Intensive Care Med (2013) 39:838–846
DOI 10.1007/s00134-012-2785-8

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Blood oxygenation and decarboxylation determinants during venovenous ECMO for respiratory failure in adults

Received: 5 April 2012
Accepted: 5 December 2012
Published online: 5 January 2013

Electronic supplementary material
The online version of this article (doi:10.1007/s00134-012-2785-8) contains supplementary material, which is available to authorized users.

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Abstract *Purpose:* This study was designed to optimize the latest generation venovenous (vv)-extracorporeal membrane oxygenation (ECMO)-circuit configuration and settings based on the evaluation of blood oxygenation and CO_2 removal determinants in patients with severe acute respiratory distress syndrome (ARDS) on ultraprotective mechanical ventilation. *Methods:* Blood gases and hemodynamic parameters were evaluated after changing one of three ECMO settings, namely, circuit blood flow, FiO_{2ECMO} (fraction of inspired oxygen in circuit), or sweep gas flow ventilating the membrane, while leaving the other two parameters at their maximum setting. *Results:* Ten mechanically ventilated ARDS patients (mean age 44 ± 16 years; 6 males; mean hemoglobin 8.0 ± 1.8 g/dL) on ECMO for a mean of 9.0 ± 3.8 days) receiving femoro–jugular vv-ECMO were evaluated. vv-ECMO blood flow and FiO_{2ECMO} determined arterial oxygenation. Decreasing the ECMO flow from its baseline maximum value (5.8 ± 0.8 L/min) to 40 % less (2.4 ± 0.3 L/min) significantly decreased mean PaO_2 (arterial oxygen tension; 88 ± 24 to 45 ± 9 mm Hg; $p < 0.001$) and SaO_2 (oxygen saturation; 97 ± 2 to 82 ± 10 %; $p < 0.001$). When the ECMO flow/cardiac output was >60 %, SaO_2 was always >90 %. Alternatively, the rate of sweep gas flow through the membrane lung determined blood decarboxylation, while $PaCO_2$ (arterial carbon dioxide tension) was unaffected when the ECMO blood flow and FiO_{2ECMO} were reduced to <2.5 L/min and 40 %, respectively. In three additional patients evaluated before and after red blood cell transfusion, O_2 delivery increased after transfusion, allowing lower ECMO flows to reach adequate SaO_2. *Conclusions:* For severe ARDS patients receiving femoro–jugular vv-ECMO, blood flow was the main determinant of arterial oxygenation, while CO_2 elimination depended on sweep gas flow through the oxygenator. An ECMO flow/cardiac output >60 % was constantly associated with adequate blood oxygenation and oxygen transport and delivery.

Keywords Extracorporeal membrane oxygenation · Salvage therapy · Shock · Cardiogenic · Outcome predictors · Doppler echocardiography

Introduction

Acute respiratory distress syndrome (ARDS) is a severe lung disease with a high mortality rate [1–4]. Patients acquiring its most severe forms, with severe hypoxemia, have the worst prognosis, and mortality can exceed 60 % [5]. In these situations, extracorporeal pulmonary assistance (oxygenation and CO_2 removal from the blood), also known as extracorporeal membrane oxygenation (ECMO) [6, 7], is a therapeutic option that may minimize the trauma caused by mechanical ventilation (MV) and allow the lungs to rest while recovering. However, most trials evaluating ECMO for this indication over the past few decades [8, 9] have demonstrated no benefit because of the prolonged interval between ARDS onset and assistance initiation, the poor oxygenation and CO_2-removal capacities of the devices used, and the high rate of apparatus-linked complications (significant bleeding resulting from intense anticoagulation required to overcome the poor biocompatibility of the circuits).

In recent years, major progress has been made in the manufacture of ECMO circuits, and they have become more biocompatible, with a higher performance and increased durability. The encouraging results of the CESAR trial [10] and the good outcomes of patients who received the latest generation of ECMO as rescue therapy during the recent A(H1N1) influenza pandemic [11–13] have reignited interest in ECMO for severe ARDS.

This study was designed to optimize the latest generation of venovenous (vv)-ECMO circuit configuration and settings based on an evaluation of blood oxygenation and CO_2 removal determinants in patients with severe ARDS who were on ultraprotective MV with a restrictive transfusion policy.

Patients and methods

This study was conducted between October 2009 and April 2010 in the medical–surgical Intensive Care Unit (ICU) of the Hôpital de la Pitié–Salpêtrière (Paris, France). The protocol was approved by the hospital's Institutional Review Board. Informed consent was obtained from all patients or their surrogates.

Patients

Despite optimized protective MV and other adjuvant treatment (i.e., prone positioning, inhaled nitric oxide, recruitment maneuvers), ten ARDS patients received vv-ECMO due to an arterial oxygen tension/fraction of inspired oxygen (PaO_2/FiO_2) of <80 mmHg and/or severe respiratory acidosis. Additional details are provided in the Electronic Supplementary Material (ESM).

Study protocol

To assess the impact of ECMO settings on blood oxygenation and decarboxylation, as well as hemodynamic parameters, we conducted this study in three stages. First, ECMO flow was gradually decreased from 100 to 80 to 60, and finally to 40 % of its maximum value, while the FiO_{2ECMO} and the fresh gas flow rate were kept at 100 % and 10 L/min, respectively. After a 10-min stabilization period with the ECMO flow returned to its baseline value, FiO_{2ECMO} was gradually reduced from 100 to 90, 80, 70, 60, 50, and finally to 40 %, while the fresh gas flow rate and ECMO flow were maintained at their maximum values. Lastly, after another 10-min stabilization period with the FiO_{2ECMO} returned to 100 %, sweep gas flow was gradually lowered to 10, 8, 6, 4, and finally to 2 L/min, while the ECMO flow and FiO_{2ECMO} were left at their maximum values. During the study, ventilator settings and sedation were unchanged. If the peripheral oxygen saturation (SpO_2) dropped below 80 %, the trial was stopped and ECMO flow, FiO_{2ECMO}, or sweep gas flow was returned to its baseline value. Additional details on data acquisition are provided in the ESM.

Impact of red blood cell transfusion on O_2 content and delivery

The ECMO-flow reduction trial was performed as described above on three additional patients before and after they had received red blood cell transfusion. The time between the two trials was <24 h. At each step of the trial, blood samples for gas analysis were drawn from the right atrium, oxygenator inlet and outlet, and pulmonary and peripheral arteries, and cardiac output was measured with Doppler echocardiography. CaO_2 (arterial O2 concentration), DO_2 (oxygen delivery), and membrane oxygenator O_2 transfer were calculated.

Statistical analyses

Continuous variables were compared with Student's *t* test, the Mann–Whitney *U* test. or analysis of variance (ANOVA), as appropriate. Categorical variables were compared using the chi-square test. Changes in blood gases or hemodynamic parameters when the ECMO settings were modified were compared using repeated-measures ANOVA. Correlations between continuous variables were assessed with Spearman's correlation coefficient. Significance was defined as $p < 0.05$. Statistical analyses were computed with StatView ver. 5.0 software (SAS Institute, Cary, NC).

Results

Study population

Ten patients (mean ± standard deviation; age 44 ± 16 years; 6 males) whose clinical characteristics and ARDS causes are summarized in Table 1 were evaluated. At the time of the study, the mean blood hemoglobin concentration of these ten patients was 8.0 ± 1.8 g/dL, and they had been on MV and ECMO for 9.0 ± 3.8 and 5.1 ± 3.8 days, respectively. The mean Doppler-measured cardiac index was 3.3 ± 0.4 L/min. The ECMO system and ventilator settings during the study are given in Table 2. Six (60 %) patients survived to discharge.

ECMO flow reduction trial

In the ECMO flow reduction trial, the ECMO flow was lowered from its baseline maximum value (5.8 ± 0.8 L/min) to 40 % of the maximum (2.4 ± 0.3 L/min) (Fig. 1). This resulted in a significant decline in mean oxygen pressure [PO_2; 88 ± 24 (maximum ECMO) to 45 ± 9 mm Hg (40 % ECMO); $p < 0.001$] and oxygen saturation [SO_2; 97 ± 2 (maximum ECMO) to 82 ± 10 % (40 % ECMO); $p < 0.001$]. Mean CaO_2 decreased from 10.8 ± 2.2 mL O_2/dL at 100 % ECMO flow to 8.5 ± 2.0 mL O_2/dL at 40 % EMCO flow ($p < 0.001$).

A strong linear correlation existed between the ECMO flow/cardiac output ratio and SaO_2 ($r^2 = 0.69$, $p < 0.0001$) and PaO_2 ($r^2 = 0.80$, $p < 0.0001$). The mean ECMO flow/cardiac output ratios were 76.5 ± 17.8 versus 48.3 ± 9.9 % for patients with SaO_2 ≥90 % or <90 % ($p < 0.001$), respectively, and 84.2 ± 13.2 versus 54.2 ± 14.6 % for patients with PaO_2 ≥60 mmHg or <60 mmHg, respectively, ($p < 0.001$). All patients whose ECMO flow/cardiac output exceeded 60 % had SaO_2 >90 % and/or PaO_2 >60 mmHg (Fig. 2 and ESM 2). Alternatively, decreasing the ECMO flow had no significant effect on arterial PCO_2 (Fig. 1).

FiO_{2ECMO} reduction trial

In the FiO_{2ECMO} reduction trial, the ECMO flow (5.8 ± 0.8 L/min) and sweep gas flow (10 L/min) were maintained at their respective maximum and the FiO_{2ECMO} was decreased. This resulted in a significant reduction of the PO_2 and SO_2 ($p < 0.001$) (Fig. ESM 2). Strong linear correlations were found between FiO_{2ECMO} and SaO_2 ($r^2 = 0.68$, $p < 0.0001$) and PaO_2 ($r^2 = 0.79$, $p < 0.0001$). However, reducing the FiO_{2ECMO} had no impact on arterial PCO_2.

Table 1 Characteristics of the ten patients on ECMO support for acute respiratory distress syndrome

Patient	Sex (M/F)	Age (years)	Height (cm)	Weight (kg)	Body mass index (kg/m^2)	SAPS II	SOFA score	Cause of ARDS	ECMO (days)	MV (days)	ICU stay (days)	Outcome
1	M	33.9	180	103	31.8	52	9	A(H1N1) 2009 pneumonia	8	15	19	DA
2	M	36.8	190	105	29.1	62	10	Bacterial pneumonia	12	22	27	DA
3	M	55.4	170	84	29.1	105	15	Bacterial pneumonia	47	54	54	Died
4	F	26.1	165	66	24.2	50	7	A(H1N1) 2009 pneumonia	47	70	73	DA
5	M	37.3	168	106	37.6	87	13	Bacterial pneumonia	6	29	33	DA
6	M	64.6	170	80	27.7	79	10	A(H1N1) 2009 pneumonia	20	28	33	Died
7	M	41.3	178	72	22.7	63	13	Bacterial pneumonia	16	42	48	DA
8	F	59.5	170	86	29.8	65	11	Post operative	29	40	40	Died
9	F	18.7	165	73	26.8	60	15	Pneumo-renal syndrome	5	32	39	DA
10	F	60.9	165	76	27.9	77	13	Polymyositis	18	27	27	Died
Median (IQR)		39 (35–58)	170 (166–176)	82 (74–99)	29 (27–30)	64 (61–79)	12 (10–13)		17 (9–27)	31 (27–42)	36 (29–46)	

ARDS Acute respiratory distress syndrome, *ECMO* extracorporeal membrane oxygenation, *F* female, *ICU stay* total duration of stay in the intensive care unit (days), *IQR* inter-quartile range, *M* male, *MV* total duration of mechanical ventilation, *SAPS II* Simplified Acute Physiology Score II, *SOFA* Sequential Organ Failure Assessment at admission, *DA* discharged alive

Table 2 Characteristics of the ECMO system, ventilators settings, blood gases and hemodynamic parameters at inclusion

Patient	ECMO setting	Drainage cannula size (Fr)	Return cannula size (Fr)	Distance between cannulas (cm)	ECMO flow (L/min)	Pump speed (rpm)	VT (mL)	PEEP (cmH_2O)	Pplat (cmH_2O)
1	F-J	23	17	18	6.8	4,500	100	8	20
2	F-J	24	19	13	5.6	4,530	200	6	21
3	F-J	24	18	9	5.3	4,530	100	12	26
4	F-SC	24	15	9	4.5	4,530	100	8	22
5	F-J	23	17	14	5.6	4,960	140	10	26
6	F-J	24	19	7	5.3	3,750	100	10	25
7	F-J	24	18	11.5	6.9	5,000	100	8	19
8	F-J	20	18	8	6.8	4,540	120	5	20
9	F-J	24	16	10	6.0	3,500	150	12	21
10	F-J	24	16	20	5.0	4,540	120	10	22
Median (IQR)		24 (23–24)	18 (16–18)	11 (9–14)	5.6 (5.3–6.6)	4,530 (4,508–4,540)	110 (100–135)	9 (8–10)	22 (21–25)

Patient	RR (/min)	FiO_2 (%)	Cardiac index ($L/min/m^2$)	SaO2 (%)	Hb (g/dL)	CaO_{2PA} (mLO_2/dL)	CaO_2 (mLO_2/dL)	DO_2 ($ml/min/m^2$)	Lactate (mmol/L)
1	20	50	3.2	95	12.8	16.6	16.8	527	1.6
2	30	50	3.3	96	7.6	9.3	10.2	303	1.8
3	30	40	3.5	93	7.9	9.9	10.2	342	2.2
4	30	40	2.7	98	8.1	10.8	11.0	292	2.1
5	30	50	2.7	99	6.9	9.4	9.7	255	1.4
6	30	40	3.6	97	8.8	11.8	11.8	422	2.7
7	30	40	3.7	97	7.2	9.4	9.8	352	1.3
8	30	40	3.4	97	7.2	9.5	9.7	329	1.7
9	30	40	3.3	100	6.9	9.6	9.7	316	1.8
10	30	40	3.2	99	6.8	9.6	9.6	304	1.8
Median (IQR)	30 (30–30)	40 (40–48)	3.3 (3.2–3.5)	97 (96–99)	7.4 (7.0–8.1)	9.6 (9.4–10.6)	10.0 (9.7–10.8)	323 (303–349)	1.8 (1.6–2.1)

CaO_{2PA} blood oxygen content in the pulmonary artery, *CaO_2* blood oxygen content in peripheral artery, *DO_2* oxygen delivery per m^2 calculated according to the equation: $DO_2 = (CO \times CaO_2)$/total body surface, where CO is cardiac ouput, *FiO_2* inspired oxygen fraction, *F-J* femoral vein-left jugular vein, *F-SC* femoral vein-right subclavian vein, *Fr* French, *Hb* hemoglobin, *IQR* interquartile range, *PEEP* positive end-expiratory pressure, *RR* respiratory rate, *VT* tidal volume

ECMO sweep gas flow reduction trial

In the ECMO sweep gas flow reduction trial, decreases in the sweep gas flow rate through the membrane oxygenator had no significant impact on arterial PO_2, but they were associated with significantly increased arterial $PaCO_2$ ($p < 0.001$) and systolic pulmonary arterial pressure ($p < 0.001$) (Fig. 3). Right atrium and pulmonary artery occlusion pressures remained unchanged at each gas flow level (data not shown).

Impact of red blood cell transfusion on O_2 content and delivery

Hemoglobin levels for the three patients studied before and after a red blood cell transfusion were 5.1 and 8.1, 8.6 and 11.2, and 7.5 and 10.5 g/dL, respectively. The cardiac index remained stable when the PaO_2, SaO_2, and CaO_2 decreased with reduced ECMO flow (Fig. ESM 3). The CaO_2 and DO_2 were higher after the transfusion (Table 3). Interestingly, while before the transfusion patients tolerated a reduction in the ECMO blood flow to only 60 % of the baseline value, it was possible after transfusion to decrease the ECMO flow to 40 % of the maximum value in two of the three patients while maintaining the SaO_2 in the safe zone (>80 %). Membrane oxygenator O_2 delivery was 104–149 mL/min (Table 3). Blood lactate remained within the normal range during these experiments.

Discussion

The results of this pilot physiological in vivo study demonstrate that, for patients who received vv-ECMO for refractory hypoxemia and whose native lung gas-exchange function was almost completely abolished, the factors determining arterial oxygenation were vv-ECMO blood flow and FiO_{2ECMO}. Specifically, using the femoro–jugular ECMO setting, achieving a vv-ECMO flow of >60 % of systemic blood flow was consistently associated with an arterial blood saturation of >90 % and/or PaO_2 of >60 mmHg. Alternatively, sweep gas flow rate ventilating the membrane lung determined blood

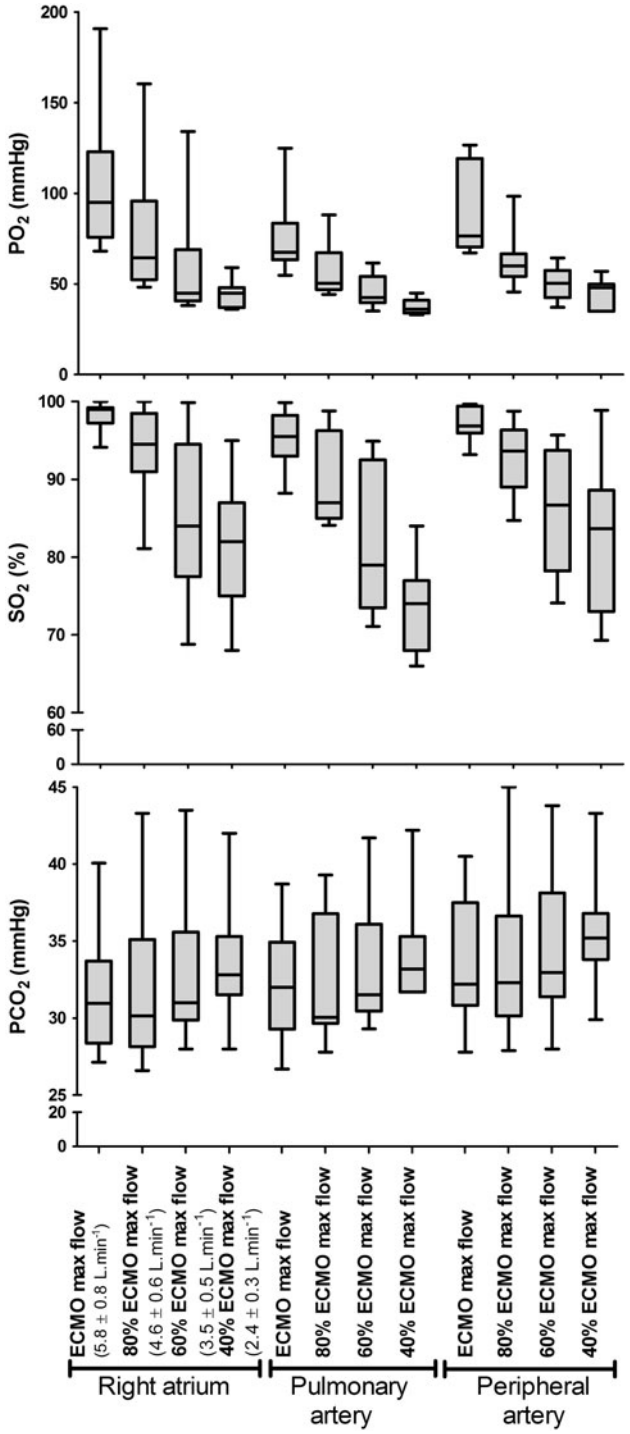

Fig. 1 Whisker plots illustrating the impact of extracorporeal membrane oxygenation (*ECMO*) flow reduction on oxygen pressure (PO_2), oxygen saturation (SO_2) and carbon dioxide pressure (PCO_2) in the right atrium, pulmonary artery, and peripheral artery. The impact was determined during the last step (i.e., 40 % of ECMO maximum flow) for seven patients. *Horizontal line inside box* Median, *upper and lower box limits* 25–75 percentiles, respectively, *T-bars* (*whiskers*) 10–90 percentiles

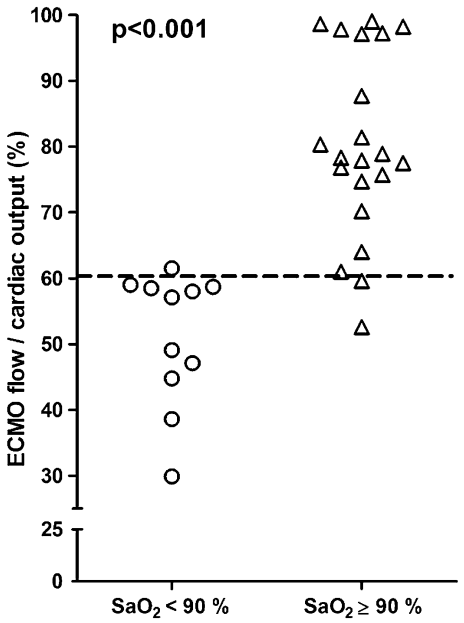

Fig. 2 Percentages of ECMO flow/cardiac output according to patients with a peripheral artery oxygen saturation (SaO_2) of ≥90 % (*triangles*) or <90 % (*circles*) (86.2 ± 26.4 % vs. 53.9 ± 17.7 %, respectively; $p < 0.001$)

decarboxylation, while arterial PCO_2 was unaffected when the ECMO blood flow and FiO_{2ECMO} were reduced to <2.5 L/min and 40 %, respectively. Lastly, high flows obtained through the ECMO circuit permitted adequate oxygen delivery (DO_2) in our anemic patients. Increasing the transfusion threshold to 10 g/dL allowed a higher DO_2 at a lower ECMO flow.

The main determinants of DO_2 to peripheral tissues, which is critical for the preservation of organ function, are hemoglobin concentration, SaO_2, and cardiac output [14]. When DO_2 falls below a critical threshold, oxygen consumption becomes dependent on DO_2 and the lactate concentration may increase, reflecting activation of anaerobic metabolism. To prevent tissue hypoxia in mechanically ventilated ARDS patients, an SaO_2 ≥88 % using high positive end-expiratory pressure (PEEP) and high FiO_2 are recommended [1, 15]. However, when refractory hypoxemia does develop, recourse to vv-ECMO is a reasonable therapeutic option [10, 12, 13, 16, 17]. In that context, blood oxygenation may become completely dependent on membrane-oxygenator oxygen-transfer capability, as was the case for the patients included in our study. Factors determining oxygenator oxygen transfer in this setting are blood-oxygen saturation in the ECMO drainage cannula, hemoglobin concentration, blood flow in the ECMO circuit, and intrinsic membrane-oxygenator properties, which depend on exchange-membrane surface and O_2 diffusibility through hollow microfibers. When the blood flow through the ECMO circuit is >6 L/min, O_2

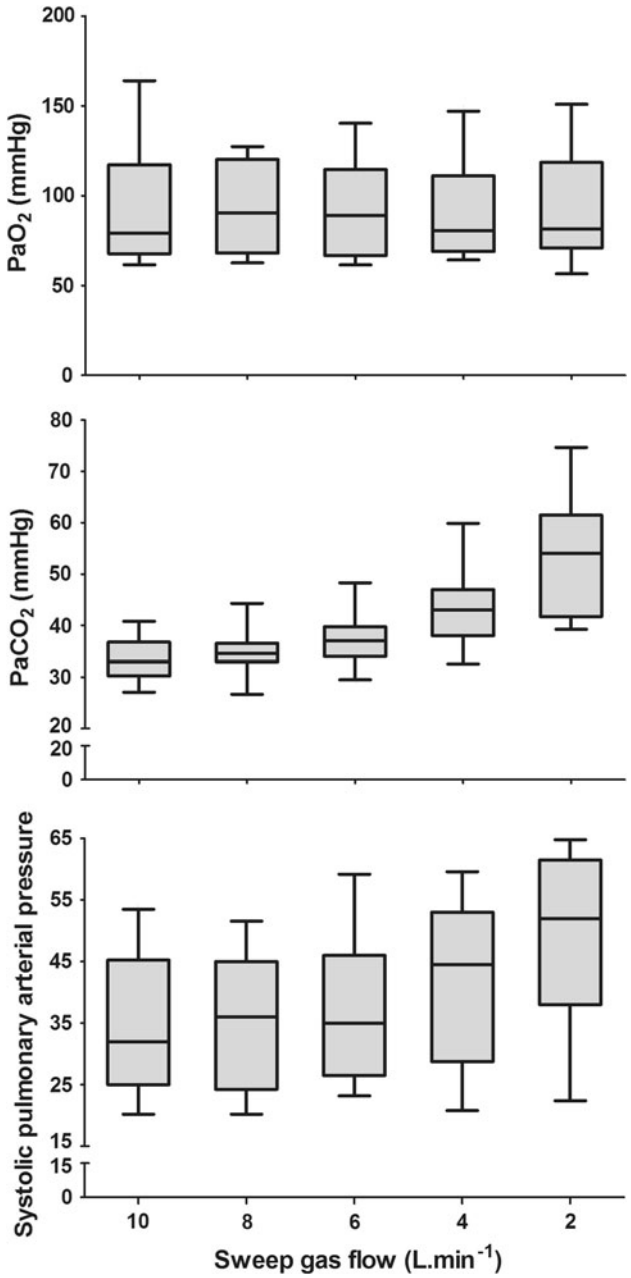

Fig. 3 Whisker plots illustrating the impact of ECMO sweep gas flow reduction on arterial oxygen pressure (PaO_2), arterial carbon dioxide pressure ($PaCO_2$), and systolic pulmonary arterial pressure (sPAP). Decreasing the sweep gas flow through the membrane oxygenator had no significant impact on PaO_2, but was associated with significantly increased $PaCO_2$ ($p < 0.001$) and sPAP ($p < 0.001$). *Horizontal line inside the box* Median, *upper and lower box limits* 25–75 percentiles, respectively, *T-bars* (*whiskers*) 10–90 percentiles

transfer through the Quadrox® oxygenator (Quadrox, Henderson, NE) is theoretically >400 mL of O_2/min, while oxygen saturation in the ECMO drainage canula is 70 % and hemoglobin concentration is 15 g/dL [18].

However, since both drainage and return cannulae are positioned within the venous system in vv-ECMO, blood recirculates into the oxygenator, i.e., some of the returned blood is once again drained into the circuit instead of passing through the right heart, thus markedly reducing O_2 transfer efficiency [19]. To minimize blood recirculation, the circuit can be configured in several ways [16, 17]. In the bi-femoral configuration, the drainage cannula is positioned in the inferior vena cava and a femoral return cannula is advanced to the right atrium. However, 50 % of the patients who received bi-femoral vv-ECMO for A(H1N1)-induced ARDS in the ANZICS ICUs also needed a second (jugular) drainage cannula because of insufficient blood drainage [13].

Alternatively, a single bicaval dual-lumen cannula (Avalon Elite®; Avalon Laboratories, Los Angeles, CA) can be inserted via the right jugular vein and positioned to allow drainage from the inferior and superior vena cavae; oxygenated blood then returns via a second lumen to the right atrium [20]. This configuration minimizes blood recirculation, but insertion of the jugular catheter requires an experienced and skilled operator, as well as recourse to fluoroscopy or trans-esophageal echocardiography guidance for correct positioning. Because >50 % of our vv-ECMO patients receive emergency ECMO support at primary-care hospitals by our institution's Mobile Circulatory/Respiratory Assistance Unit, we chose the femoro–jugular set-up for vv-ECMO, which is the most simple and rapid configuration. To minimize blood recirculation, it is important to ascertain that the tip of the return cannula is positioned away from that of the inflow cannula. Indeed, the mean distance between the two cannulae was 13 cm in our patients.

We chose the femoro–jugular configuration because it has also been shown that, compared to the jugulo–femoral set, it provides higher maximum ECMO flow and higher pulmonary artery mixed venous oxygen saturation and requires comparatively less flow to maintain an equivalent mixed venous oxygen saturation [21].

In terms of improving blood oxygen transfer in the oxygenator and increasing oxygen transport to peripheral organs, our findings demonstrate that in addition to the ECMO cannula configuration, ECMO flow through its circuitry is the major determinant of blood oxygenation. An ECMO flow of >60 % of systemic blood flow obtained adequate peripheral oxygenation. Thus, depending on patient size, cardiac output, oxygen consumption, and lung shunt, a circuit blood flow of 4–7 L/min will typically be required to achieve arterial oxygen saturations of >88–90 %, while maintaining safe lung ventilation. Therefore, large-sized (24–30 Fr) and multi-holed drainage cannula should be preferred to obtain high flows with reasonable negative pressure in that cannula. Indeed, when small cannulae are used with high flows, the suction created by the centrifugal pump

Table 3 Characteristics of the ECMO system and blood O_2 content and delivery in three patients before and after blood transfusion

$N = 3$ patients	Mean hemoglobin = 7.0 g/dL		Mean hemoglobin = 9.9 g/dL	
	Max ECMO pump flow	Min ECMO pump flow	Max ECMO pump flow	Min ECMO pump flow
Pre oxygenator SaO_2 (%)	81.2 (63.2–93.7)	62.5 (60.6–65.3)	84.9 (80.2–87.6)	74.6 (63.9–88.5)
Post oxygenator SaO_2 (%)	100 (100–100)	100 (100–100)	100 (100–100)	100 (100–100)
Pre oxygenator PO_2 (mm Hg)	37 (30–42)	28 (26–29)	42 (38–45)	34 (27–45)
Post oxygenator PO_2 (mm Hg)	449 (427–484)	400 (327–444)	449 (410–493)	375 (323–423)
Pre-oxygenator CaO_2 (mL O_2/dL)	8.0 (4.4–10.1)	6.0 (4.2–7.6)	11.5 (8.8–13.2)	10.2 (7.0–10.9)
Post oxygenator CaO_2 (mL O_2/dL)	9.6 (6.9–11.7)	9.6 (6.9–11.7)	13.5 (11.0–15.2)	13.5 (11.0–15.2)
ECMO pump flow (L/min)	6.8 (5.6–7.6)	4.2 (3.4–4.9)	6.8 (5.6–7.6)	3.1 (2.3–4.5)
Circuit oxygen delivery (mL/min)	106 (49–182)	149 (115–193)	134 (113–153)	104 (100–112)
Arterial CaO_2 (mL O_2/dL)	9.2 (6.1–11.4)	8.4 (5.5–10.9)	13.3 (10.6–15.1)	12.0 (8.7–14.4)
DO_2 (ml/min/m^2)	358 (234–434)	308 (190–391)	516 (399–583)	441 (309–532)
Estimated[a] DO_2/VO_2	2.9 (1.9–3.6)	2.6 (1.6–3.3)	4.3 (3.3–4.9)	3.7 (2.6–4.4)

PaO_2 Arterial oxygen pressure, *SaO_2* peripheral artery oxygen saturation
Data are presented as the mean with the range given in parenthesis
[a] Based on an estimated VO_2 (oxygen uptake) of 120 mL/min/m^2

can cause excessive depression and cavitation in the inflow line, resulting in massive intravascular hemolysis [16, 17].

The other important parameter that can be manipulated to enhance tissue DO_2 and maximize oxygen transfer through the membrane oxygenator is the blood hemoglobin concentration [14]. Guidelines from the Extracorporeal Life Support Organization (ELSO) and the CESAR trial recommend maintaining a normal hematocrit (40–45 %) and hemoglobin concentrations at 14 g/dL, respectively, for patients on ECMO support [10, 22]. However, critically ill patients, and especially those already suffering from diffuse alveolar damage, may be at high risk of transfusion-related acute lung injury [23–25]. The transfusion of blood products increases volume, which might also complicate the ARDS course, as a slower improvement in lung function and a longer MV duration were reported when a liberal fluid-management strategy was applied to patients with acute lung injury [26].Therefore, at our hospital, we have been applying a restrictive transfusion strategy with the red blood cell transfusion threshold set at 7–8 g/dL in most patients on EMCO. Herein, despite a mean hemoglobin concentration and DO_2 of 7–8 g/dL and 300–350 mL/min/m^2, respectively, each patient in our study had adequate SaO_2, and no sign of an oxygen uptake (VO_2)/DO_2 mismatch was observed. Nevertheless, in patients for whom SaO_2 and DO_2 remain low despite maximal ECMO flow or when high ECMO flows induce marked hemolysis, increasing the transfusion threshold to 10 g/dL might re-establish a sufficient oxygen reserve and adequate DO_2 and allow lower ECMO flows.

CO_2 transfer through the membrane lung also depends on ECMO flow, with the maximum transfer being >300 mL/min when the ECMO flow is >6 L/min with the Quadrox® oxygenator. However, since CO_2 diffuses 20-fold faster than O_2, large amounts of CO_2 can be exchanged through the membrane lung even when flow through the circuit is low. This capacity was confirmed by our results showing that $PaCO_2$ remained unchanged when ECMO blood flow was lowered to <2.5 L/min. Indeed, this property is the basis for developing low-flow extracorporeal CO_2-removal devices, whose CO_2 removal rate is 30–70 mL/min at blood flows of only 300–450 mL/min [27, 28]. Alternatively, sweep gas flow across the oxygenator is the main determinant of CO_2 removal by ECMO. We observed a $PaCO_2$ increase from 33 to 50 mmHg when the sweep gas flow was reduced from 10 to 2 L/min, which was paralleled by a significantly higher pulmonary artery pressure. While we observed no PaO_2 change when sweep gas flow was decreased, a recent experimental study involving six patients treated with vv-ECMO and neurally adjusted ventilatory assist during the recovery phase of ARDS [29] reported that a 50 % reduction of the maximal sweep gas flow for 30 min resulted in a significant increase in the minute ventilation and PaO_2 through the recruitment of previously non-ventilated areas. Indeed, Kolobow et al. [30] had shown in the 1970s that minute ventilation is directly coupled to extracorporeal CO_2 elimination, and Karagiannidis et al. [29] confirmed that the main factor determining the upregulation of ventilation was not oxygenation, but the respiratory drive to achieve CO_2 homeostasis and pH. The differences in PaO_2 variation between that latter study and our findings can be explained by our patients having been evaluated during the early acute phase of ARDS, when deeply sedated; minute ventilation could therefore not be improved.

Some limitations of our study must be noted. First, all of our patients were hemodynamically stable with no catecholamine infusion during the study. Patients with ARDS caused by severe sepsis or septic shock might have higher cardiac output and impaired peripheral oxygen extraction. In that situation, even ECMO flows of up to

6 L/min might not achieve adequate blood oxygenation and DO_2, particularly if the pulmonary gas-exchange capacity is severely impaired and ultraprotective (low volume, low pressure) MV is applied. In that context, every effort to decrease VO_2 should be made (i.e., fever control, muscle paralysis), and the transfusion threshold should possibly be increased to >10 g/dL. Second, the use of a single double-lumen cannula was associated with less blood recirculation and a greater efficiency of the membrane oxygenator. Using this type of cannula might enable lower ECMO blood flow to reach similar oxygenation objectives. Third, when this study was conducted, we were using drainage cannulae with a smaller diameter(mean 23 Fr) compared to those used at the present time. We now use a 29-Fr multi-perforated femoro-atrial drainage cannula, which allows better blood drainage, enables a lower suction pressure, and is associated with less blood trauma. Under these conditions, reaching an ECMO blood flow of 6.5–7 L/min is possible with the drainage pressure remaining above −100 mmHg. Lastly, hemodynamic and blood-gas measurements in deeply sedated patients were obtained after a 10-min stabilization period. Therefore, we cannot exclude the possibility that signs of tissue hypoxia might have been observed if a longer stabilization period had been used and patients had received less sedation.

In conclusion, we demonstrated that in our patients with ARDS, ECMO flow was the main determinant of arterial oxygenation supported by vv-ECMO, while CO_2 elimination mainly relied on sweep gas flow through the oxygenator. The femoro-jugular ECMO configuration we used permits easy and rapid vascular access that is well adapted to the emergency and patient-retrieval setting, and high ECMO flows when large-diameter drainage cannulae are used. In the context of our study, with hemoglobin maintained at around 7–8 g/dL for preventing transfusion-associated lung injury and worsening of lung damage, an ECMO flow/cardiac output ratio of >60 % was constantly associated with adequate blood oxygenation and oxygen transport and delivery. Increasing the transfusion threshold to 10 g/dL might re-establish adequate DO_2 in patients for whom the SaO_2 and DO_2 remain low despite maximal ECMO flow.

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