualized PEEP levels using MP monitoring or other techniques [43,44] remains a challenging issue that requires further investigation. In this study, the ICU mortality (32%) was comparable to other reports [37]. According to the baseline data of our population, the higher SAPS II score in non-survivors (68 vs. 49) suggested a possible negative effect on outcomes of extra-pulmonary organ failure before VV ECMO. However, median SAPS II values were below the threshold of 80, which has been suggested as an indicator of poor outcome in ECMO patients [45,46]. This finding confirms the need for a complete evaluation of patients' conditions before ECMO and underlines the utility of prognostic scores to identify patients who are more likely to benefit from ECMO therapy. The comparison of MV parameters between ICU non-survivors and survivors was limited to the first quartile of ECMO length for each patient, because this period requires the maximal effort to optimize lung protection and to limit VILI [6,47]. Later on during the ECMO run, when healing of lung parenchyma takes place, a less-protective approach

is possible and efforts can be directed to promote ECMO weaning [48,49]. The lack of association between early MP changes and mortality is not inconsistent with this approach. Mortality during ECMO is not only due to persistent lung injury but also determined by secondary complications (i.e., bleeding, sepsis, acute ischemic stroke) and decisions to withdraw life-sustaining therapies. Nonetheless, MP should not be overlooked while on ECMO. Other MV parameters that account for MP computation, such as PEEP, VT/IBW and RR should also be carefully monitored. The lower PEEP values in ICU non-survivors (10 vs. 14 cmH2O) could support the open lung strategy [40–43]. At the same time, the lower VT/IBW in ICU deaths (3.0 vs. 4.0 mL/kg) might suggest a limit value in VT reduction, even on ECMO [9,50,51]. We also observed differences in ICU mortality when RR was categorized according to a specific threshold (i.e., 15 breaths/min). In clinical studies, RR has progressively received more attention, gaining relevance over VT and airways pressures on VILI prevention and limitation [52]. A near-apneic MV (RR 5 breaths/min) revealed decreased lung injury in ARDS patients treated with VV ECMO [53]. Furthermore, while maintaining other MV parameters stable (Pplat, DP, VT, PEEP), an animal model showed for each 5-fold increase in RR an 11-fold increase in MP [17]. To date, the literature is still lacking in well-defined clinical recommendations concerning RR for MV adjustment during VV ECMO [23,54,55]. Our results corroborate the crucial role of the duration of exposure to the delivered injuring strain (i.e., numbers of cycles) to determine thresholds [56], highlighting RR as one of the main determinants for energy transmission [18,30].

Study Limitations

This pilot study has several limitations, mostly due to the small sample size. As a consequence, we had a limited number of observations to run a multivariable model to assess independent predictors of ICU mortality. We involved three different experienced ECMO centers, with specific patient selection criteria, which could reduce generalizability of overall findings. For practical issues, MV parameters and settings were only collected once a day and may thus not properly describe all the potential settings changes in a 24-h period, especially in the first stages of ECMO run. For this reason, we evaluated the MV variations after ECMO initiation taking into account, for each patient, the mean values of the first 48 h of ECMO length. Furthermore, our population showed a significant variability among ECMO run duration, with a mean value of 10 days and a standard deviation of 8 days. We believe that the correlation analysis between MV settings and ICU mortality based on the first quartiles of ECMO length for each patient, rather than on a fixed number of days (as presented in other VV ECMO studies), better mirrors the actual acute phase of ARDS for a given patient. Lastly, we would underline that all the MP values were calculated from the MV parameters' datasheet.

Conclusions

There are no recommendations on optimal MV settings during VV ECMO. The results from this pilot study confirmed that VV ECMO allows a significant reduction of MP. Early MP values did not predict patients' outcome in this cohort. Further larger studies are needed to assess the

prognostic role of MP and other MV parameters in VV ECMO patients. Importantly, these parameters should still be adequately monitored in this setting.

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Chapter 3.

Continuous monitoring of membrane lung carbon dioxide removal during ECMO: experimental testing of a new volumetric capnometer

Alice Montalti, Mirko Belliato, Sandro Gelsomino, Sandro Nalon, Francesco Matteucci, Orlando Parise, Monique de Jong, Maged Makhoul, Daniel M Johnson and Roberto Lorusso

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Background

In recent years, there has been a significant increase of extracorporeal membrane oxygenation (ECMO) utilization for both cardiac (veno-arterial (VA)-ECMO) and respiratory (veno-venous (VV)-ECMO) support [1]. However, ECMO is a complex system that requires prompt changes in its settings on the basis of the rapid variations in patients' conditions. Accurate monitoring of vital body parameters is, therefore, a key factor for the early detection of complications and the proper management of the cardiac and respiratory support [2]. Thus, an optimal monitoring equipment should provide information regarding the pump function as revolution per minute (r/min), blood flow (BF) (l/min), inlet and outlet pressures (mmHg) and the membrane lung (ML) performance [3]. Evaluation of the ML performance is of paramount importance during ECMO, not only because it might indicate a gradual or sudden functional impairment and therefore the need and timing for ML replacement due to clot formation inside the oxygenator but may also provide information regarding both the native lung (NL) and the ML contribution to the global ventilation, hence guiding the weaning process [4]. Furthermore, as for NL, ML performance is assessed by measuring both O2 transfer through the ML (V'O2ML) and CO2 removal (V'CO2ML) through the oxygenator. While some devices applied to the ECMO circuits already allow for continuous monitoring of V'O2ML, there are only two systems currently available for continuous monitoring of V'CO2ML. However, the continuous evaluation of CO2 removal by ML (V'CO2ML) is extremely important, since it also allows the ML dead space calculation (VDsML), which can be altered due

to clot formation inside the oxygenator and fibres oedema (as the plasma leakage phenomenon). In this situation, fractions of the ML are ventilated but not perfused, hence, they do not participate in the CO2 removal. Moreover, a continuous measurement of the CO2 removed by the oxygenator allows a more precise distinction between the different contributions of both the patient and the oxygenator to the global ventilation and, hence, provides significant information during weaning from the ECMO machine. Moreover, a continuous monitoring of CO2 percentage in the exhaust gas could be used as an alarm for gas flow failure or disconnection. In our experimental study, we tested the accuracy and reliability of a new volumetric capnometer which enables continuous monitoring of V'CO2ML by direct measurement of the CO2 partial pressure at the exhaust gas port of the ML (%) and the gas flow (l/min), and to calculate the dead space during ECMO.

Methods

The current animal model experiment was conducted at the University Hospital of Maastricht, The Netherlands, on nine pigs undergoing veno-arterial ECMO (VA ECMO). The protocol was approved by the ethical committee of the University Hospital of Maastricht (protocol number WP 2015-003-001). The pigs were anaesthetized, intubated and ventilated by constant ventilator settings. This study was conducted as part of a major study aimed at comparing the effects of treatments alone with VA ECMO in addition to intra-aortic balloon pump (IABP) in pigs in cardiogenic shock. Such a condition was obtained by inducing an acute myocardial infarction

(left anterior descending coronary artery ligature) and, after 4 hours of monitoring, the two capnometers were tested. The tubing set and the ECMO oxygenators (model 'adult ECMO 14 days') were provided by Eurosets srl, Medolla, Italy. In more details, we evaluated the accuracy and reliability of the prototype of a new volumetric capnometer device (CO2RESET™, Eurosets srl, Medolla, Italy) that provides directly and continuously the V'CO2ML values and the VDsML calculation, by comparing the obtained measurements with the new device with those obtained with a control standard method. As a control device, we used a capnometer (Microcap Plus®Capnograph, Medtronic, Minneapolis, Minnesota, USA) which is routinely used in clinics for measurements of the CO2 concentration in the exhaled air of the patient (the end-tidal CO2, expressed as %) and the values of gas flow displayed on the standard gas blender. We measured V'CO2ML and VDsML at five different levels of gas flow/BF ratio, (0.5-1.5) and we obtained three V'CO2ML measurements for each level of gas flow/BF ratio (in total, 135 couples of values expected), while only one for the VDsML at each level of gas flow/ BF (in total, 45 couples of values expected). We performed a blood gas analysis at each level of gas flow/BF to obtain the CO2 blood partial pressure in the inlet blood from oxygenator (pCO2) and the CO2 blood partial pressure in the outlet blood from oxygenator (pCO2). Moreover, we also continuously recorded both pig body and pig exhaust gas temperatures. The new device consists of a mid-range infrared sensor placed mainstream (compared with the control device with side-stream sampling) to the oxygenator exhaust connector, combined with a flow sensor device placed at the oxygenator

gas inlet (Figure 3.1). The CO2 concentration is calculated on the basis of the radiation variation caused by the CO2 absorption characteristics, as with the common capnometers. However, not only does the combination of the capnometer and flowmeter allow continuous evaluation of the percentage of CO2 exhaust by the ML, but also the continuous V'CO2ML calculation. Furthermore, a system placed inside the capnometer maintains the temperature of the gas exhaust between 40 and 42°C, avoiding condensation as well as misleading measurements. Ultimately, a dedicated software tool calculates the measurements and shows CO2 [%], CO2 [mmHg], inlet gas flow [l/min] and V'CO2ML [ml/min]. The control capnometer is a clinically validated device for measuring the CO2 concentration in patient exhaled gases. It works with an internal sensor (based on radiation absorption technology) by sampling the gases from the exhaust gas port of the oxygenator through a narrow tube. It is possible to calculate intermittently the V'CO2ML combined CO2 percentage obtained by the hand-held standard capnometer with the contemporary value of sweep gas set on the gas blender.

Figure 3.1. The new volumetric capnometer is applied to the ECMO machine. Top and bottom red circles are the flowmeter and capnometer, respectively.

V'CO2ML and dead space monitoring

While the concentration (%) of carbon dioxide in exhaust gas (%CO2) from the ML and V'CO2ML was directly shown on the screen by 'CO2RESET' capnometer's software, the value of V'CO2ML derived from the measured %CO2 with the second method was calculated as follows:

$$V'CO_2\,ML[ml/min] = \%CO_2 \times GF[l/min] \times 10$$

where GF is the gas flow, %CO2 is the concentration as percentage of CO2 in exhaust gas and V'CO2ML is the ML carbon dioxide removal. In addition, the two methods were compared for the dead space calculation, which was obtained by the following equation:

$$VDsML[\%] = \frac{100(pCO_2\,out[mmHg] - \%CO_2)}{pCO_2\,out[mmHg]}$$

where VDsML is the ML dead space, pCO2out is the carbon dioxide partial pressure into the outlet blood and %CO2 is the concentration of carbon dioxide in the gas sampled at the exhaust gases port of the oxygenator.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 24, IBM Corporation 2015, Armonk, NY, USA. The correlations between all the obtained measurements with the new volumetric capnometer and those obtained with the control method (Microcap Plus Capnograph, Medtronic, Minneapolis, Minnesota, USA) were calculated using the Spearman's correlation coefficient. A level of $p < 0.05$ was chosen to indicate the statistical significance. The Bland–Altman5 method was used to evaluate the agreement between the measurement taken with the control and new methods, after assessing the normal distribution of the differences. The lack of agreement was summarized by calculating the bias, estimated by the mean difference (d) and the standard deviation of the

differences (s). We expected that 95% of differences were between d-1.96s and d + 1.96s.

Results

We obtained 120 coupled measurements for each method suitable for the V′CO2ML calculation and 40 coupled measurements suitable for the VDsML calculation. Because of a failure in the capnometer's heater system, the data recorded by one animal was judged potentially not reliable and was not included. As seen in Figure 3.2(a) and (b), we observed a strong correlation between the measurements of V′CO2ML, (rs = 0.991; p = 0.0005) taken with the volumetric capnometer, and those obtained with the control method. Moreover, the volumetric capnometer showed a low mean percentage bias for V′CO2ML measurements at exactly 3.86% (12.07-4.35%). Regarding the dead space calculation, not only did we observe a significant correlation between the two methods for VDsML calculation (rs = 0.973; p = 0.0005), but we also identified a very low mean percentage bias with the volumetric capnometer at 2.62% (8.96-14.20%), as can be seen in Figure 3.3(a) and (b). In addition, although a negative proportional bias for V′CO2ML estimation with the volumetric capnometer was observed, such underestimation in the lower range of V′CO2ML was less than 4%, which represents an acceptable limit for the clinical setting. Moreover, we investigated whether variations in gas temperature and gas flow/BF ratio could have affected the differences in the coupled measurements obtained with the two devices. In this regard, we found no significant correlations between the difference in the coupled V′CO2ML

and VDsML measurements for either the gas flow/BF ratio or temperature. Finally, Figure 3.4 shows the variation of VDsML at increasing gas flow/BF ratios. As it can be observed, increasing gas flow/BF ratios (increased ventilation per unit of blood) correspond to higher values of VDsML. This can be explained by the fact that the increase in the ventilation per unit of blood implies a corresponding increase in the ventilation per mm^2 of oxygenator's membrane up to a certain threshold, which is determined by the permeability properties of the membrane. Once the threshold has been reached, a further increase in ventilation will create an increase in dead space (in series).

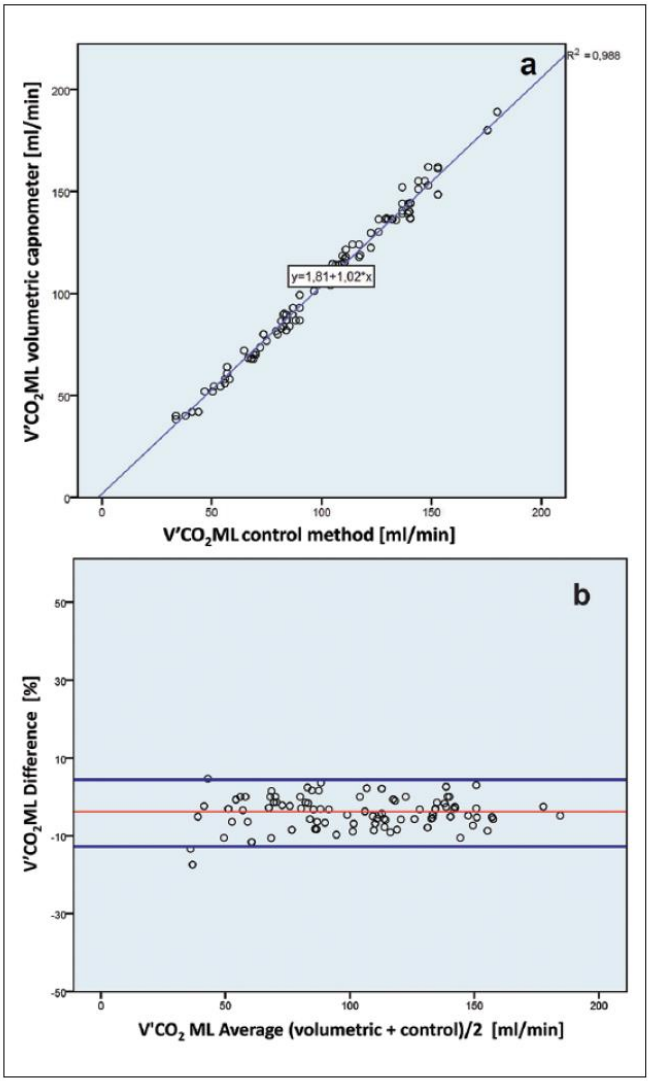

Figure 3.2. (a) Correlation between the V'CO2ML values obtained with the volumetric capnometer with the values calculated with the control method. (b) Mean bias and precision of V'CO2ML values obtained with the volumetric capnometer compared with the values calculated with the control method.

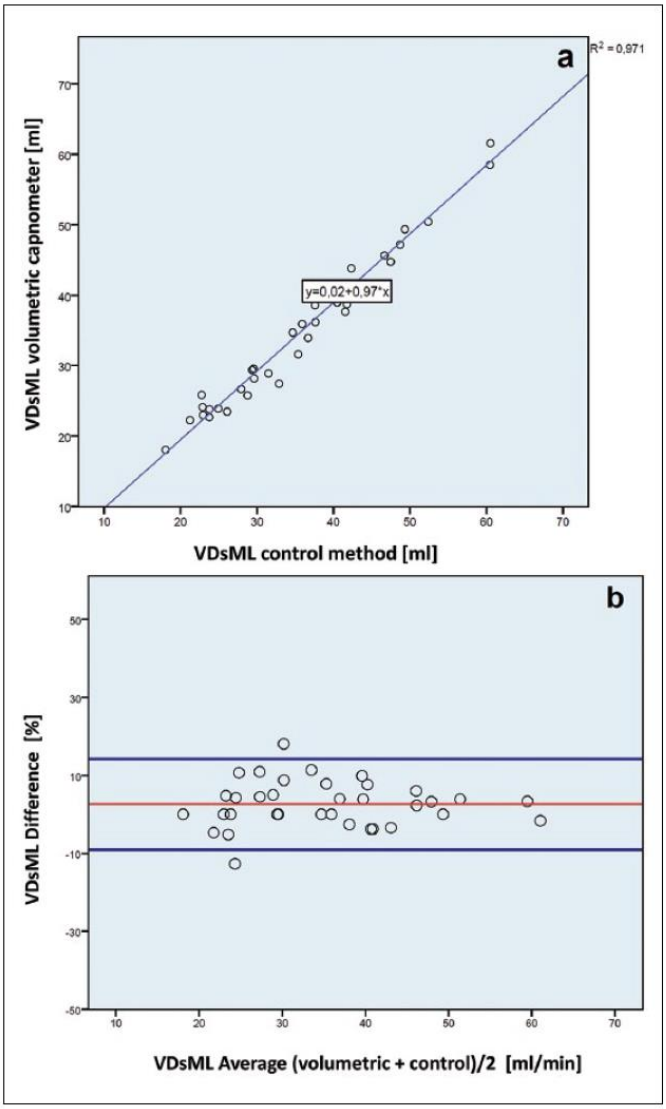

Figure 3.3. (a) Correlation between the values of VDsML obtained by new volumetric capnometer versus the values calculated with the control method. (b) Mean bias and precision of VDsML values obtained with the volumetric capnometer compared with the values calculated with the control method.

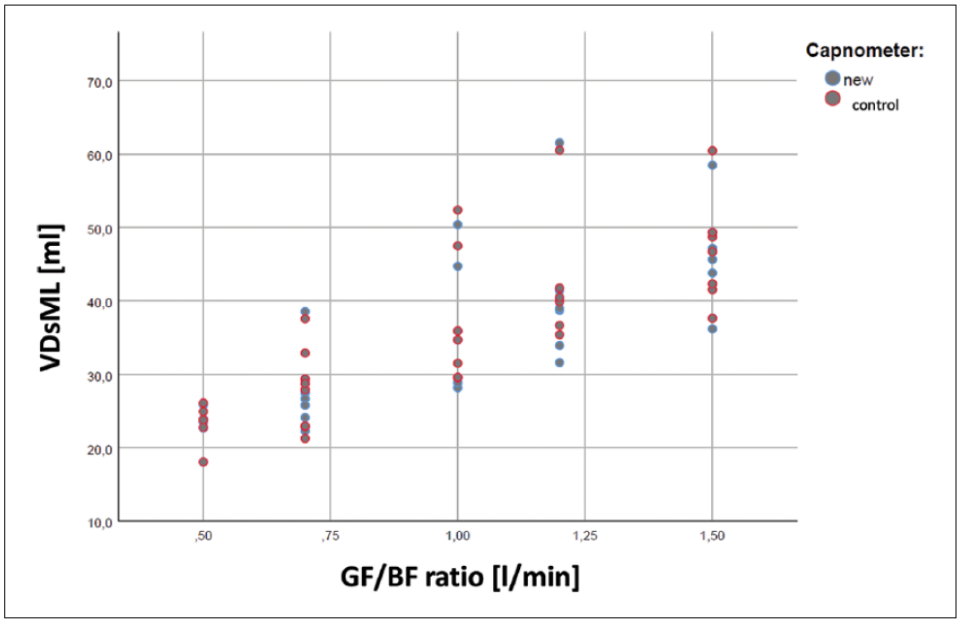

Figure 3.4. Scatter plot showing the values of the VDsML measured by the two methods at five different levels of BF/GF ratio. These data show that the increase in gas BF/GF ratios corresponds to an increase in the VDsML values, as a consequence of the overcome capacity of the ML membrane in terms of CO2 elimination.

Discussion

In this study, we evaluated the accuracy and reliability of a new volumetric capnometer which allows the continuous V'CO2ML monitoring and VDsML calculation, thanks to its two components. The flowmeter was placed in series to the sweep gas line, and the capnometer was positioned at the exhaust gas port of the oxygenator. ECMO constitutes a life-saving mechanical support which often requires accurate monitoring and potentially prompt interventions because of either variation in patient clinical conditions, the occurrence of possible complications, or ECMO system malfunction. Thus, an appropriate and continuous monitoring of

gas exchange inside the oxygenator is useful in order to evaluate both the ML performance and to distinguish between the ML and NL ventilation [2]. Currently, data regarding ML gas exchange are usually obtained by taking blood samples by the ECMO circuit added to the volumetric capnometry of the ML during the routine ECMO check at least daily. However, due to the complexity of the support machine, of the patient–machine interactions, together with the high risk of system-related complications during prolonged use, there could be great benefit by the use of an online monitoring system, which can provide real-time information regarding both the ML and the pump performances. In fact, the study of the trend in the V'CO2ML permits to avoid bias related to the specific moment in which the single measurement has been taken, constituting a more reliable tool. Hence, we believe that the continuous monitoring of both CO2 removal and ML dead space with the volumetric capnometer allows better timing for the detection of ML dysfunction and can potentially guide the ECMO weaning process by integrating ML and mechanical ventilator information. In addition, with regard to the patient complications related to ECMO use, it is reported that ML failure constitutes the second most common mechanical complication [6]. Moreover, despite the advent of new ML coated with a tip-to-tip antithrombotic surface coating, the interactions of blood with non-biological surfaces boost the systemic inflammatory response and lead to clotting within the ML [7]. Such deposits are responsible for the worsening of ML gas exchanges because of an increased dead space inside the oxygenator and, hence, of an increased proportion of ventilated but not perfused areas. Therefore, we believe that

continuous evaluation of the V'CO2ML other than the dead space can not only highlight an ML performance reduction, but also guide the ML replacement timing. For instance, provided that ML replacement does not constitute a no-risk procedure in those patients, the V'CO2ML evaluation could allow a monitored delay in its replacement, whenever the CO2 clearance is sufficient for the patient's clinical needs. In addition, discontinuing extracorporeal respiratory support is another crucial step in ECMO patient management, and it often constitutes a difficult decision, mainly due to the lack of definite criteria. Mols et al. [8] indicated the successful weaning from the ECMO machine when at least 80% of total oxygen delivery was supplied by the patient's own lung [8]. Similarly, Grasselli et al. [9] suggested that the respiratory mechanics and patient blood gases should also be considered in the decision of ECMO withdrawal. On the other hand, we previously reported how the combined evaluation of CO2 removal through the ML (V'CO2ML) and CO2 removal through the NL (VCO2NL) obtained by the volumetric capnometry function integrated in the modern ventilators could provide additional information regarding NL recovery such as improvements in its CO2 clearance capability.[10] In our opinion, in fact, in order to estimate the residual function of the NL more accurately, clinicians should analyze not only the oxygenation function (V'O2ML) of the ML, but also the extracorporeal CO2 removal (V'CO2ML). Thus, the continuous V'CO2ML monitoring by the new volumetric capnometer could potentially help in analyzing NL/ML interaction, guiding the ECMO weaning process and choosing the best timing for the ECMO discontinuation [3].

Limitation of the study

Since there is still no standard method of measuring CO2 in the exhaust of the oxygenator, calculating CO2 removal would be appropriate by taking blood gases before and after the ML compared with exhaust blood gas analysis. Therefore, future evaluation should address the comparison between pre/post-ML blood and exhausted gas analysis to conclusively validate the new method, hoping that a low difference within a clinically acceptable range will be detected.

Conclusion

In conclusion, our experimental study demonstrates that the volumetric capnometer used in conjunction with the ECMO oxygenator is reliable for continuous monitoring of V'CO2 and useful for oxygenator dead space calculation, as the measurements obtained with a control method by a normal capnometer. Moreover, we believe that the information provided by such a device is helpful to promptly detect oxygenator malfunction and its impaired performance in terms of CO2 removal. Furthermore, if these monitoring approaches are confirmed in future studies, the V'CO2ML continuous monitoring could help to better guide ECMO weaning and improve the patient management. Further studies are vital in order to confirm our results in a clinical setting.

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Chapter 4.

Carbon Dioxide Elimination During Veno-Venous Extracorporeal Membrane Oxygenation Weaning: A Pilot Study

Mirko Belliato, Luca Cremascoli, Francesco Epis, Fiorenza Ferrari, Maria Giovanna Quattrone, Maximiliam Valentin Malferthiener, Lars Mikael Broman, Anna Aliberti, Fabio Silvio Taccone, Giorgio Antonio Iotti and Roberto Lorusso

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10.1097/MAT.0000000000001282. PMID: 33074866.

Background

Veno-venous extracorporeal membrane oxygenation (VV ECMO) is a fixed component of the treatment strategy to ensure gas exchange to patients with respiratory failure not responding to optimal conventional therapies, while the underlying disease is treated [1,2]. Recent studies show increased survival in patients treated with V-V ECMO for acute respiratory distress syndrome (ARDS) [3–5]. The importance of the management on outcome has been also demonstrated from specialized centers.6 According to extracorporeal life support organization (ELSO) international registry, adult pulmonary ECMO patients' cumulative survival rates to extracorporeal support and to hospital discharge increased over years, reaching 69% and 60%, respectively, in 2019 [7]. Although mechanical ventilation could potentially expose the patient to ventilator-induced lung injury (VILI),8 the extracorporeal treatment provides adequate gas exchange (i.e. oxygenation and decarboxylation),[9] allowing for less injurious lung ventilation [10] and potentially promoting lung healing [11]. Nonetheless, there is still no consensus on the optimal management of native lung (NL) ventilation during V-V ECMO. As a consequence, there is a wide variability in clinical practice today,[12] from protective [13] via ultra-protective ventilation, [14] to "lung rest" strategies, [15] or different levels of spontaneous breathing ventilation support [16]. Therefore, the NL optimal ventilation settings and the best strategy to manage respiratory workload represent a main concern [17] and there is no univocal agreement on the amount of gas exchange provided by NL during V-V ECMO. Moreover, there is currently limited evidence to guide weaning from V-V ECMO

support, especially concerning the correct timing during the healing of the NL in terms of compliance and gas exchange [18]. Theoretically, the weaning process should start once NL function improves up to supply patient's metabolic demand entirely while maintaining protective ventilation [19]. According to the ELSO guidelines, NL conditions could be considered adequate to allow V-V ECMO trial off once extracorporeal support is less than 30% of the total [1]. After the successful treatment of the underlying disease, patients are usually ready for disconnection when it is possible to sustain acceptable oxygenation and decarboxylation, maintaining protective ventilation settings, with a NL inspired oxygen fraction (FiO2) around 40% and a positive end-expiratory pressure (PEEP) lower than 10 cm H2O [18,19]. However, neither specific nor homogenous withdrawal criteria exist, and the different strategies applied in V-V ECMO weaning are based on limited scientific evidence and rather on expert opinions [20]. A suggested physiologic approach to wean a patient is conducted in two sequential steps, maintaining the same level of extracorporeal blood flow (BF). The first one consists in the gradual reduction of ECMO oxygenation capacity (ML sweep gas oxygen fraction, FSO2) maintaining an 88% peripheral oxygen saturation (SpO2) cut-off and an airway occlusion pressure [21] lower than 10 cm H2O. The second step involves decarboxylation, with gradual decrease of ECMO gas flow (GF) and measurement of patient's ventilatory load response [22]. If NL gas exchange is adequate at acceptable protective ventilator settings, the patient could be ready for decannulation [1,18]. During V-V ECMO, oxygen (O2) delivery and carbon dioxide (CO2) removal required to meet the

patient's metabolic and hemodynamic demands result from the close interaction between the membrane lung (ML) performance and the patient's NL conditions and cardiac output (CO) [23]. In this complex three-dimensional relationship, monitoring the balance between the gas exchange of both the NL and the ML may be crucial for the improved overall management of the extracorporeal support of the patient [24] (Figure 4.1). From a physiologic point of view, it is better to evaluate the ECMO oxygenation and decarboxylation functions separately. In fact, O2 transfer is mainly determined by extracorporeal BF, but also by the intrinsic proprieties of ML and the GF partial pressure through the oxygenator [25]. On the other hand, CO2 elimination is controlled by GF and relatively independent from BF [26]. Unlike oxygenation, total CO2 elimination (V'CO2TOT) is easy to determine in clinical practice while on V-V ECMO, as the sum of both NL and ML contributions [10]. ML CO2 elimination (V'CO2ML) is calculated from the ML GF and the CO2 concentration at ML sweep gas outlet, measured by a capnometer. The NL CO2 removal (V'CO2NL) is obtained from the volumetric capnometry integrated in most ventilators by plotting the eliminated CO2 concentration over the airway flow in a single breath [27].

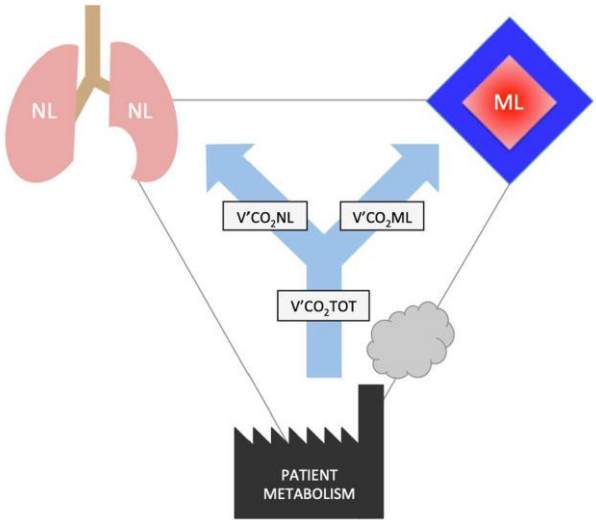

Figure 4.1. *During ECMO, carbon dioxide removal (V'CO2TOT) required for the patient's metabolic pattern is partitioned between the native lung (V'CO2NL) and the membrane lung (V'CO2ML). Therefore, it should be considered that there is a close interaction and interdependency between the NL condition and the ML performances in a three-dimensional relationship. ECMO, extracorporeal membrane oxygenation.*

The relationship between V'CO2NL and V'CO2ML might not only be a useful tool to evaluate the interdependency of ML performances and NL conditions. It might potentially provide additional information on NL recovery and identify potential patients who could be successfully weaned off V-V ECMO with safe removal of cannulae. Assessment of V'CO2ML and V'CO2NL in patients on V-V ECMO has not been adequately studied and no data on the potential role of such parameters to guide ECMO weaning are available [1]. In our research, we introduced the V'CO2NL ratio to express to NL contribution to V'CO2TOT and we analyzed it over ECMO run period. The aim of this study was to evaluate whether the V'CO2TOT partitioning between the NL and the ML might reveal the global improvement of NL

conditions in case of ARDS. According to the role of CO2 clearance during NL recovery[1,18,22], we analyzed the potential function of V'CO2NL ratio to identify patients for successful weaning off V-V ECMO.

Materials and Methods

This prospective observational pilot study was performed between December 2015 and June 2019 in an intensive care unit (ICU) experienced in ECMO, at the Foundation IRCCS San Matteo Hospital, Pavia, Italy. The study protocol was approved by the institutional review board and local Ethical Committee. The investigator of the center screened potential candidates from inclusion criteria. Informed consent was obtained retrospectively from each patient or a surrogate (as next of kin, when appropriate) in case of unconscious or dead patient. Eligible patients suffered from severe ARDS according to the Berlin Definition [28]. V-V ECMO indications complied with the ELSO guidelines for adult respiratory failure [1]. Study exclusion criteria were age <18 years, bridge-to-transplant, mechanical ventilation before ECMO implantation ≥7 days, futility, and participation in other intervention trials conflicting with the current study. Enrolled patients were dismissed from the study in case of extubation during extracorporeal support, transfer to another department or unexpected circumstances that would not allow for continual monitoring and assessments, like systems malfunctioning or defective data sheets. All patients were recruited in the study within 12 hours from cannulation and ECMO start. Standard general critical care was administered according to our clinical practice.

Data Collection

All data were manually registered in an anonymous form in an Excel spread-sheet (Microsoft Corporation, Albuquerque, NM, USA). After enrolment, demographic data were retrieved: personal data (age, body weight, height, gender), medical history, hospital-admitting diagnosis, and reason for ICU admission. Sequential Organ Failure Assessment (SOFA), Simplified Acute Physiology Score (SAPS II), and the Respiratory ECMO Survival Prediction RESP (RESP) scores were calculated at ICU admission. Measurements of V'CO2ML and V'CO2NL were performed twice daily (every 12 hours) during the ECMO treatment, given stable hemodynamic and respiratory conditions. On the day of discontinuation, the last V'CO2ML and V'CO2NL values were determined while still on extracorporeal support, before the trial off evaluation phase. Arterial blood gas analysis (ABG), ECMO (BF [L/min], GF [L/min], FSO2 [%]), and mechanical ventilation settings (ventilation mode, minute ventilation [MV, L/min], tidal volume [TV, ml], respiratory rate [RR, breaths/min], PEEP [cm H2O], FiO2 [%]) were recorded concurrently. Blood samples for complete blood count and blood chemistry were made at least once a day. The time of successful weaning from ECMO as well as ICU mortality was also recorded.

V'CO2 Measurement

V'CO2ML (ml/min) was obtained from the ML GF (ml/min) and the CO2 concentration at ML sweep gas outlet ([CO2]e,ratio) [29], measured with an infrared analyzer (Nellcor Oxi-Max N-85 Handheld Capnograph/Pulse

Oximeter; Medtronic Parkway, Minneapolis, MN, USA) and calculated as follows:

$$V'CO_2ML = GF \times [CO_2]_e$$

V′CO2NL (ml/min) was obtained from a specific function of the mechanical ventilator (Hamilton G5; Hamilton Medical AG, Bonaduz, GR, Switzerland), performing volumetric capnography by a mainstream CO2 sensor (CAPNOSTAT 5; Hamilton Medical AG), at the patient's airway opening. Single breath CO2 elimination was measured, as the area under the curve, by plotting the CO2 concentration against the corresponding expired TV [30]. The total volume of exhaled CO2 can be expressed as ml/min and it is assumed to be equal to the CO2 production under steady and stable conditions of circulation and ventilation [31]. Mainstream volumetric CO2 sensors allow accurate calculation of mixed expired CO2 pressure (PĒCO2) and physiologic dead space [32]. Volumetric capnography could represent a surrogate of metabolism in ventilated patients [33]. It could be also useful for noninvasive measurement of CO [34]. It has been proven that dead space measurement obtained by volumetric capnography is a sensitive and specific indicator of the NL gas-exchange efficiency during PEEP titration conducted after a recruitment maneuver in ARDS [35]. Furthermore, it could be a useful diagnostic tool in case of pulmonary embolism and a bedside monitoring method of the efficacy of thrombolysis [36]. Then we considered the total amount of CO2 elimination (V′CO2TOT), given from the sum of V′CO2ML and V′CO2NL as following:

$$V'CO_2TOT = V'CO_2ML + V'CO_2NL$$

Finally, we computed the V′CO2NL ratio, representing the NL relative contribution to total decarboxylation:

$$V'CO_2NL\ ratio = \frac{V'CO_2NL}{V'CO_2TOT}$$

A V′CO2NL ratio of "zero" represents the state of total ECMO support, whereas an increase towards "1" is a sign of improved CO2 elimination by the NL. Both V′CO2ML and V′CO2NL (along with the V′CO2TOT and V′CO2NL ratio resulting values) can be readily monitored at patient bedside, during hemodynamic and respiratory steady conditions [31]. It takes few minutes, during routine mechanical ventilator and ECMO parameters checking.

Mechanical Ventilation Settings and Sedation

All patients were mechanically ventilated according to the principles of lung protective ventilation, as recommended by ELSO guidelines [1]. We used pressure-controlled ventilation (PCV) mode with RR set on 8–10 breaths/min, reduced TV (≤6 ml/kg), plateau pressure limited to 25 cm H2O, driving pressure (ΔP) lower than 15 cm H2O, and FiO2 reduced to maintain a SpO2 cut-off of 93%. PEEP was set on a case-by-case respiratory mechanics evaluation to avoid alveolar de-recruitment. During the first 24–48 hours after ECMO onset, we maintained neuromuscular blocking agent continuous infusion according to the clinical conditions, with deep sedation (Richmond Agitation- Sedation Scale [RASS-4]). Once the neuromuscular blocking agent was suspended, sedation was reduced depending on the patient conditions (RASS ≤ 0), maintaining the patient tolerant to

endotracheal intubation, without risks of decannulation. In this phase, we adopted pressure support ventilation (PSV) mode when suitable to the clinical circumstances, keeping ventilator load within safe limits to avoid VILI. V-V ECMO Weaning Procedure There is not any formal V-V ECMO removal protocol at our institution, even though, in the clinical practice, we follow a common approach, into sequential steps. Before to proceed it is essential to corroborate the resolution of the underlying pathology, along with radiologic examinations and lung compliance improvements, even though without fixed cut-off values. Hemodynamic stability is another mandatory condition. Pressure-controlled ventilation and PSV are both accepted while maintaining protective parameters, with PEEP values lower than 10–15 cm H2O, according to the clinical conditions. Veno-venous extracorporeal membrane oxygenation (V-V ECMO) trial off is started by gradually decreasing GF until zero within half an hour, monitoring SpO2 and ABG. If the patient tolerates GF reduction, the gas tubes are physically removed from the flowmeter to avoid any air leak around them. The ECMO BF is kept unchanged throughout the 6–12 hours long trial procedure. Meanwhile the patient is closely monitored, paying attention to the hemodynamic stability, proving the adequacy of gas exchange, and assessing the respiratory pattern. If the patient conditions remain stable, with an acceptable ventilatory load, the extracorporeal support is definitively discontinued and the cannulas are removed at patient bedside.

Statistical Analysis

Statistical analysis was conducted with Stata 14.1 (Stata Statistical Software: Release 14 [2015]; StataCorp LP, College Station, TX, USA). We

described categorical data as counts and percentage. Continuous data are expressed as mean (SD) or median (ICR 27^{th}–75^{th} percentiles) according to distribution, evaluated with the Shapiro–Wilk test and graphical assessment. We used the t-test (or equivalent nonparametric test) and the exact chi-squared test (Fisher's test) to compare ECMO weaned and unweaned patient groups. Considering successful weaning, the ECMO treatment length was divided into quartiles. Afterward we compared the V'CO2NL ratio median values of the first and the last quartile using the Wilcoxon test. We made a trend gradient over time for the V'CO2NL ratio in patients weaned from ECMO. As expressed in the following formula, it is represented by the difference of two consecutive values, divided by 0.5 because of the twice-daily V'CO2 measurement frequency, considering the day as a unit of time:

$$grad[V'CO_2NL\ ratio] = \frac{V'CO_2NL\ ratio_i - V'CO_2NL\ ratio_{i-1}}{0.5}$$

For every patient who achieved ECMO weaning, we established a cut-off point in the V'CO2NL ratio series. It denotes the moment when this value is equal to or greater than 0.4 (≥0.4) and its trend gradient remains positive (>0) for two consecutive measurements. We then used the Wilcoxon test to compare the ventilation and ECMO parameters reported before and after the stated cut-off. A p value of <0.05 defined as statistically significant.

Results

Study Population

According to the study protocol criteria, among the 25 eligible V-V ECMO patients during the study period, we excluded seven patients in total, as described in Figure 4.2. Therefore, a total of 18 patients were included in the study. Any enrolled patient was subsequently excluded from the study according to the dropout criteria. The most common diagnosis requiring V-V ECMO support was primary ARDS from bacterial (10 patients, 56%) or viral (6 patients, 33%) pneumonia. Of the remaining two patients (11%), one had fungal pneumonia and one had secondary ARDS after major trauma (Figure 4.3). The demographic and anthropometric baseline data of the study population are summarized in Table 4.1. Furthermore, Table 4.1 shows the respiratory variables, the mechanical ventilation settings before ECMO cannulation, the parameters and the prognostic scores at ICU admission and ECMO run duration. Three patients (17%) failed ECMO weaning. According to this result, we divided the study population into two groups (ECMO weaned vs. ECMO unweaned), comparing the two from the previous records, as reported in Table 4.1. We found significant differences for the PaO2/FiO2 ratio before ECMO implantation (81 [63–120] vs. 50 [40–70] mmHg, p = 0.035), respectively, and the ICU admission SOFA score (10 [6–12] vs. 16 [12–19], p = 0.032). No other statistically significant differences were found between the two subgroups. All the patients of this study were on PCV mode during the first 24–48 hours from ECMO cannulation. After the acute phase, PSV mode was adopted for 11 patients (61%). Among these, two (11%) were switched back to PCV during their

clinical course on ECMO. Among the patients successfully weaned off V-V ECMO, nine patients (60%) were weaned while on PSV, the remaining on PCV mode.

The overall ICU mortality was 22% (4/18 patients). All three patients who failed weaning died on ECMO. One additional patient died due to complications during the ICU stay after successful weaning. V′CO2NL Ratio Trend in ECMO Patients We divided the ECMO treatment length into quartiles to consider the V′CO2NL ratio trend during ECMO support in successfully weaned patients (n = 15). As shown in Figure 4.4, we observed a significant increase in the V′CO2NL ratio (0.32 vs. 0.53, p = 0.0045), from the first to the last quartile of treatment. Figure 4.5 shows the corresponding V′CO2NL ratio in patients who failed weaning (n = 3). Two of them died on ECMO due to causes different from respiratory failure (intracranial hemorrhage, cardiac arrest) and it is possible to distinguish a rise in V′CO2NL ratio before casualties. We did not observe any improvement in the only patient who died on ECMO due to failed NL recovery. In this patient, the treatment withdrawal was decided because of refractory multiple organ failure. We observed V′CO2NL ratio decline to 0 in the fourth quartile.

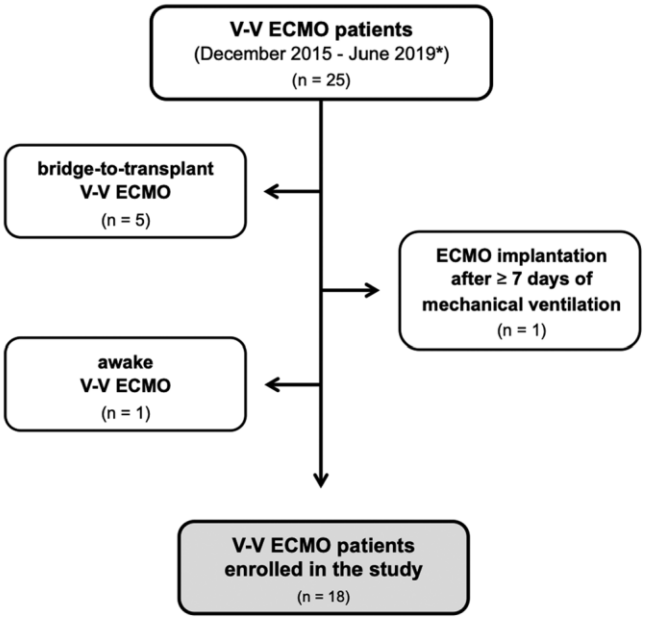

Figure 4.2. Flow-chart of selection process: seven patients in total were excluded from the 25 eligible V-V ECMO patients. Five patients were excluded as bridge-to-transplant V-V ECMO, one patient was not included since awake V-V ECMO, another because treated with ECMO after ≥7 days of mechanical ventilation.

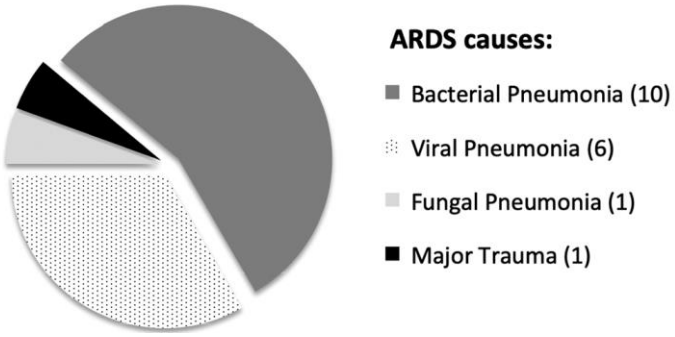

*Figure 4.3. ARDS pathogenic causes of the 18 patients enrolled in the study. ARDS, acute respiratory distress syndrome. *Patient enrolment and data collection were suspended from December 2017 to May 2018 for logistical problems related to ICU relocation in a new compound within the hospital. ICU, intensive care unit; V-V ECMO, veno-venous extracorporeal membrane oxygenation.*

	Study Population (n = 18)	ECMO Weaned (n = 15)	ECMO Inweaned (n = 3)	z	p value
Demographic and anthropometric variables					
Age (y), median value (25p–75p)	55 (40–64)	55 (40–65)	47 (30–64)	–0.534	0.571
Male sex, n (%)	12 (66.7%)	9 (60.0%)	3 (100.0%)	.	.
Weight (kg), median value (25p–75p)	79 (70–100)	80 (67–100)	70 (70–81)	–0.653	0.514
Height (cm), median value (25p–75p)	170 (165–175)	170 (165–180)	170 (168–170)	–0.300	0.764
BMI (kg/m^2), median value (25p–75p)	26 (24–33)	24 (24–29)	24 (26–40)	–0.654	0.513
Mechanical ventilation and respiratory variables					
preECMO TV (ml), median value (25p–75p)	449 (410–529)	435 (410–563)	500 (333–528)	–0.338	0.735
preECMO RR (n/min), median value (25p–75p)	18 (15–22)	19 (15–23)	16 (12–22)	–0.595	0.552
preECMO MV (L), median value (25p–75p)	9.02 (4.36–11.62)	9.58 (4.36–11.67)	8.00 (4.00–11.62)	–0.507	0.612
preECMO PEEP (cm H_2O), median value (25p–75p)	15 (14–18)	16 (14–20)	15 (12–17)	–0.599	0.549
preECMO F_iO_2 (ratio), median value (25p–75p)	100 (80–100)	100 (80–100)	100 (100–100)	1.363	0.173
preECMO P/F (mmHg), median value (25p–75p)	76 (60–110)	81 (63–120)	50 (40–70)	–2.104	0.035
preECMO S_aO_2 (ratio), median value (25p–75p)	90 (83–97)	95 (85–99)	77 (60–90)	–1.949	0.051
preECMO RESP score (n), median value (25p–75p)	–1 (–5–2)	–3 (–5–1)	2 (0–3)	1.428	0.153
ICU admission parameters and prognostic scores					
preECMO MAP (mmHg), median value (25p–75p)	75 (70–88)	77 (70–87)	72 (70–105)	0.278	0.781
SOFA score (n), median value (25p–75p)	11 (8–13)	10 (6–12)	16 (12–19)	2.141	0.032
SAPS II score (n), median value (25p–75p)	52 (42–67)	51 (40–62)	69 (59–105)	1.954	0.051
ECMO variables					
ECMO run length (days), median value (25p–75p)	12 (7–16)	11 (7–15)	17 (3–22)	0.594	0.552

BMI, body mass index; ECMO, extracorporeal membrane oxygenation; F_iO_2, native lung inspiratory oxygen fraction; MAP, mean arterial pressure; MV, minute ventilation; P/F, oxygen arterial blood partial pressure to oxygen inspiratory fraction ratio; PEEP, positive end-expiratory pressure; RESP, respiratory ECMO survival prediction; RR, respiratory rate; S_aO_2, arterial haemoglobin oxygen saturation; SAPS II, simplified acute physiology score; SOFA, sequential organ failure assessment; TV, tidal volume.

Table 4.1. *Comparison Between Demographic and Anthropometric Variables, Mechanical Ventilation and Respiratory Variables, ICU admission Parameters and Prognostic Scores and ECMO Variables Between Patients Successfully Weaned from V-V ECMO and Patients Who Failed V-V ECMO Retrieval.*

In every patient successfully weaned from ECMO, V'CO2NL ratio cut-off was recognized when the V'CO2NL ratio was ≥0.4, with a positive trend gradient for two consecutive measurements. We compared the mechanical ventilation and ECMO parameters reported before and after this cut-off point.

As shown in Table 4.2, there were no differences in ventilation parameters (TV, RR, MV, PEEP, FiO2), while ECMO BF decreased significantly (4.10 [3.70–4.20] vs. 3.65 [3.46–4.04] L/min, p = 0.017).

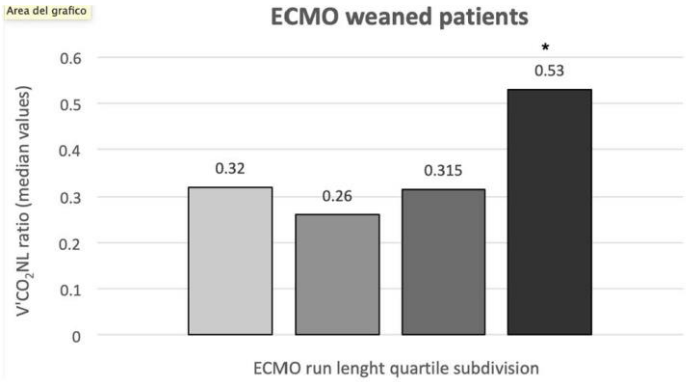

Figure 4.4. The V'CO2NL ratio median (IQR: 25–75%) in V-V ECMO weaned patients (15 in total). It is possible to observe a significant increase in V'CO2NL ratio (0.32 vs. 0.53, z = –2.840, p = 0.0045), comparing the first and the last quartiles. IQR, interquartile range; V'CO2NL ratio, native lung carbon dioxide removal ratio to total carbon dioxide removal; V-V ECMO, veno-venous extracorporeal membrane oxygenation.

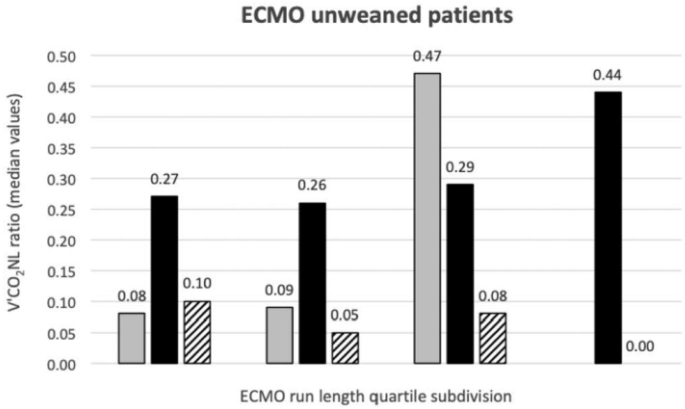

Figure 4.5. The V'CO2NL ratio trends after quartile subdivision in patients who failed V-V ECMO weaning (3 in total). It is possible to note that the V'CO2NL ratio increase in two patients (grey and black bars) who died on ECMO due to causes different from respiratory failure (intracranial hemorrhage, cardiac arrest). It is not possible to observe any improvement in the single patient (diagonal striped bars), who died on ECMO due to a failed NL recovery, with a null V'CO2NL ratio value in the last quartile. For the first patient (grey bars), a proper quartile subdivision was not possible due to the short ECMO run length, with three V'CO2NL ratio measurements only. V'CO2NL ratio, native lung carbon dioxide removal ratio to total carbon dioxide removal; V-V ECMO, veno-venous extracorporeal membrane oxygenation.

Discussion

The general lack of consensus in V-V ECMO weaning, including a proper timing, leads to heterogeneous clinical practice [18]. Ideally, the patient weaning process from V-V ECMO starts once lung function begins to improve. The key histological changes in ARDS reveal the presence of alveolar edema in areas of affected lung tissue. From a histopathological point of view, ARDS passes through an early exudative phase to a proliferative phase, which occurs about 7–14 days after the injury and some patients show signs of a further fibrotic phase. During ARDS resolution, inflammation is ceased, barriers are reestablished, fluid is reabsorbed, and cells begin to proliferate [37]. Notably, it is thought that if these mechanisms are impaired, the sustained inflammation and tissue injury make the host unable to attain homeostasis. Native lung recovery process could be clinically recognized by improving gas exchange, clearing radiographic opacity, and rising respiratory system compliance. Unfortunately, these are not always practical measurable parameters during ECMO and it may be difficult to find a reliable correlation with the level of extracorporeal support. In this study, we have evaluated the V'CO2TOT partitioning between the NL and the ML, focusing on the patient's contribution to total decarboxylation. Instead of an absolute value, we considered the NL CO2 transfer ratio to the total CO2 elimination, integrating the influence of the patient's metabolic need for CO2 clearance. We focused our attention on the V'CO2NL ratio as a measurable parameter, evaluating its potential role to reveal NL healing and to identify patients undergoing a positive V-V ECMO retrieval. Taking into account

patients with successful V-V ECMO weaning, we observed a significant increase in V'CO2NL ratio during the extracorporeal support length. The few patients who failed ECMO weaning (three cases) limited our statistical analysis in this subgroup. In any case, it is remarkable that we did not observe any V'CO2NL ratio improvement in the sole patient who died due to a failed NL recovery.

	Pre Cut-Off (n = 15)	Post Cut-Off (n = 15)	z	p value
Mechanical ventilation settings				
TV (ml), median value (25p–75p)	380 (301–505)	409 (339–504)	0.973	0.331
RR (breaths/min), median value (25p–75p)	10 (8–14)	12 (8–17)	1.103	0.270
MV (L), median value (25p–75p)	3.84 (2.34–5.63)	5.07 (3.16–8.15)	−1.449	0.347
PEEP (cm H_2O), median value (25p–75p)	12 (10–14)	12 (10–14)	−0.730	0.465
F_iO_2 (ratio), median value (25p–75p)	0.50 (0.50–0.70)	0.50 (0.40–0.60)	0.941	0.147
ECMO settings				
BF (L/min), median value (25p–75p)	4.10 (3.70–4.20)	3.65 (3.46–4.04)	−2.386	0.017
GF (L/min), median value (25p–75p)	4.50 (2.50–6.00)	4.50 (2.00–6.00)	−0.257	0.797
F_sO_2 (ratio), median value (25p–75p)	0.70 (0.50–0.80)	0.50 (0.40–0.80)	−1.382	0.167

BF, (ECMO) blood flow; ECMO, extracorporeal membrane oxygenation; F_iO_2, native lung inspiratory oxygen fraction; F_sO_2, membrane lung sweep gas oxygen fraction; GF (ECMO), gas flow; MV, minute ventilation; PEEP, positive end-expiratory pressure; RR, respiratory rate; TV, tidal volume; $V'CO_2$NL ratio, native lung carbon dioxide removal ratio to total carbon dioxide removal.

Table 4.2. *Comparison Between Mechanical Ventilation and ECMO Settings, in Patients Successfully Weaned from V-V ECMO, Before and After a Stated V'CO2NL Ratio Cut-Off Point (Stating a Substantial Improvement in V'CO2NL Value, With a Positive Gradient for Two Consecutive Measurements, Higher Than 0.4).*

In patients successfully weaned from V-V ECMO, we did not observe significant variations in invasive mechanical ventilation parameters after an arbitrary cut-off point stating a substantial improvement in V'CO2NL ratio. This result could be considered as a clinical expression of lung recovery, irrespective of any change in NL ventilation. Therefore, V'CO2NL has not to be considered a merely ventilator- controlled value. The high levels of intra-pulmonary shunt in ARDS are related to the increasing physiologic dead space [31,35,38], along with the augmented alveolar ventilation/perfusion ratio (V'A/Q') heterogeneity. [39] Dead space represents then a useful index of lung dysfunction and could be a predictor

of survival.[40] From a speculative point of view, the increasing V'CO2NL ratio might mirror the improvements in shunt and V'A/Q' abnormalities typical in the hypoxemic lung failure. According to our findings, it could be possible to evaluate lung function using V'CO2NL and monitor its recovery with the NL V'CO2 ratio. The patient clinical history, from ECMO cannulation to lung recovery and ECMO decannulation, passes from a period when V-V ECMO is essential to meet the patient metabolic needs to a phase in which the NL function has recovered enough to autonomously satisfy the patient demands. A continuum between these two points exists in which it is mandatory to know the real state of lung recovery. We believe that a standardized approach to a functional assessment during ECMO treatment and weaning could be achieved with parameters that describe the state of the lung, and the V'CO2NL ratio could be useful for this purpose. The decision to dismiss extracorporeal support needs a proper assessment of lung function to support alone all the metabolic needs of the patient, maintaining protective ventilation. Our evidence of a significant rise of the V'CO2NL ratio in the last quartile, without any significant change in ventilator settings, could represent the clinical demonstration of lung function improvement and healing after hypoxemic failure. On the other hand, the absence of a major increase in this parameter expresses no recovery or a prolonged lung recovery. The V'CO2NL ratio may serve as a predictor for unsuccessful weaning from V-V ECMO. In patients successfully weaned, the V'CO2NL ratio value we observed in the last quartile (0.53) could be considered as a V-V ECMO support reduction to 47% of the total. It denotes how the NL sustained over half of the

decarboxylation function at the extracorporeal support retrieval. This result is concordant with ELSO guidelines that suggest a trial off attempt when the extracorporeal support is reduced to a not further specified 30% of the total. The same guidelines contemplate values up to 50% in case of special circumstances, such as uncontrolled bleeding.1 Although further larger studies are needed, our conclusions may suggest a higher threshold even in standard conditions, evaluating for removal in an earlier phase. Even if V'CO2NL ratio should not be the sole parameter to consider during the weaning off the extracorporeal support, it could represent an efficient and readily available index to quantify the actual reduction of the relative V-V ECMO support.

Study Limitations

This study has several limitations related to the research design and the small sample size. This is a single center study, restricted to the V-V ECMO weaning process adopted during the clinical practice at our institution. At present, we have not any formal clinical protocols regarding ECMO removal. However, V'CO2NL ratio trend is simultaneously observed with other parameters to reach a clinical decision. Forthcoming larger studies should correlate V'CO2NL ratio with others parameters taken into account during the V-V ECMO weaning phase.

Conclusions

The management of the V-V ECMO patient and the continuous evaluation of time to wean should be conducted following a holistic approach. One

such approach could be monitoring of the interdependence between the NL and the extracorporeal ML, both of which are fundamental in the acute phase and in the following recovery. The concept presented in this pilot study based on the V'CO2NL ratio may provide a valuable tool to assess lung recovery and identify patients with a good chance for successful weaning from V-V ECMO. Further studies are needed to evaluate the accuracy of this parameter.

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Chapter 5.

A retrospective analysis of the hemolysis occurrence during extracorporeal membrane oxygenation in a single center

Silvia Costantini, Mirko Belliato, Fiorenza Ferrari, Giulia Gazzaniga, Marta Ravasi, Miriam Manera, Maria Elena De Piero, Antonio Curcelli, Alessandra Cardinale and Roberto Lorusso

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Background

In-vivo hemolysis refers to the premature disruption of red blood cells (RBCs) within a living organism. When the bone marrow is unable to compensate for RBC breakdown, hemolytic anemia can occur. In-vivo hemolysis can be extravascular (i.e., outside the circulatory system) or intravascular (i.e., within the circulatory system), and the latter is more likely to result in an elevation in plasma free hemoglobin (pfHb). Intravascular hemolysis can have several causes, such as genetic disorders (e.g., sickle cell disease), drug-induced diseases, and other mechanical factors, including microangiopathic hemolytic anemia (e.g., disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome).[1-3]

In the intensive care unit (ICU), hemolysis, diagnosed by a combination of laboratory findings such as increased levels of pfHb or decreased levels of haptoglobin (Hpt), might be directly related to a patient's primary disease (e.g., sepsis, severe hemorrhage, major surgery, multiple transfusions) [4-6] or secondary to treatments such as technical-induced hemolysis in patients supported by extracorporeal membrane oxygenation (ECMO).[7]

Along with thromboembolic events and bleeding, hemolysis represents, in itself, an intrinsic complication of extracorporeal circulation, defined in this case as pfHb exceeding 50 mg/dL by the Extracorporeal Life Support (ELSO) Registry.[8] Accumulating evidence suggests that an increased pfHb level few hours after ECMO placement may be an independent predictor of mortality among patients receiving ECMO support with various indications, [9] and it is also associated with the risk of non-hemorrhagic stroke,

thrombosis, pulmonary and systemic hypertension, [10-14] and decreased organ perfusion. The release of pfHb, the activation of the complement system, and the generation of inflammatory mediators are all known to be directly related to acute kidney injury (AKI) [15] during ECMO, leading to the possibility that blood purification techniques might be required.[9, 16] The main consequences of intravascular hemolysis generally include the formation of oxygen radicals, the direct toxicity to renal tubules, [17] and the scavenging of nitric oxide [18] (NO). NO depletion, determined by its reaction with pfHb, leads to a reduction in guanylate cyclase activity, smooth muscle contraction, vasoconstriction, a pro-inflammatory state, abnormal coagulation, and platelet activation and aggregation. [19-21]

During the last decades, several mechanical improvements have been made to achieve prolonged and safer extracorporeal circuit duration, less hemolysis, and, accordingly, lower pfHb levels. While shear stress and blood pumps are still influential triggering factors for hemolysis, the recent introduction of a new generation of polymethylpentene membrane oxygenators (MOs), along with Mendler-designed centrifugal pumps and biocompatible coatings, have reduced the above-mentioned phenomenon. [22-28] Therefore, during ECMO support, hemolysis is less frequently associated with pump head thrombosis and more commonly triggered by excessive mechanical stress caused by an inadequate preload (i.e., an excessively negative pressure secondary to cavitation or drainage cannula chattering, [7, 22] or altered flow or cannula performance [29]).

This study aimed to identify the predictive factors of hemolysis during ECMO support through the correlations between ECMO setting

parameters (revolutions per minute [RPM], blood flow, gas flow), MO efficiency indices (D-dimer dosage, pressure drop, dead space, P/F), laboratory coagulation tests, and pfHb.

Methods

Study population, duration and setting

This study is a retrospective single-center case series. We enrolled 35 consecutive adult patients (age > 18 years) who, between April 2014 and February 2020, were admitted to the ICU of Fondazione I.R.C.C.S. Policlinico San Matteo, Pavia, Italy, with the diagnosis of severe adult distress respiratory syndrome (ARDS), according to the Berlin Definition, and who underwent ECMO support. [30] Only those patients who had been treated for at least 48 hours with a veno-venous (VV) were included.

Defining hemolysis when pfHb exceeded its normal range or Hpt was decreased, and considering the purpose of this analysis, cases in which the designated hemolysis markers had not been tested during the first 15 days of ECMO support were excluded.

In case a transition to hybrid ECMO configurations (veno-arterial-venous VAV or veno-veno-arterial VVA), for clinical reasons, was needed after VV-ECMO placement, only days during VV-ECMO treatment were included. The study was approved by the local ethics committee (ref. 26372/2020) and was conducted in accordance with the Declaration of Helsinki and international ethical principles and good clinical practices. Informed consent was acquired retrospectively from each patient or, in case of unconsciousness or death, a substitute (next of kin, when appropriate),

according to local laws. All devices were approved for clinical use, and non-personalized data and routine laboratory parameters were used.

ECMO procedure

In our ECMO center, circuits with centrifugal pumps are used (Rotaflow RF-32 centrifugal pumps or Cardiohelp powered HLS sets; Maquet, Rastatt, Germany) and two MOs are available in clinical practice: Quadrox PLS (Maquet, Rastatt, Germany) and Eurosets ECMO adult (EUROSETS s.r.l., Medolla, Italy). ECMO management, indications, and limitations were employed according to the ELSO guidelines for adult respiratory failure, [8, 31] and standard care was provided according to clinical practice. ICU nurses, perfusionists, and physicians performed the circuit's routine management and check-ups. Unfractionated heparin (UFH) was habitually used because, in our institution, it represents the first choice for anticoagulation therapy and no contraindication was found in the considered patients group.

Patients who developed AKI during their hospitalization in ICU received CRRT accordingly to Kidney Disease: Improving Global Outcomes (KDIGO) guidelines and clinical practice. [32] CRRT was performed using Prismaflex machines (Gambro Ltd, Sweden).

Data collection

Once patients had been enrolled in the study, demographic and clinical data were recorded through electronic medical record review. ECMO management data were collected as follows: every two hours pump speed (expressed as RPM), circuit blood flow (BF), and fraction of inspired oxygen

(FiO2) were recorded, while drainage pressure (P-drain), pre- and post-oxygenator pressures (P-in and P-out), dead space (DS), and pre- and post-oxygenator blood gas analysis were collected twice a day, or as clinically needed. Particular attention was paid to the eventual presence of oxygenator clots, cannula movements or chattering, and bleeding at cannula insertion sites.

According to our clinical practice, aPTT was measured every 8 hours, and a target of 2 times the normal values (20–32 sec) was set. A complete blood count was requested every 8 hours, with D-dimer (normal values <500.0 µg/L) once in 24 hours. Hpt (normal range 34.0–200.0 mg/dL) and pfHb (normal values < 5.0 mg/dL) were measured when hemolysis was suspected.

Since blood samples were routinely collected in early mornings once daily, of all the variables listed so far, only morning values were usually included in the statistics, matching laboratory and mechanical parameters.

For our study, we considered also daily changes in hemoglobin levels, analyzing them in the form of delta-Hb—that is, the difference between Hb and its value the day before—as it would address both blood loss from any source and transfusion of blood. In fact, this number tends to be positive in case of transfusion the day before, and negative in case of blood loss. MO DS was calculated according to the following formula: [33]

ECMO DS=(PpostCO_2-PeCO_2)/(PpostCO_2)

We registered all data in an Excel file (Excel2010, v14.0, Microsoft Corporation, Redmond, WA, USA) that contained anonymized patient details.

Statistical analysis

Statistical analysis was conducted with SPSS software (IBM SPSS Statistics for Windows, v. 25.0, IBM Corp., Armonk, NY, USA). Patients' baseline characteristics were summarized using counts and percentages for categorical measures. For continuous data, normality was tested with the Shapiro–Wilk test. They were then presented as means and standard deviations (SD) when normally distributed; median and 25th–75th percentiles when not normally distributed.

The primary endpoint of our study was the association between daily clinical, biochemical and ECMO characteristics with the corresponding measurements of pfHb, while possible associations with changes in Hpt were set as the secondary endpoint.

Spearman's correlation for monotonic distributions was used to assess the correlation between continuous variables and hemolysis markers; the distribution around the slope was visually checked through scatterplots. The relationship between clinical and mechanical characteristics and pfHb was modeled considering the B regression coefficient in a multiple linear regression analysis. Confidence intervals around the slope of the regression line were also defined. To identify independent predictors of pfHb rise, two-tailed p-values were used, with the significance level for p-values set at below 0.05. Collinearity of the independent predictors was assessed by

variance inflation factor (VIF); a fair level of multicollinearity was considered when VIFs < 7.

The adequacy of such models was investigated by visually inspecting the plots of residuals vs. predictors: homoscedasticity and non-linearity was verified.

The sample size was established by the time window of the study. To check whether significance was due to statistical power, a post hoc power analysis for multiple linear regression was conducted using GPower software package 3.1.9.6 (Faul, Erdfelder, Buchner & Lang, 1992–2020).

Results

Mean age was 50.1 years, with females accounting for 28.6% (n=10). Median BMI upon initial admission was 26.6 with 68.6% of patients being overweight or obese.

Epidemiological features, laboratory tests and ECMO parameters are summarized in Table 5.1(a) and Table 5.1(b).

Table 5.1(a). *Baseline characteristics of patients under ECMO support*

Characteristics	All patients (n=35)
Male gender (n, %)	25 (71.4%)
Age at ECMO start (y)	50.0 ± 16.3
Weight (Kg)	80 [74.5 - 90.5]
Body mass index at PTA (kg/m^2)	26.6 [24.2 - 30.1]
WBC count at ECMO cannulation (10^3/µL)	11 [7.8 - 22.3]
C-reactive protein at ECMO cannulation (mg/dL)	25.0 ± 13.0
PaO2/FiO2 ratio at ECMO cannulation (mmHg)	71.5 [58.0 - 93.0]
ICU length of stay (d)	36 [22 - 50]
Duration of ECMO support (d)	12 [8.5 - 18.5]
CRRT (n, %)	25 (71.4%)
Decease (n, %)	11 (31.4%)

**Data are expressed as number (%), mean ± SD or median [25° - 75°]*

WBC= white blood cells count; PaO2/FiO2= ratio of arterial oxygen partial pressure to fractional inspired oxygen; CRRT= continuous renal replacement therapy; y= years; d= days; n= number.

Table 5.1(b). *ECMO settings and laboratory findings of patients under ECMO support*

Characteristics	All patients (n=35)
Mean ECMO Pdrain in the first 15 days after initiation (mmHg)	-71.6 ± 20.0
Mean ECMO RPM in the first 15 days after initiation (min-1)	3050.1 ± 329.8
Median ECMO BF in the first 15 days after initiation (L/min)	3.7 [3.5 - 4.1]
Median ECMO pressure drop in the first 15 days after initiation (mmHg)	28.2 [20.2 - 41.0]
Median ECMO dead space in the first 15 days after initiation (L/min)	0.4 [0.3 - 0.5]
Mean ECMO P/F ratio in the first 15 days after initiation (mmHg)	350.5 ± 112.2
Median drainage cannula size (Fr)	21 [20.5 - 23]
Mean PTT ratio in the first 15 days after ECMO initiation	1.3 ± 0.3
Mean DD in the first 15 days after ECMO initiation (µg/L)	11170.8 ± 7051.3
Mean Hpt in the first 15 days after ECMO initiation (µg/L)	186 ± 113.5
Median pfHb in the first 15 days after ECMO initiation (µg/L)	8.3 [6.2 – 12.0]

**Data are expressed as number (%), mean ± SD or median [25° - 75°]*

Pin= pre-oxygenator pressure; Pdrain= drainage pressure; RPM= rates per minute; BF= blood flow; GF= gas flow; P/F= ratio of oxygen partial pressure to fractional oxygen; PTT= partial thromboplastin time; ACT= activated coagulation time; MPV= mean platelet volume; n= number.

Median duration of ECMO support was of 12 days and ranged from 5 to 95 days. PfHb was regularly monitored when hemolysis was suspected, but not every day, whereas Hpt was tested more frequently as it was part of a routine ICU laboratory panel. The distribution of pfHb values among patients under VV ECMO support is displayed on Figure 5.1. The completeness percentage of daily measurements in our data set amounted to 40% for pfHb and almost 90% for Hpt.

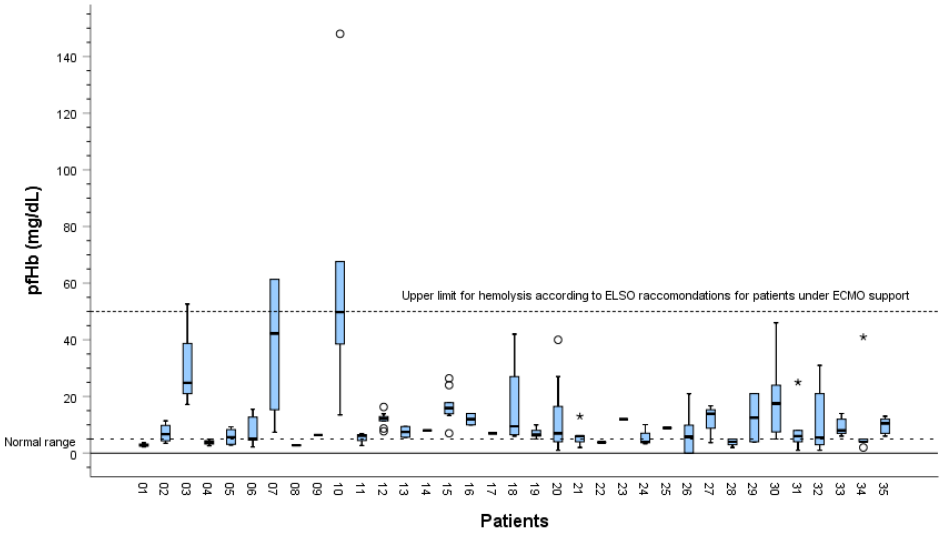

Figure 5.1. *Distribution of pfHb among patients under VV and hybrid ECMO support.*

Among the patients with successful ECMO weaning, no one showed pfHb levels above 50 mg/dL, whereas this occurred in 27.3% of patients whose ECMO support failed, resulting in a fatal outcome (p = 0.025). As shown in Table 5.2, the latter group also had higher values of mean pfHb and mean

Hpt (p = 0.003). Further, hemolysis seems to play a role in patient and circuit management: on average, it was more marked among patients who needed CRRT, as pfHb was higher (9.4 vs. 6.7 mg/dL) and they presented lower levels of Hpt (181.4 vs. 203.4 mg/dL). In addition, patients who needed at least one circuit change had higher pfHb (11.2 vs. 7.8 mg/dL) and more consumed Hpt (146.0 vs 213.3 mg/dL), even if these differences showed no statistical significance.

Out of 35 cases, 13 (37.1%) necessitated one circuit change in the first 15 days of ECMO therapy, although no recannulation was needed.

Performing multiple linear regression on all collected data, clinical and biochemical features, and the mechanical factors of the ECMO circuit did not show any influence on the daily changes in pfHb levels (see Table 5.3). Instead, the use of CRRT represented a significant predictive factor for pfHb increments (p = 0.048), increasing pfHb by 10.550 mg/dL, all else being equal. Altogether, in this case, residual plots showed a sufficient symmetrical distribution and this model explained 24.9% of pfHb variability (R2), which resulted in a medium effect size (0.33). The statistical power to detect an effect of this size, considering the total sample size of non-missing pfHb determinations, an alpha level of < 0.05, and 12 predictors, was determined to be 0.95.

These observations suggest a more complex influence on hemolysis involving pfHb filtration, CRRT-exacerbated hemolysis, and RBC trauma due to the extracorporeal circuit when CRRT is set up, especially if considering that in our center CRRT is routinely connected to the ECMO circuit, as illustrated in Figure 5.2.

Table 5.2. Multiple linear regression - Independent factors associated with pfHb variations

Determinants	B coefficient	95% CI for B	p-value
Patient weight	0.094	-0.150 – 0.339	0.443
Daily D-dimer	0.000	0.000 – 0.001	0.216
Daily PTT ratio	4.797	-2.263 – 11.857	0.179
Drainage cannula size	1.284	-1.148 – 3.716	0.295
CRRT	**11.388**	**0.267 – 22.509**	**0.045**
Daily ECMO BF in the first 15 days after start	0.323	-6.816 – 7.462	0.928
Daily ECMO RPM in the first 15 days after start	-0.001	-0.016 – 0.014	0.898
Daily ECMO Pdrain in the first 15 days after start	-0.022	-0.212 – 0.167	0.815
Daily ECMO Dead space in the first 15 days after start	6.245	-13.454 –25.944	0.529
Daily ECMO P/F ratio in the first 15 days after start	-0.011	-0.038 – 0.015	0.407
Daily ECMO pressure drop in the first 15 days after start	0.119	-0.063 – 0.300	0.196

CRRT= continuous renal replacement therapy; Pdrain= drainage pressure; BF= blood flow; P/F= ratio of oxygen partial pressure to fractional oxygen; PTT= partial thromboplastin time.

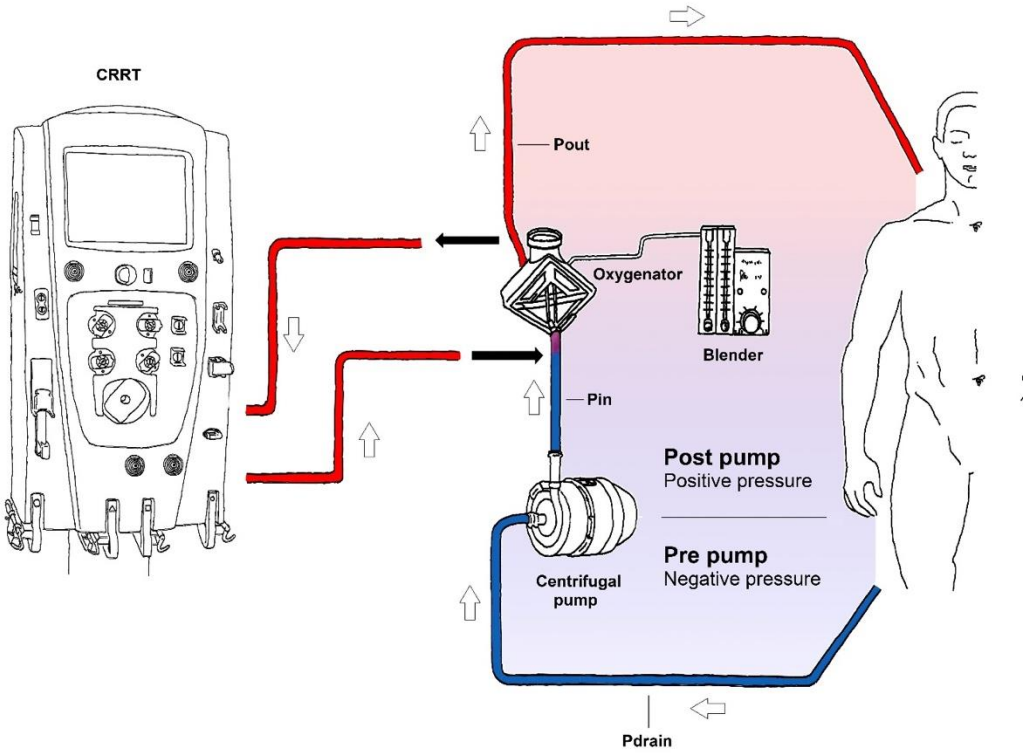

Figure 5.2. Schematic of an ECMO circuit incorporating a CRRT device, with the routinary connection used in our center.

We also investigated the relationship between ECMO features and Hpt in our sample, as shown in Table 5.4. During hemolysis, this serum-binding protein is known to be inversely related to pfHb, as it is a carrier for pfHb; the relationship between pfHb and Hpt was confirmed in our dataset (Pearson's r = −0.275, with p = 0.002). In this multiple linear regression, we found that the partial effect of a single unit increment in aPTT was a drop of 1.822 mg/dL in the expected Hpt value (95% CI, −3.537 to −0.108, p = 0.037). A 10% increase of ECMO DS would decrease, all else being equal, the expected Hpt levels by 21.53 mg/dL (95% CI, −39.936 to −13.634, p = 0.004), whereas a reduction of 1 L/min of BF led to Hpt consumption of

93.371 mg/dL (95% CI, 36.960 to 149.781, p = 0.001). Furthermore, with this approach, the role of CRRT seems to be crucial, as its use cet. par. would cause an Hpt decrease of 104.430 mg/dL (95% CI, −171.298 to −37.562, p = 0.002).

This analysis explained 26.3% of Hpt variability (R2). It produced symmetrical residual plots and a normal distribution, showing no pattern. The post hoc power analysis, considering an alpha level $p < 0.05$, a 12-predictor variable equation, and the determined effect size of 0.36, revealed a statistical power of 0.95.

A separate analysis of the different oxygenators and pumps was also performed to determine whether different hemolysis parameters may be individuated in our data set for the different structures and membranes. Most analyzed factors failed to reach statistical significance as predictive factors in the proposed linear model. The reduced numerosity of some subgroups may have played a role in the loss of significance and in the worsening of statistical adequacy, as most VIFs were >10 for the Euroset/Rotaflow subgroup.

Thus, with the necessary limitations, as displayed in Table 5.5 and Table5.6, it can be observed that aPTT prolongation and BF increase were confirmed as predictive of Hpt consumption when Quadrox oxygenators and Rotaflow pumps were used (p = 0.018 and p = 0.008, respectively).

A higher patient weight was associated with lower Hpt in the subgroup of patients using a Quadrox oxygenator (B = −2.989, 95% CI, −5.199 to −0.778, p = 0.009).

Table 5.3. Multiple linear regression - Independent factors associated with pfHb variations

Determinants	B coefficient	95% CI for B	p-value
Patient weight	0.025	-0.228 – 0.278	0.842
Daily D-dimer	0.000	0.000 – 0.001	0.252
Daily aPTT	0.062	-0.277 – 0.401	0.714
Drainage cannula size	1.289	-2.588 – 5.166	0.508
CRRT	**10.550**	**0.088 – 21.011**	**0.048**
Daily ECMO BF in the first 15 days after start	-0.485	-9.149 – 8.179	0.911
Daily ECMO RPM in the first 15 days after start	-0.006	-0.019 – 0.006	0.314
Daily ECMO P-drain in the first 15 days after start	-0.044	-0.241 – 0.153	0.655
Daily ECMO Dead space in the first 15 days after start	0.752	-18.404 – 19.908	0.938
Daily ECMO P/F ratio in the first 15 days after start	-0.011	-0.037 – 0.014	0.382
Daily ECMO pressure drop in the first 15 days after start	0.144	-0.022 – 0.309	0.087
Daily change in intracellular Hb	2.696	-0.722 – 6.113	0.120

Table 5.4. Multiple linear regression - Independent factors associated with Hpt variations

Determinants	B coefficient	95% CI for B	p-value
Patient weight	-0.609	-2.236 – 1.018	0.460
Daily D-dimer	0.000	-0.002 – 0.003	0.832
Daily aPTT	**-1.822**	**-3.537 – (-0.108)**	**0.037**
Drainage cannula size	-12.753	-36.342 – 10.835	0.287
CRRT	**-104.430**	**-171.298 – (-37.562)**	**0.002**
Daily ECMO BF in the first 15 days after start	**93.371**	**36.960 – 149.781**	**0.001**
Daily ECMO RPM in the first 15 days after start	-0.052	-0.124 – 0.020	0.152
Daily ECMO P-drain in the first 15 days after start	1.029	-0.183 – 2.241	0.096
Daily ECMO Dead space in the first 15 days after start	**-215.307**	**-358.958 – (-71.656)**	**0.004**
Daily ECMO P/F ratio in the first 15 days after start	0.080	-9.096 – 0.257	0.368
Daily ECMO pressure drop in the first 15 days after start	-0.006	-0.946 – 0.933	0.989
Daily variation in intracellular Hb	0.506	-18.069 – 19.082	0.957

Table 5.5. *Multiple linear regression - Independent factors associated with pfHb variations, separated according to oxygenator/pump types*

Determinants	Eurosets oxygenator + Rotaflow pump (pt=10)			Quadrox oxygenator + Rotaflow pump (pt=25)		
	B coefficient	CI	p-value	B coefficient	CI	p-value
Patient weight	-4.079	-9.035 – 0.878	0.091	-0.121	-0.452 – 0.209	0.461
Daily D-dimer	0.000	-0.002 – 0.003	0.807	0.000	0.000 – 0.001	0.630
Daily aPTT	-0.793	-2.072 – 0.486	0.180	-0.010	-0.467 – 0.447	0.964
Drainage cannula size	10.171	-6.213 – 26.555	0.180	3.486	-1.410 – 8.382	0.157
CRRT	– *	– *	– *	12.546	-2.976 – 28.068	0.110
Daily ECMO BF in the first 15 days after start	-10.304	-50.885 – 30.276	0.557	-2.898	-13.037 – 7.242	0.566
Daily ECMO RPM in the first 15 days after start	-0.055	-0.120 – 0.010	0.083	0.004	-0.015 – 0.023	0.674
Daily ECMO Pdrain in the first 15 days after start	-0.477	-1.592 – 0.637	0.335	-0.024	-0.257 – 0.210	0.837
Daily ECMO Dead space in the first 15 days after start	-88.176	-246.835 – 70.483	0.223	0.732	-22.610 – 24.074	0.950
Daily ECMO P/F ratio in the first 15 days after start	-0.008	-0.085 – 0.070	0.818	-0.021	-0.054 – 0.012	0.199
Daily ECMO pressure drop in the first 15 days after start	0.114	-0.932 – 1.161	0.798	0.106	-0.166 – 0.379	0.434
Daily change in intracellular Hb	2.806	-5.871 – 11.484	0.459	1.278	-2.912 – 5.467	0.540

* Excluded from the analysis because they are constants or have missing correlations

Table 5.6. *Multiple linear regression – Independent factors associated with Hpt variations, divided according to oxygenator/pump types*

Determinants	Eurosets oxygenator + Rotaflow pump (pt=10)			Quadrox oxygenator + Rotaflow pump (pt=25)		
	B coefficient	CI	p-value	B coefficient	CI	p-value
Patient weight	11.700	-0.676 – 24.075	0.063	**-2.989**	**-5.199 – -0.778**	**0.009**

Daily D-dimer	-0.002	-0.006 – 0.003	0.482	0.000	-0.003 – 0.003	0.878
Daily aPTT	-2.580	-6.534 – 1.374	0.192	**-2.857**	**-5.214 – -0.501**	**0.018**
Drainage cannula size	-26.784	-80.846 – 27.277	0.319	3.058	-26.316 – 32.431	0.837
CRRT	– *	– *	– *	-81.560	-164.795 – 1.675	0.055
Daily ECMO BF in the first 15 days after start	26.532	-119.541 – 172.605	0.713	**88.882**	**23.442 – 154.322**	**0.008**
Daily ECMO RPM in the first 15 days after start	0.105	-0.062 – 0.273	0.209	0.012	-0.100 – 0.124	0.832
Daily ECMO Pdrain in the first 15 days after start	1.492	-1.146 – 4.131	0.256	1.204	-0.246 – 2.654	0.103
Daily ECMO Dead space in the first 15 days after start	-3.746	-398.800 – 391.308	0.985	-83.928	-271.496 – 103.641	0.376
Daily ECMO P/F ratio in the first 15 days after start	0.181	-0.092 – 0.455	0.184	0.057	-0.177 – 0.291	0.629
Daily ECMO pressure drop in the first 15 days after start	0.105	-1.612 – 1.822	0.901	0.012	-1.565 – 1.588	0.988
Daily change in intracellular Hb	0.600	-25.050 – 26.250	0.962	-4.015	-28.394 – 20.365	0.744

* Excluded from the analysis because they are constants or have missing correlations

Discussion

Abnormal intravascular hemolysis during ECMO support can be triggered by several risk factors. It is most commonly related to the mechanical shear stress applied to the erythrocytes within the ECMO circuit, and to MO and pump thrombosis, and it appears to be associated with increased morbidity through renal impairment.

CRRT is an efficient tool, and it is potentially beneficial for the management of hemolysis-induced AKI, as it may decrease the inflammatory cytokines that have been released during ECMO. However, its intrinsic mechanical "nature" also provides an additional surface for platelet adhesion, and its pump system can be responsible for an increase of pfHb values.

In our current work, we highlight the role in RBC damage of connecting the CRRT machine directly to the ECMO circuit and the effect of doing so on

the pressure balance and on mechanical stress due to the extracorporeal circuit, the hemolytic potential itself, and the buffering capacity of the hemofilters. Several authors reported a more frequent use of CRRT corresponding with rising pfHb values in ECMO pediatric and adult populations [34-36], but its independent predictivity has not been established. A relevant hemolytic impact is, in fact, considered to be lacking when using CRRT alone [37] and, in contrast, a certain grade of pfHb clearance of various dialysis filters was reported[38]. Lehle[7], indeed, noted that patients undergoing VV ECMO treatment without CRRT had lower pfHb levels than those with CRRT when considered as univariate; nevertheless, with their multivariable statistical approach, an independent effect of renal replacement therapy on hemolysis could not be proved. Our analysis fits into this context and gives some more consistency to the thesis of a key role played by this extracorporeal circuit on hemolysis.

When increased intravascular hemolysis is associated with thrombosis of the circuit or its components, activation of the coagulation cascade and platelet dysfunction might be observed.[35] The influence of aPTT and hemolysis on ECMO in our analysis can be graphically visualized through the scatter plots on Figure 5.3: when aPTT and pfHb were analyzed through Spearman's correlation, a small positive Spearman's rho (ρ = 0.036) showed no statistical significance (p = 0.669). The same analysis applied on the relationship between aPTT and Hpt was statistically significant (Spearman's □ = −0.232, p < 0.0001), which is confirmed in the multiple linear regression, where increments in aPPT were associated with Hpt consumption, both in the whole group and in the group that used Quadrox

oxygenator and Rotaflow pump. Dufour et al. [39] hypothesized that the consumption of clotting factors resulting from the hypercoagulability state present during ECMO support may also be responsible for a tendency toward longer coagulation times; thus, the latter is determined not only by the anticoagulant therapy.

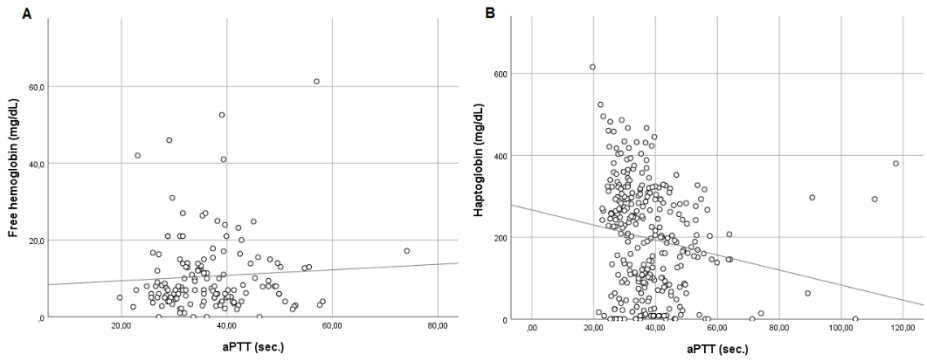

Figure 5.3. *Correlation of aPTT and pfHb (graph A, R2 0.4%); correlation of aPTT and Hpt (graph B, R2 3%).*

As for higher patient weight, individuated as a predictive factor of hemolysis only in the subgroup of patients using a Quadrox oxygenator and Rotaflow pump, few other works have made observations about this topic. Even when a role for weight was found, it was actually mainly in studies about pediatric populations and, anyway, with conclusions always in the opposite direction, that is, that higher hemolysis analytes seemed to be associated with lower body weight.[36, 40-42] So, being an unprecedented and isolated finding in a single subset of our data set, it may be spurious.

In addition, ECMO blood flow is a well-known factor associated with hemolysis, which has been confirmed in our analysis. In particular, in the literature it is described that, when BF is too high,[7] it increases shear

stress–related blood trauma, whereas when it is too low, it relates to an increased pump internal recirculation rate [43-45] and low hydraulic efficiencies.[46] The tendency observed in the present analysis—that is, higher hemolysis associated with lower blood flow values both in the whole group and in the group that used Quadrox oxygenator and Rotaflow pump—may also be influenced by an unbalanced distribution of our data. Pairing Hpt under the normal range (34–200 mg/dL in our internal laboratory) with the corresponding BF of the same day, we found non-normal distributed values with a median of 3.69 (3.4–4.14), ranging from 1.25 to 4.58 L/min. When considering BF values when Hpt is in the normal range (see Figure 5.4), the median BF is slightly higher (3.85; 3.48–4.29, ranging from min. 1.25 to max. 5.86), even if the difference between medians is not statistically significant (p = 0.129).

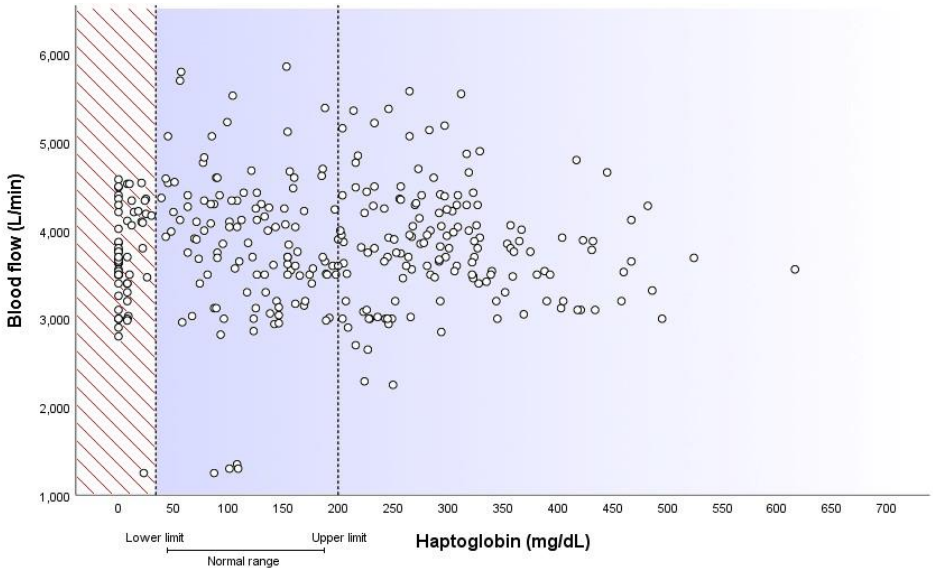

Figure 5.4. Correlation of Hpt levels and extracorporeal blood flow on VV ECMO.

Among the different ECMO circuitry components, we also identified one component of MO efficiency, MO dead space, as a predictive factor of hemolysis worsening. In fact, as MO performance declines and MO dead space increases, Hpt is consumed. Still, in terms of MO performance, we were unable to retrospectively retrieve a proper MO shunt estimation[47] from our data. Therefore, to approximate the MO shunt rate, we opted for the MO P/F ratio, although it could not correlate accurately with MO global performance.[33, 48] Adding this parameter to our model, no significant influences on the hemolysis rate were shown, even though it would have been interesting to observe the model's behavior using the appropriate MO shunt formula.

Lastly, in our study, P-drain values within the ranges that are commonly believed to be safe do not seem to be connected with blood trauma, while hemolysis is fairly recognizable when an excessively negative pressure causes a suction effect. [7, 29, 49]

When interpreting the conclusions of this study, a cautious approach is needed, since a number of notable weaknesses has to be considered. First, although the correlation between CRRT and both pfHb and Hpt levels in our study appears to be strong, the lack of data regarding CRRT treatment prescriptions (i.e., modality, dose, duration of the filter, BF rates, membrane surface area) might represent a limit of this work, as does the inability to exactly relate the timing of pfHb level measurements with the start of the renal replacement therapy.

As a side note, the CRRT machine was connected with the ECMO, as shown in Figure 5.2, via standard, serial 3-way stopcocks with Luer locks, one on

the arterial and one on the venous side of the oxygenator. This too may have contributed to the creation of local turbulent blood motions and thus hemolysis.

Mentioning CRRT placement, a comparison between ECMO circuit connection and vascular catheter through a perspective study may also be fundamental to better assess the real impact of CRRT on hemolysis in patients on ECMO.

Moreover, an anticoagulation strategy, specific only for the CRRT circuit, was not set, this means that the standard was a systemic UFH therapy with the same anticoagulation target as for the ECMO circuit. In that sense, alternative therapeutic approaches toward anticoagulation might constitute an alternative variable and might have a different clinical impact.

One last limitation that needs to be mentioned is missing data about blood product consumption. Delta-Hb may be a valid substitute of this information, but it may be inaccurate, introducing a confounder for our findings.

In addition to the last comments, the differences encountered by analyzing pfHb or Hpt as dependent variables, respectively, can be ascribed to the diverse pfHb kinetics during circuit-connected CRRT or to the dissimilar sample sizes due to the retrospective design of our study, rather than to stochastic changes alone. Besides, other confounding factors might be responsible for a Hpt reduction, such as liver impairment, malnutrition, or inflammatory state, as Hpt is an acute-phase protein.

Finally, in the current work, hemolysis fitted to a linear model with acceptable approximation; however, it could diverge from this pattern in

clinical reality if the considered variables are set outside an optimal safety interval.

As important strength of this work, no other study has focused, to the best of our knowledge, on the influence of the performance of ECMO MO efficiency indices on hemolysis, although some have correlated the pressure drop across the MO with hemolysis.[24, 50] It is still a subject of debate,[44, 51-53] as other elements in the internal design may have a clinical impact, but in general it seems to be worth paying attention to all different ECMO mechanical components for the early detection of hemolysis.

As a final highlight, this is one of the few studies that, to our knowledge, correlate the daily trend of hemolytic laboratory parameters (pfHb and Hpt) to recorded changes in clinical parameters in the adult population for a time of up to 15 days.

Conclusion

ECMO circuit setup and management-related variables seem to play a significant role in generating or worsening hemolysis, even when in a range that is considered safe, and in interacting in a complex model, although it is not fully understood yet. Further studies with a prospective design should assess the difference in daily hemolytic outcomes confronting different types of CRRT connections and setups during extracorporeal support, with the aim to address a comprehensive index, that could describe the risk rate of hemolysis by combining the characteristics of the patient, the laboratory data, and the technical setting.

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Chapter 6.

Neurological complications during veno-venous extracorporeal membrane oxygenation: Does the configuration matter? A retrospective analysis of the ELSO database

Roberto Lorusso, Mirko Belliato, Michael Mazzeffi, Michele Di Mauro, Fabio Silvio Taccone, Orlando Parise, Ayat Albanawi, Veena Nandwani, Paul McCarthy, Zachary Kon, Jay Menaker, Daniel M. Johnson, Sandro Gelsomino and Daniel Herr

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Background

Veno-venous (V-V) extracorporeal membrane oxygenation (ECMO) can be lifesaving in severe respiratory failure [1]. According to Extracorporeal Life Support Organization (ELSO), the reported survival rate is 66%, when considering more than 15,000 treated adult patients [2]. In particular, young patients with severe respiratory failure, who are typically treated during the influenza epidemics, may demonstrate even major benefits when V-V ECMO is implemented [3, 4]. However, the use of V-V ECMO is not without risks and neurologic complications have been reported, although their incidence is lower than in patients undergoing veno-arterial (V-A) ECMO [5–7]. According to a recent retrospective cohort study from the Extracorporeal Life Support Organization (ELSO) Registry including 4,988 patients treated with V-V ECMO, 356 (7%) of them suffered from neurological complications, in particular intra-cranial hemorrhage (42.5%), stroke (19.9%), seizures (14.1%) and brain death (23.5%) [8]. The current mechanistic understanding of neurologic injury during V-V ECMO is limited. Several putative risk factors have been proposed, including acute renal failure and a rapid PaCO2 decrease at the time of ECMO cannulation [5]. Cerebral micro-emboli have also been detected in patients undergoing both V-V and V-A ECMO and may play a role in the cerebrovascular injury [9]. Another potential contributing factor to neurologic injury during V-V ECMO is cerebral venous congestion, which may be caused by large cannulas in the internal jugular veins or venous thrombosis [10, 11, 13]. This phenomenon has been also confirmed in an animal ECMO models [12]. V-V ECMO is currently performed using either single-(SL) or dual-lumen

(DL) cannulas. DL V-V ECMO cannulas have several potential advantages, including single vessel cannulation, facilitation of ambulation and less recirculation [14, 15]. However, DL V-V ECMO cannulas are also characterized by larger sizes (i.e. 27–31 French in most of cases) than SL, which might predispose patients to cerebral venous congestion [15]. A previous single-center observational study conducted in patients undergoing V-V ECMO with DL cannulation reported a rate of intracranial hemorrhage of 7%; only 20% of these patients survived to hospital discharge [16]. In an additional study focusing on a pediatric population on V-V ECMO, no differences were observed in the total complications and survival rate between SL and DL cannulations [17]. Interestingly, there was a nonsignificant trend towards a lower rate of neurological complications in the SL group. Taking all these data into account, we hypothesize that the use of DL in V-V ECMO patients may be associated with a higher rate of neurologic injury. For these reasons, we evaluated the occurrence and the type of neurologic complications in a large cohort of adult patients on V-V ECMO, according to the SL or DL cannulation.

Methods

Study design, setting and participants

This is a retrospective study including adult patients undergoing V-V ECMO from 2011 to 2017. All data were extracted from the ELSO database (until 2018). Patients supported with V-A ECMO, those supported with V-V ECMO for cardiac indications, and those supported with multiple ECMO runs were excluded. Patients less than 18 years of age were also excluded.

The ELSO registry collects data on all ECMO cases from approximately 800 centers around the world since 1989. Data are collected using a standardized data collection form. Data user agreement between ELSO and member centers allows the use of deidentified datasets for research without need for further regulatory approval.

Collected variables

For all patients, we collected the following variables from the ELSO database: age, gender, weight, cannulation type (SL vs. DL), total ECMO hours, pre-ECMO arrest, fraction of inspired oxygen (FiO2) before ECMO, peak inspiratory pressure before ECMO, positive end expiratory pressure before ECMO, pH before ECMO, PaCO2 before ECMO, PaO2 before ECMO, serum bicarbonate level before ECMO, intubation hours before ECMO, and pump flow at 4 h and 24 h after ECMO initiation.

Study end point

The primary end point of the study was to evaluate the occurrence of neurological complications in the SL and DL group. ELSO registry categorizes “neurologic injury” as intracranial hemorrhage (ICH), acute ischemic stroke (AIS), seizures (either clinical and/or on electroencephalography,EEG) and brain death (BD) that occur during the ECMO run. All the cases are also confirmed, at least for ICH and AIS, by a neurologist and serial CT scans. Additional data on severity, site, timing and functional long-term neurologic recovery were not available. Secondary outcomes included the type of neurological complications (i.e. hemorrhagic stroke, ischemic stroke and seizure) in the two groups.

Statistical analysis

Propensity score (PS) inverse probability of treatment weighting estimation for multiple treatments was used. The balance was tested either graphically or utilizing balance tables. Graphical estimation used standardized effect plots and quantile–quantile plots, which provide an immediate visual evaluation of balance quality. In each model, absolute standardized mean differences (ASMD) were calculated using a cutoff of less than 0.10 for bias statistics. The average treatment effect (ATE) was chosen as the causal effect estimate of each outcome. It was the entire population undergoing one treatment over the impact of the outcome of the entire population under another treatment [18]. Inverse Probability of Treatment Weighting (IPTW) was used to correct for imbalances between groups on pre-treatment covariates so that the distribution of the pre-treatment characteristics would be similar across all the groups. A machine learning technique, generalized boosted model (GBM), was used to estimate the PS weights. GBM estimation captures complex relationships between treatment assignment and pre-treatment variables without over-fitting data, and GBM can be fine-tuned to find the best balance among groups. IPTW is one technique for reducing the bias due to observed variables. It relies on two key conditions for obtaining unbiased estimates 1: (1) No unknown or unmeasured confounders assumption or exchangeability and (2) Sufficient overlap or positivity: $0 < Pr(Ti = t|X) < 1$, for all X and t, where Ti is the random treatment assignment variable, Pr is probability, X is the vector of observed treatment covariates and t is the treatment. The first assumption states that the set of observed variables is

rich enough to include all variables influencing both treatments and outcomes. The second condition states that each patient has a non-zero probability of receiving each treatment. Both assumptions were met in our models. For our outcomes, many simple regression trees were generated starting from a single regression tree and adding another tree at each new iteration to create an overall piecewise constant function. This iterative fitting algorithm was chosen so as to provide the best fit to the residuals of the model from the previous iteration and because it offers the greatest increase to the log likelihood for the data. Indeed, each iteration increases the likelihood making the model sufficiently flexible to perfectly fit data. To avoid data overfitting, GBM selects an intermediate iteration (or number of trees) for the final model so as to "minimize an external criterion such as out-of-sample prediction error or—in the case of propensity score estimation—imbalance on the pre-treatment covariates across the treatment and control groups. Therefore, the key is to use GBM iteratively with the optimal iteration (number of trees) for estimating the PS and minimizing a "stopping rule" criterion based on the difference between the weighted distributions of the pre-treatment variables in the two treatment conditions. In practice, different stopping rules have been used to select the optimal iteration of GBM for use in estimating propensity score weights: maximum or minimum absolute standardized bias (SB, also referred to as the absolute standardized mean difference) or the Kolmogorov–Smirnov (KS) statistic, each of which compares the means or the distributions of the covariates between treatment groups. Since the

balance was nearly invariant with the stopping rule, we used the max Kolmogorov–Smirnov (KS) statistic.

For 2 groups the KS is:

$$[[KS]]\_k = [[\sup]]\_x \left| EDF1k(x) - EDF0k(x) \right|$$

where EDF is the empirical distribution function for the treatment and control samples and k is the covariate. Causal effects can be estimated through two different summaries: average treatment effect (ATE) and average treatment effect between treatments (ATT). The ATE of treatment "ti" versus treatment "tj" is the comparison of mean outcome had the entire population been observed under treatment "ti" versus had the entire population been observed under treatment "ti". The ATT of "ti" versus "tj" is the comparison of the mean "ti" patient outcome with the mean outcome they would have had if they had instead been treated by "tj" treatment. The casual effect was estimated by ATE which takes into account summary statistics of the effects across populations of interest. R software v. 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) and the TWANG and SURVEY packages were used for analysis.

Results

Study population

A total of 6,834 patients met the inclusion criteria; of those, 4367 (63.9%) had SL cannulation and 2467 (36.1%) had DL cannulation. Table 6.1 shows characteristics of the study population by cannulation type. Interestingly, patients who underwent SL cannulation were older, less likely female, had

fewer total ECMO hours and lower body weight. Despite similar ventilatory parameters prior to ECMO, peak inspiratory pressures were slightly lower in the SL than in the DL group. Also, mean PaCO2, PaO2, and bicarbonate levels were significantly lower and pump flows higher in SL group than others. After propensity score, a total of 6245 patients (i.e. 91% of the total cohort; 4175 with SL and 20,270 with DL cannulation) were included for the outcome analysis. The maximum pairwise ASMD was 0.10 for all selected variables.

Variable	DL *N* = 2467	SL *N* = 4367	*p* value
Age (years)	46 (32–58)	48 (35–60)	< 0.0001
Male gender [*n* (%)]	1386 (56.5)	2612 (62.0)	< 0.0001
Weight (kg)	83 (70–102)	80 (68–100)	0.0001
Total ECMO hours	191 (97–362)	189 (96–336)	0.058
Pre-ECMO arrest [*n* (%)]	165 (6.7)	294 (6.7)	0.984
FiO_2 prior to ECMO (%)	100 (100–100)	100 (100–100)	0.608
PIP prior to ECMO (cmH_2O)	35 (30–40)	34 (30–38)	< 0.0001
PEEP prior to ECMO (cmH_2O)	13 (10, 16)	14 (10, 16)	0.367
pH prior to ECMO	7.24 (7.14–7.33)	7.24 (7.15–7.34)	0.152
$PaCO_2$ prior to ECMO (mmHg)	57 (43–75)	52 (37–69)	< 0.0001
PaO_2 prior to ECMO (mmHg)	59 (45–75)	56 (41, 72)	< 0.0001
HCO_3 prior to ECMO (mEq/L)	25 (21–31)	24 (20–29)	< 0.0001
Intubation hours prior to ECMO	45 (13–131)	41 (15–120)	0.166
Pump flow at 4 h (L/min)	4.0 (3.4–4.5)	4.0 (3.4–4.8)	< 0.01
Pump flow at 24 h (L/min)	4.0 (3.4–4.6)	4.1 (3.4–4.8)	< 0.01
Alive at hospital discharge [*n* (%)]	1580 (64.0)	2595 (60.8)	0.002

Data are presented as count (%) or median (IQRs)

DL double lumen cannula, *SL* single-lumen cannula, *ECMO* extracorporeal membrane oxygenation, *PEEP* positive end expiratory pressure, *PIP* peak inspiratory pressure

Table 6.1. *Main patients characteristics, before weighing using a propensity score.*

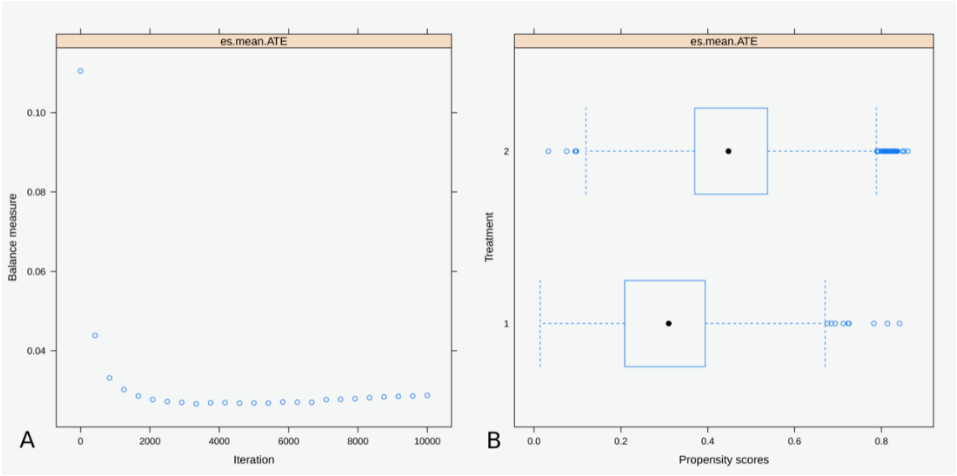

Figure 6.1 supplement. Panel A = Optimize plot. *The plot is a graphical display of the balance criteria as a function of the GBM iteration. The graph demonstrates that a favorable balance was achieved with 1000 iterations and that a higher number of iterations that, thus were unnecessary.* ***Panel B = Overlap Assessment.*** *The figure presents the two sets of box plots of the distributions of propensity scores. An overlap between the groups is desirable meaning that there are no values of the pretreatment variables that occur only in one of the treatment conditions. However, there are no specific rules for what constitutes sufficient overlap so, in doubtful cases the combination of the overlap plot and the balance table are used. In the selected model, there is clearly a good overlap between the two boxplots.*

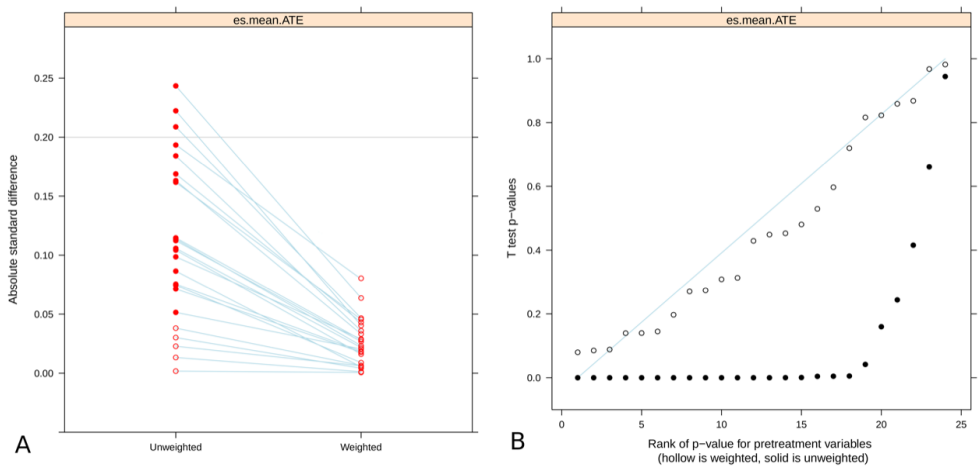

Figure 6.2 supplement. Panel C = Standardized Effect Size plot*. It assesses the balance of pretreatment variables before and after weighting. It shows the maximum pairwise absolute standardized mean differences (ASMDs). The ASMDs cutoff for defining unbalanced variables was 0.10. The light blue line represents pretreatment covariates for which the maximum pairwise ASMD reduced after weighting. The red lines mean the pretreatment covariates for which the maximum pairwise ASMD increased after weighting. A good balance is obtained when, after weighting in the majority of variables the ASMDs are lower than 0.10 and there is a prevalence of light blue lines. The weighted ASMD values were lower than 0.10 in all cases.* ***Panel D = Quantile-quantile (Q-Q) plot.*** *This plot also assesses the balance of pretreatment variables. In the plot, the Kolmogorov-Smirnov p-value is plotted against the rank of p-value for pretreatment variables. Along a 45-degree fitting line, open symbols represent weighted covariates and solid symbols represent unweighted covariates. A good balance is obtained when open symbols lie close, below or above, the 45-degree line. Before weighting, all the values were below the 45-degree line. A good balance was achieved after weighting, with p-values that lie around the 45-degree line.*

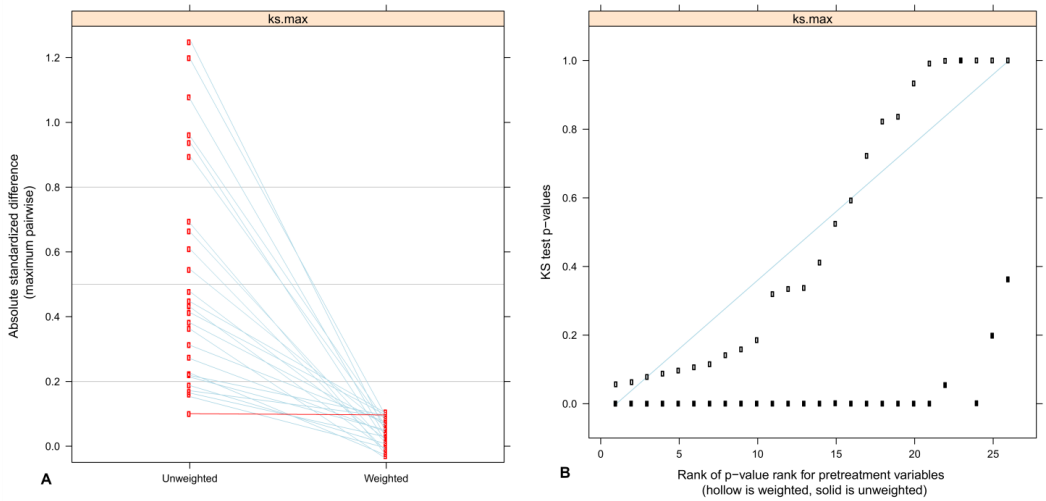

Figure 6.3 supplement. *Model stratification by surgical technique, 8000 iterations.* ***Panel A = Standardized Effect Size plot.*** *The weighted ASMD values were lower than 0.20 in all cases.* ***Panel B = Quantile-quantile (Q-Q).*** *Before weighting, most of the values were below the 45-degree line. A good balance was achieved after weighting, with p-values that lie close the 45-degree line.*

Types of neurologic injury and outcome

Considering the entire cohort, 306 (7.2%) patients in the SL group had at least one neurological injury: ICH in 161 patients (3.8%), AIS in 73 patients (1.7%), seizures in 52 patients (1.2%; 44/52 clinically determined) and BD in 44 patients (1.8%) (Table 6.2 – Figure 6.1). One hundred-eighty-nine (7.7%; OR 1.10 [0.91–1.32]; p = 0.33 vs. SL group) patients in the DL group had at least one neurological injury: ICH in 99 patients (4.0%; OR 1.09 [0.84–1.41]; p = 0.51 vs. SL group), AIS in 42 patients (1.7%; OR 1.01 [0.69–1.49]; p = 0.92 vs. SL group), seizures in 33 patients (1.3%; 27/33 clinically determined—OR 1.10 [0.72–1.67]; p = 0.66 vs. SL group) and BD in 44 patients (1.8%; OR 1.02 [0.71–1.48]; p = 0.92 vs. SL group) (Table 6.2 – Figure 6.1). When comparing DL to SL configuration, the ATE for the

occurrence of least one neurological complication was 0.005 (95% CI − 0.009 to 0.018; p = 0.50), for ICH was 0.003 (95% CI − 0.007 to 0.013; p = 0.50), for AIS was 0.001 (95% CI − 0.007 to 0.007; p = 0.95), for seizures was 0.001 (95% CI − 0.005 to 0.006; p = 0.81) and for BD was − 0.002 (− 0.008 to 0.005; p = 0.63). The overall survival rate was lower in the DL than the SL group (64.0% vs. 60.8%, p = 0.002—Table 6.3—ATE: 0.033 [0.008–0.059]; p = 0.01). However, survival was similar among DL and SL among all the subgroups of neurological injuries (Table 6.3). When comparing DL to SL configuration, the ATE for survival in patients with at least one neurological complication was − 0.046 (− 0.127 to 0.035; p = 0.27).

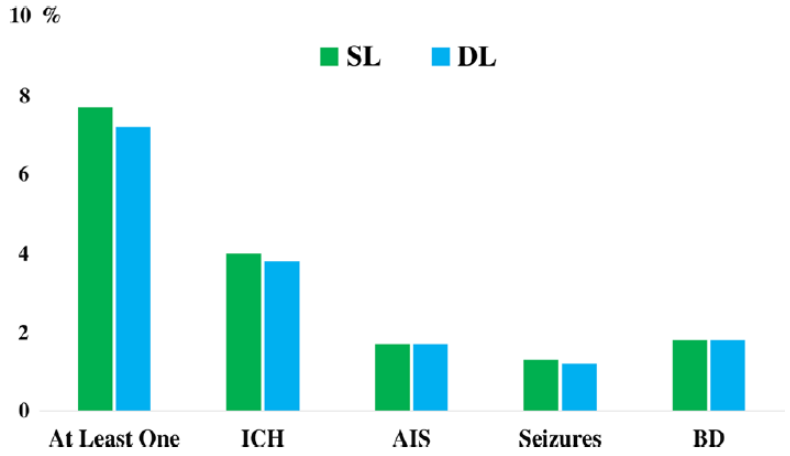

Figure 6.4. Occurrences of various neurological injuries in the study population, according to the cannulation strategy. DL dual lumen, SL single lumen.

Variable	DL N = 2467	SL N = 4367	OR	Lower 95% CI	Upper 95% CI	p value
Patients with CNS Complications	189 (7.7%)	306 (7.2%)	1.10	0.91	1.32	0.33
ICH	99 (4.0%)	161 (3.8%)	1.09	0.84	1.41	0.51
AIS	42 (1.7%)	73 (1.7%)	1.01	0.69	1.49	0.92
Seizures	33 (1.3%)	52 (1.2%)	1.10	0.72	1.67	0.66
Brain death	44 (1.8%)	76 (1.8%)	1.02	0.71	1.48	0.92

DL double lumen cannula, *SL* single-lumen cannula, *OR* odds ratio, *CI* confidence intervals, *ICH* intracranial hemorrhage, *AIS* acute ischemic stroke, *CNS* central nervous system

Table 6.2. *Neurologic complications according to the cannulation strategy, before weighing using a propensity score.*

Discussion

In this study based on a large international registry, we observed that DL V-V ECMO cannulation was associated with a similar occurrence of neurological complications than SL cannulation. Also, mortality was higher in the SL group, but similar across different types of neurological injury, regardless of the type of cannulation. DL cannulation has several potential advantages over traditional cannulation, including easier ambulation and reduced recirculation. However, it remains unclear whether this approach would increase the risk of specific complications in such patients. We analyzed a large registry including ECMO centers which report routinely their data; also, using a matching method, we compared similar populations of patients undergoing V-V ECMO and receiving two different type of cannulation. In this study, DL cannulation was associated with a similar incidence of neurological complications than DL. Few data are available on the occurrence of seizures in adult patients undergoing V-V ECMO. In a recent study including 139 patients undergoing both veno-arterial (V-A) and V-V ECMO concomitantly with EEG monitoring, Peluso et al. reported an 8% occurrence of seizures or status epilepticus [19], which

was independent from ECMO configuration. Nevertheless, no DL cannulation was used in this cohort. In a large registry analysis (N = 4988), Lorusso et al. reported 60 patients with seizures (1.2%), mostly being clinically diagnosed [7]. The use of EEG monitoring has already shown to increase the detection of seizures, which are mainly non-convulsive in critically ill patients [20]; unfortunately, in many ECMO centers continuous EEG monitoring is not routinely implemented or not available, and the real occurrence of seizures might have been largely underestimated. Also, as some seizures were "clinically determined", it remains unknown whether they were convulsions or other forms of abnormal movements, which might occur in critically ill patients. Moreover, few studies have tried to assess the causes of epileptic complications in ECMO patients. If in critically ill patients admitted for medical causes, sepsis, drug toxicity, metabolic disturbances or discontinuation of antiepileptic drugs have been associated with a higher probability of seizures [21–23], our study was unable to assess those factors and suggested no additional role for the selection of cannulation on the occurrence of such complication.

Variable	DL *N* = 2467	SL *N* = 4367	OR	Lower 95% CI	Upper 95% CI	*p* value
Discharged alive, all	1580 (64.0)	2595 (60.8)	1.13	0.96	1.34	0.002
Discharged alive, ICH	21/99 (21.0%)	35/161 (21.7%)	0.96	0.52	1.78	>0.99
Discharged alive, AIS	7/42 (16.6%)	24/73 (32.8%)	0.41	0.16	1.03	0.08
Discharged alive, seizures	13/33 (39.4%)	26/52 (50.0%)	0.65	0.28	1.56	0.38
Discharged alive, CNS complications	38/189 (20.1%)	79/306 (25.8%)	0.72	0.46	1.11	0.16

DL double lumen cannula, *SL* single-lumen cannula, *OR* odds ratio, *CI* confidence intervals, *CNS* central nervous system

Table 6.3. *Patient outcomes, according to the cannulation strategy, before weighing using a propensity score*

In this study, the occurrence of other type of neurological injuries, such as intracranial hemorrhage, acute ischemic infarction and brain death, was

also similar between DL than SL cannulation. A previous analysis of a French cohort consisting of 135 consecutive patients undergoing V-V ECMO showed that 14.1% had a neurologic injury [5]. The majority of these events were ICH, with only a small number of ischemic strokes or diffuse microbleeds. In the present study, with more than 2000 patients included, the total number of neurological events was less than half when compared to that previously reported [5, 7]. Of course, differences in age, indications for ECMO, use of anticoagulation, the presence of previous neurological diseases and different policies to obtain cerebral CT scan might also explain these findings. The pathophysiology of neurologic injury during V-V ECMO is complex with many processes potentially playing a role. These include frequent changes in PaO2 and PCO2, that can affect cerebral blood flow, formation of cerebral micro-emboli and venous congestion from cannulation of the internal jugular veins. Furthermore, abrupt changes in local and systemic blood pressure, ischemia/reperfusion, anticoagulation and venous hypertension caused by distal internal vein ligation have also been reported to play a contributory role [24, 25]. To date, there are few detailed investigations of cerebral blood flow and cerebral venous return in ECMO patients. In one study of pediatric ECMO patients, cerebral blood flow velocities were below normal ranges [26]; the authors of this study concluded that reduced blood flow velocities could be due to the decreased cerebral metabolic demands associated with sedation, cerebral venous congestion, or reduced cardiac function during ECMO. Future studies using more precise assessment of cerebral blood flow (i.e. cerebral CT-perfusion) in association with additional neuromonitoring are necessary

to understand the pathophysiology of neurological complications in ECMO patients and potentially help for their prevention. DL cannulas in adults are large, because both the inflow and outflow cannulas must be accommodated within a single catheter. This provides the advantage in that only one vein needs to be accessed to provide full ECMO support to the patient. However, it is unclear whether large cannulas can be safely accommodated in the internal jugular veins without affecting cerebral blood flow dynamics. Cases of cerebral edema have been previously reported with internal jugular vein thrombosis, particularly when the contralateral internal jugular vein is hypoplastic or compromised [27]. In one small study of neurosurgical patients who had continuous intracranial pressure monitoring, cannulation of the right internal jugular vein was not associated with increases in intracranial pressure [28]. However, a previous case report indicated that bilateral cannulation in the internal jugular vein should be avoided, since it can increase the risk of intracranial hypertension due to impaired venous drainage. This could ultimately have repercussions on intracranial blood volume and pressure [29]. Recently, Sutter et al. [30] published a systematic review on neurological complication during VA and VV ECMO support, and they observed a similar proportion of neurological complications than in our study, with a higher incidence in patients treated with VA ECMO respect VV ECMO. Moreover, they observed a eightfold increased risk for AIS if the pre-ECMO lactates were above 10 mmol/L and a 18-fold increased risk for ICH in patients with thrombocytopenia. These additional factors should be taken into consideration for future studies dealing with the association of

neurological complications and type of cannulation in ECMO patients. Importantly, the findings of this study should be approached with caution, since there are several important limitations in our analysis. First, a number of centers use large return cannulas with DL cannulation (i.e. 25–27 French or greater) [31], so that the risk in terms of jugular vein obstruction would be similar in the two study groups. Unfortunately, the ELSO database does not contain data on cannula size for all patients, so we do not know how many patients in the SL group had large size return cannulas and could not adjust our analysesaccordingly. Secondly, we do not know how many patients in each group had bilateral internal jugular vein cannulation; it is possible that a significant number of patients in both groups had a contralateral central venous catheter placed for vasoactive medication infusion or for other purposes and this might also contribute to alter the cerebral venous return. Thirdly, neurologic events are likely to be under-reported in the ELSO database because neurologic events during ECMO are often unrecognized or not confirmed. Obtaining magnetic resonance imaging scans is not feasible in ECMO patients and many patients are not taken for computed tomography scans because of the technical difficulties in moving ECMO patients or their inherent hemodynamic or respiratory instability. Forth, some other factors, including changes in PaCO2 after ECMO implementation, pre-ECMO bilirubin levels or the use of renal replacement therapy [32], have been associated with a higher risk for neurological complications in VV ECMO patients but were not available in our database. Finally, although reporting data to the ELSO database, it remains unknown whether participating centers had similar practices in

managing ECMO patients as treatment variability might represent a significant confounder for our findings. Our study also has important strengths. First, it is the largest study to examine whether DL ECMO cannulation is associated with an increased rate of adverse neurologic events. Furthermore, we used data from a well-established registry that has quality controls in place and represents a worldwide population. Finally, we used a propensity matching score to reduce imbalances between groups.

Conclusions

Our findings showed that DL cannulation during V-V ECMO was not associated with an increased risk of neurological complications when compared with SL. Despite a higher survival rate in patients treated with DL, no differences in survival between the two cannula configurations were observed when patients with neurological injury were analyzed. Additional prospective studies should be encouraged to compare the effects of VV-ECMO cannulation on neurological events.

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Chapter 7.

General Discussion

In this thesis we studied which is the most crucial factor that affect the safeness of the mechanical ventilation during ECMO for ARDS patients and we describe which could be a safer pattern of settings. It has been proved that the respiratory rate is an independent variable of mortality, despite the mechanical power. Mechanical power (MP) is a useful parameter to describe and quantify the forces applied to the lungs during mechanical ventilation (MV).

Chapter 2: in our multi-center, prospective, observational study, we analyzed MP variations following MV after veno-venous extra-corporeal membrane oxygenation (VV ECMO) initiation. We also investigated whether the MV parameters (including MP) in the early phases of VV ECMO run may be related to the intensive care unit (ICU) mortality. Thirty-five patients with severe acute respiratory distress syndrome were prospectively enrolled and analyzed. After VV ECMO initiation, we observed a significant decrease in median MP (32.4 vs. 8.2 J/min, $p < 0.001$), plateau pressure (27 vs. 21 cmH2O, $p = 0.012$), driving pressure (11 vs. 8 cmH2O, $p = 0.014$), respiratory rate (RR, 22 vs. 14 breaths/min, $p < 0.001$), and tidal volume adjusted to patient ideal body weight (VT/IBW, 5.5 vs. 4.0 mL/kg, $p = 0.001$) values. During the early phase of ECMO run, R (17 vs. 13 breaths/min, $p = 0.003$) was significantly higher, while positive end-expiratory pressure (10 vs. 14 cmH2O, $p = 0.048$) and VT/IBW (3.0 vs. 4.0 mL/kg, $p = 0.028$) were lower in ICU non-survivors, when compared to the survivors. The observed decrease in MP after ECMO initiation did not influence ICU outcome. Waiting for large studies assessing the role of these

parameters in VV ECMO patients, RR and MP monitoring should not be underrated during ECMO.

Chapter 3: we tested on an animal model a new volumetric capnometer, which was designed for the ECMO oxygenator, with the aim of giving to the user the values of V'CO2ML in real time, as to understand which the CO2 removal is done by the ECMO and which is the efficiency of the oxygenator. In fact, ECMO constitutes a complex support modality, and accurate monitoring is required. An ideal monitoring system should promptly detect ECMO malfunctions and provide real-time information to optimize the patient–machine interactions. The new volumetric capnometer that we tested, it enables continuous monitoring of membrane lung carbon dioxide removal (V'CO2ML), to help in estimating the oxygenator performance, in terms of CO2 removal and oxygenator dead space (VDsML). The accuracy and reliability of the prototype of the volumetric capnometer was evaluated for V'CO2ML and VDsML measurements by comparing the obtained measurements from the new device to a control capnometer with the sweep gas values.

Chapter 4: the new tool was fundamental for performing a study, chapter fourth, in which we investigate the total CO2 removal done by the binomial ECMO-Lungs, to understand the single contribution given by the ECMO or by the patient's lungs. In this study we tested an index that could be useful for detect when the patient is ready to be weaned from ECMO support, in terms of CO2 removal, and if combined with the total respiratory system compliance and with the oxygenation performance, it could be a novel way for predicting ECMO liberation. In fact, we demonstrated that an increase

in the V'CO2NL ratio, independently from any change in ventilation could, despite the limitations of the study, indicate an improvement in pulmonary function and may be used as a weaning index for ECMO.

After these three studies about the relationship between the ECMO machine and the patients, we moved to studied deeply some complications that occurs during the extracorporeal support.

Chapter 5: we dedicated a study to explore which are the causes or main determinants of free hemoglobin increase during ECMO. This aspect was selected because the FHb is one of the most important factors that can cause acute kidney injury, systemic inflammation, and alteration of the coagulation. This is retrospective single-center case-series of 35 consecutive adult patients undergoing veno-venous ECMO support at our center between April 2014 and February 2020. Daily plasma free hemoglobin (pfHb) and haptoglobin (Hpt) levels were chosen as hemolysis markers and they were analyzed along with patients' characteristics, daily laboratory findings and corresponding ECMO system variables, as well as continuous renal replacement therapy (CRRT) when administered, looking for factors influencing their trends over time. Among the many settings related to the ECMO support, the presence of CRRT connected to the ECMO circuit has been found associated with both higher daily pfHb levels and lower Hpt levels. After correction for potential confounders, hemolysis was ascribable to circuit-related variables, in particular the membrane oxygenation dead space was associated with a Hpt reduction (B= −215.307, p = 0.004). Moreover, a reduction of ECMO blood flow by 1 L/min has been associated with a daily Hpt consumption of 93.371mg/dL (p = 0.001).

Technical induced hemolysis during ECMO should be monitored not only when suspected, but also during quotidian management and check-ups. While considering the clinical complexity of patients on ECMO support, clinicians should not only be aware of and anticipate possible circuitry malfunctions or inadequate flow settings, but they should also take into account the effects of an ECMO circuit-connected-CRRT, as an equally important key factor triggering hemolysis.

Chapter 6: we explored another ECMO's complication, the neurological ones that are reported to affect the mortality and morbidity of the ECMO patients. Our retrospective observational study based on data from the Extracorporeal Life Support Organization (ELSO) registry, evaluated the differences in the occurrence and the type of neurological complications in adult patients undergoing V-V ECMO when treated with single-lumen (SL) or double-lumen cannulas (DL). The result was the proportion of patients with at least one neurological complication was similar in the SL (306, 7.2%) and DL (189, 7.7%; odds ratio 1.10 [95% confidence intervals 0.91–1.32]; p = 0.33). After weighted propensity score, the ATE for the occurrence of least one neurological complication was 0.005 (95% CI − 0.009 to 0.018; p = 0.50). Also, the occurrence of specific neurological complications, including intracerebral hemorrhage, acute ischemic stroke, seizures, or brain death, was similar between groups. Overall mortality was similar between patients with neurological complications in the two groups. We concluded that the occurrence of neurological complications was not related to the type of cannulation.

As general conclusion, this thesis demonstrate that it could be possible better understand the recovery of the lung of the patient with ARDS supported by ECMO, with the real-time monitoring of the CO2 elimination done by a novel device tested by our team and minimizing the ventilation lung injury. Moreover, we explored two of the most frequent and dangerous complications that occur to ECMO patients, the hemolysis and the neurological injury and we found that the hemolysis could be reduced with a proper use of dialysis machine and with maintenance of low negative drainage pressure, and the choose of the type of cannula (single or double lumen) did not affect the incidence of brain injury or intracranial complications.


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Chapter 8.

Impact

The clinical value of this dissertation is to be found in the extensively approach to the management of the patients with severe ARDS that needs full respiratory support due to the native lungs' failure.

We approached the crucial point about the identification of the most important variable that could affects the outcome of the patients that received an ECMO support due to the respiratory insufficient. The respiratory rate during the first days of ECMO seems to be one of the key point factors to keep under tight control to apply the lungs rest strategy. In this study we highlighted that despite a safe value of mechanical power applied by the ventilator, the respiratory rate could be related to a better outcome in terms of ECMO weaning and mortality. Practically the threshold values that we found was 15 b/min, and the patients that have been ventilated during the VV ECMO support with less the 15 b/min are associated with a statistically significant lower mortality. The logical consequence is that we suggest setting on the ventilator, during an ECMO for respiratory insufficient a respiratory rate lower that 15 b/min.

Moreover, we thought about which is the possible monitored variable that could be used to define which is the support given by the ECMO in terms of CO_2 elimination, that means work of breathing or mechanical power applied, and we concentrated our effort to study the CO_2 removal done by the membrane lung (the oxygenator) and by the native patient's lungs. If the measurement of the CO_2 removal by the lungs ($V'CO_2NL$) is well established with the clinical use of the volumetric capnometer, it is not well assessed for the measurement of the CO_2 removal done by the membrane or artificial lung ($V'CO_2ML$). For this reason, we tested a brand new

volumetric capnometer, in an experimental animal setting, designed and engineered especially for the ECMO. The result of our experimental tests confirmed the value of the new device that can provides the measurement of the V'CO_2ML continuously during the ECMO support. This finding suggest that the clinical implementation of such device is available and trustable, so it was integrated in a commercial device that is already available on the market (Landing monitor, Eurosets srl, Italy).

Starting from this satisfactory result of the new device for the continuous monitoring of the V'CO2ML, we went deeply inside the question about which is the partition between the native lungs and the membrane lung during the ECMO support. Particularly, we studied the CO2 removal during the weaning phase from ECMO, this because in a clinical setting it's fondant to understand which the contribution of the native lungs, as indirect representation of the lung's potential performance and recovery from the respiratory failure. Our pilot study concluded that if the clinicians keep monitored day by day, or better continuously, the ratio between V'CO2 NL and the total V'CO2 (equal to sum of V'Co2ML plus the V'CO2NL) it could be possible to be identified a sort of threshold that is correlated with a successful weaning. This threshold is approximately 50% that describe the moment when the workload for CO2 elimination is done equally by the ECMO e by the patient's lungs. The remarkable data is that the ratio is not statistically correlated with the ventilatory settings or ECMO settings, obviously this was a pilot study and that such important message should be confirmed with a prospective study with a more robust sample size.

After these studies we moved to understand which could be the possible or more frequent or not well-established complication of ECMO support in patient with respiratory failure. So, we analysed the risk of haemolysis during prolonged ECMO support, particularly we tried to identify which component or variables of the extracorporeal support could help the clinicians to reduce or better prevent the haemolysis phenomenon. We analysed 35 consecutive ECMO patients and we tried to discover which are the variables correlated with an important haemolysis. Our results showed that the CRRT machine directly conned tot the ECMO circuit is correlated with an arising of haemolysis sings combined with oxygenator aging. The evident clinical relapse seems to be that if we would like to prevent the arising of haemolysis (and its consequences) we could avoid the connection of the CRRT machine to the ECMO circuit and to check daily the aging of the oxygenator un terms of dead space volume.

Finally, we dedicated our attention to the neurological complication, one of the most dangerous complication during ECMO for respiratory support. Particularly, we analysed the correlation of the cannula's configuration, in terms of comparison between two single lumen cannulas versus the double-lumen cannula configuration. We prepared a retrospective analysis of 6'834 patients included into the ELSO registry, of which the 63.9% with single-lumen cannula configuration and 36.1% with double-lumen cannula configuration. Our main finding was that the choice of the configuration does not affect the incidence and prevalence of the major neurological complications such intracranial bleeding, seizure, acute ischemic stroke or brain death. The clinical relance of this last study is a different conclusion

respect previous reports, in which seems that the double-lumen configuration was associated with an increase incidence of intracranial bleeding. So, the choice of cannulation system could be based only on clinical input and needs, without the risk of improving the probability of neurological complications.

As relevant messages of this thesis we could summarized that the patients with severe respiratory insufficient that need an ECMO support should be ventilated with a respiratory rate lower than 15 b/min; they should be monitored with a volumetric capnometer for the native lungs and membrane lung and when the ratio of total CO2 elimination and the lungs elimination reach the 50% , it could considered as a positive prognostic index for the weaning from ECMO; the haemolysis during ECMO could be prevent avoiding the direct connection of the dialysis machine to the ECMO circuit and monitoring the oxygenator dead space; the neurological complications, particularly the intracranial bleeding incidence, is not correlated with the use of the single double-lumen jugular cannula.

Chapter 9.

Summary

The thesis is focused on the use of Extracorporeal Membrane Oxygenation (ECMO) for the treatment of the respiratory failure. Particularly, it takes in account: 1. Which is the major benefit in term of lung stress, offered by the ECMO support, 2. Validation of a new device, for measuring the carbon dioxide elimination (identified as one of the variables to control the lung recovery), 3. Study of a new parameter to describe the native lungs recovery (or ECMO dependency) in patients with ARDS that underwent to ECMO support.], 4. Which are the impact of the extracorporeal support to the blood rheology, in specific the hemolysis phenomenon and 5. Which are the best configuration, in terms of cannula system, to reduce the risk of neurological complications.

In the first chapter we measured the mechanical power before and after ECMO start in a population of severe ARDS, and we found that the values after the ECMO implantation are below the dangerous values, and it seems that the respiratory rate chosen during ECMO support could be correlated with a higher survival rate

In the second chapter we tested a new volumetric capnometer, created for the ECMO oxygenator/membrane lung (ML), with the capacity of measuring continuously the CO2 removal done by the ML and calculating the ML dead space, to obtain a monitoring og ECMO performance and ML aging. In the third chapter we applied the volumetric capnometry to the patient's native lungs and to the ML, in a population of ECMO patient with respiratory failure. We found that the ratio (RCO2 ratio) between the CO2 elimination provide by the ML (V'CO2ML) and the total V'CO2 produce by the patients (V'CO2 tot) is a good index to detect the right time for ECMO

liberation (ratio > 40%). In the fourth chapter we analyzed the hemolysis produced during prolonged ECMO support and we found that in our patients the factors that cause the hemolysis are the too negative drainage pressure and the dialysis machine connected to the ECMO circuit directly. In the fifth chapter we studied retrospectively the incidence of neurological complications occurred in patient on ECMO support, and we tested the cannula configuration affects the incidence of these complications. We compared the single lumen jugular cannula setting versus the double lumen cannula setting and we confirmed that both approaches are equal safe in terms on incidence of neurological complications.

As conclusion, this thesis demonstrates the safety and efficacy of ECMO as respiratory support for severe ARDS patients and suggested to use a new index, the RCO2 ratio, could help to detect the right time for ECMO liberation, the connection of the dialysis directly to the ECMO circuit enhances the hemolysis and the double lumen jugular cannula is safe as the single lumen approach in terms of neurological complication.

Chapter 10.

Samenvatting

Het proefschrift is gericht op het gebruik van Extracorporale Membrane Oxygenatie (ECMO) voor de behandeling van respiratoire insufficiëntie. Het houdt in het bijzonder rekening met: 1. Wat het grootste voordeel is in termen van longstress, aangeboden door de ECMO-ondersteuning, 2. Validatie van een nieuw apparaat, voor het meten van de kooldioxide-eliminatie (geïdentificeerd als een van de variabelen om de longherstel), 3. Studie van een nieuwe parameter om het natuurlijke longherstel (of ECMO-afhankelijkheid) te beschrijven bij patiënten met ARDS die ECMO-ondersteuning hebben ondergaan.], 4. Welke impact heeft de extracorporele ondersteuning op de bloedreologie, in specifiek het hemolysefenomeen en 5. Welke de beste configuratie zijn, in termen van canulesysteem, om het risico op neurologische complicaties te verminderen.

In het eerste hoofdstuk hebben we het mechanische vermogen gemeten voor en na de start van ECMO in een populatie met ernstige ARDS, en we ontdekten dat de waarden na de ECMO-implantatie lager zijn dan de gevaarlijke waarden, en het lijkt erop dat de ademhalingsfrequentie gekozen tijdens ECMO-ondersteuning zou kunnen zijn gecorreleerd met een hoger overlevingspercentage

In het tweede hoofdstuk hebben we een nieuwe volumetrische capnometer getest, gemaakt voor de ECMO-oxygenator/membraanlong (ML), met de capaciteit om continu de CO2-verwijdering door de ML te meten en de ML-dode ruimte te berekenen, om een monitoring en ECMO-prestaties te verkrijgen en ML-veroudering. In het derde hoofdstuk hebben we de volumetrische capnometrie toegepast op de natuurlijke longen van

de patiënt en op de ML, in een populatie van ECMO-patiënten met respiratoire insufficiëntie. We vonden dat de verhouding (RCO2-ratio) tussen de CO2-eliminatie geleverd door de ML (V'CO2ML) en de totale V'CO2-productie door de patiënten (V'CO2 tot) een goede index is om het juiste moment voor ECMO-bevrijding te detecteren (verhouding > 40%). In het vierde hoofdstuk analyseerden we de hemolyse geproduceerd tijdens langdurige ECMO-ondersteuning en we ontdekten dat bij onze patiënten de factoren die de hemolyse veroorzaken de te negatieve drainagedruk zijn en de dialysemachine die rechtstreeks op het ECMO-circuit is aangesloten. In het vijfde hoofdstuk bestudeerden we retrospectief de incidentie van neurologische complicaties bij patiënten die ECMO-ondersteuning kregen, en we testten of de canuleconfiguratie de incidentie van deze complicaties beïnvloedt. We vergeleken de canule-instelling met enkel lumen versus de canule-instelling met dubbel lumen en we bevestigden dat beide benaderingen even veilig zijn wat betreft de incidentie van neurologische complicaties.

Als conclusie, dit proefschrift demonstreert de veiligheid en werkzaamheid van ECMO als ademhalingsondersteuning voor ernstige ARDS-patiënten en stelt voor om een nieuwe index, de RCO2-ratio, te gebruiken om het juiste moment voor ECMO-bevrijding te detecteren, de directe verbinding van de dialyse met de ECMO-circuit verbetert de hemolyse en de halsslagadercanule met dubbel lumen is veilig als de benadering met één lumen in termen van neurologische complicaties.

Chapter 11.

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Chapter 12.

About the Author

Mirko Belliato is the acting Director of the 2st ICU of Foundation IRCCS Policlinico San Matteo of Pavia Italy, Adjunct Professor of Anaesthesiology and Intensive Care at the Postgraduate School of the University of Pavia, Italy. He obtained his medical degree from the University of Pavia University College as student of "Almo Collegio Borromeo", where he developed an interest in new technologies and their use in medicine. This interest was piqued during his studies of human physiology and his curiosity focused on the deeper understanding of vital life mechanisms. After starting his fellowship at the Physiology Institute, Dr. Belliato focused his interests on artificial organs, respiration and the treatment of lung failure following the teaching of Prof. Antonio Braschi and Prof. Giorgio Antonio Iotti. In addition to practicing medicine under the direction of Prof. Iotti, he has continued his research work in this area over the past 14 years and has participated in clinical and laboratory research projects on intelligent ventilation for lung support and the development of extracorporeal lung and heart support. In 2008, Dr. Belliato became formally involved in the initiation of the ECMO project at the Foundation

IRCCS Policlinico San Matteo. Since 2009, he has been part of the ECMO team in all types of support and in 2014, was conferred the "High Specialty" position as leader of the ECMO respiratory support team. Dr. Belliato leads the ICU multidisciplinary team for respiratory support at Foundation IRCCS Policlinico San Matteo, in addition to his involvement in the ELSO activity as centre coordinator. In 2016, he was appointed as leader of the EuroELSO workgroup for "Innovation on ECMO and ECLS" and is a member of the ELSO adult ECMO and the EuroELSO workgroup for neuromonitoring and from 2019 he is elected member of the Steering Committee of EuroELSO. From September 2017 to June 2020 he was the chief of the Advanced Respiratory Intensive Care Unit, part of the U.O.C. Anestesia e Rianimazione 1, at Foundation IRCCS Policlinic San Matteo of Pavia, Italy, directed by his mentor Prof. Giorgio Antonio Iotti. During the COVID 19 pandemia he founded the COVID sub-intensive care unit and the COVID ICU. At this moment he performed and managed more than 600 ECMO runs both VV ECMO, VA ECMO and the newest VAV ECMO. He was invited to more than 50 national and international scientific congresses as speaker or chair. In the last 15 years, he was the supervisor of more than 30 graduation theses in Medicine, Nursing, Cardio-Vascular Perfusion Courses and for the Specialization thesis in Intensive Care with principal topics were automatic mechanical ventilation, the ECMO support and the ARDS treatment. He is the co-inventor (without any royalty) of a patent concerning a new device on monitoring the ECMO circuit, in collaboration with Antonio Petralia and Nicola Ghelli (Eurosets srl, Italy) with n. 2853IT/MB/FZ/GR. He has published more than 135 scientific publications

mostly with Impact Factor from InCites Journal Citation Reports with H-Index: 27 (Scopus® Elsevier B.V, author ID: 6506458064), 31 (Google Scholar, Google LLC, USA), 22 (Web of Science, Clarivate Analytics, Boston, MA, USA) and i10-Index: 51 (Google Scholar, Google LLC, USA).

Chapter 13.

Publications

Scientific publications with Impact Factor from InCites Journal Citation Reports:

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