Is Extracorporeal CO_2 Removal Really "Safe" and "Less" Invasive? Observation of Blood Injury and Coagulation Impairment during ECCO2R

Johannes Kalbhenn,* Nadine Neuffer,* Barbara Zieger,† and Axel Schmutz*

Extracorporeal CO_2 removal (ECCO2R) is promoted with attributes like "safe" and "less invasive" compared with (high-flow) venovenous extracorporeal membrane oxygenation (ECMO) systems. With our experience in coagulation disorders during ECMO therapy with this observational study, we for the first time prospectively evaluate hemolysis and coagulation disorders during ECCO2R. Eight consecutive patients with predominant hypercapnic respiratory failure were treated with the Hemolung respiratory assist system (Alung-Technologies, Pittsburg, PA). Bleeding as well as changes of coagulation parameters was prospectively assessed. Overall therapy was observed in seven patients with 52 treatment days. In four of seven patients (57%), relevant clinical bleeding symptoms occurred. Thrombocytopenia, hemolysis, factor XIII deficiency and acquired von Willebrand syndrome (loss of high-molecular-weight von Willebrand factor multimers) were typical findings, and the patients spontaneously recovered after discontinuation of the extracorporeal system. In one patient, extracorporeal system stopped because of thrombotic occlusion. Six of seven patients required transfusion of red blood cells. Our observation shows that even low-flow extracorporeal lung support is associated with relevant clinical bleeding symptoms, blood cell injury, development of acquired von Willebrand syndrome and need for transfusion. In our opinion, it therefore is too early to quote ECCO2R "safe" and "less invasive." *ASAIO Journal* 2017; 63:666–671.

Key Words: ECCO2R, CO_2 dialysis, acquired von Willebrand syndrome, ARDS, bleeding

In the past years, different pump-driven low-blood-flow systems for "CO_2 dialysis," "low-flow extracorporeal membrane oxygenation (EMCO)," or "extracorporeal CO_2 removal" (ECCO2R)[1] have been introduced. Combined with a double-lumen venous catheter and blood flow rates between only 300 and 500 ml/hour, these systems exclusively allow decarboxination without significant improvement of systemic oxygenation in patients with respiratory failure. Potential indications may be the reduction of tidal volumes during mechanical ventilation in acute respiratory distress syndrome (ARDS)[2] and avoidance of intubation in chronic obstructive pulmonary disease (COPD) exacerbation[3,4] or bridging to lung transplant.[5] Some ongoing trials will probably give some support to clearly indicate these systems. The clinical acceptance until now, however, is poor: in a French national survey from January 2010 till January 2015 in 239 intensive care units (ICUs), only 303 patients were found to be treated with ECCO2R.[6]

The first system for ECCO2R was described in 1978 for facilitating low-frequency positive-pressure ventilation in a lamb model.[7] As in this trial, pumpless arteriovenous systems were subsequently assessed mainly in ARDS patients to either lower peak pressure or decrease tidal volume during mechanical ventilation.[8,9] Besides this, venovenous systems have also been developed and evaluated.[10] In contrast to circuits using the pressure gradient between artery and vein to generate blood flow through the membrane, venovenous systems[11] are dependent on a mechanical pump.

Because the catheters used are relatively small and the blood flow with only about 500 ml/min is only one-tenth compared with ECMO, ECCO2R systems are embellished with attributes like "less invasive" and "safe"[12]; some authors even proclaim ECCO2R systems to be used in ICU not experienced with (high-flow) ECMO therapy.[13]

The main complication of (high-flow) ECMO, however, is clinical bleeding in at least every third patient.[14] Besides systemic anticoagulation, various acquired coagulation disorders such as thrombocytopenia, thrombocytopathy, fibrinogen and factor XIII deficiency,[15] and acquired von Willebrand syndrome (AVWS) with loss of high-molecular-weight (HMW) von Willebrand factor (VWF) multimers[16] are typically found in ECMO patients and may be responsible for hemorrhagic diathesis. These disorders partly cannot be monitored using standard coagulation tests or may be masked by heparin therapy, *i.e.*, clinicians observe bleeding symptoms in their patients despite unsuspicious values of International normalized ratio (INR) and activated Partial Thromboplastin Time (aPTT).[17]

This study was designed for the first time to assess the influence of ECCO2R on blood cells and the coagulation system to appraise whether low-flow systems are really "less invasive" with regard to blood injury. We hypothesized that coagulation disorders known from ECMO would also be identified during ECCO2R.

Materials and Methods

Patients with predominant hypercapnic respiratory failure were connected to the Hemolung respiratory assist system (RAS; ALung Technologies Inc, Pittsburg, PA) when indicated by two

From the *Department of Anesthesiology and Critical Care and † Division of Pediatric Hematology and Oncology, Department of Pediatrics and Adolescent Medicine, Medical Center – Faculty of Medicine, University of Freiburg, Freiburg im Breisgau, Germany.

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Correspondence: Johannes Kalbhenn, Hugstetter Strasse 55, 79106 Freiburg, Germany. Email: Johannes.kalbhenn@uniklinik-freiburg.de.

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experienced intensivists between May 2013 and January 2015 in a German university ECMO center. Indications were avoiding endotracheal intubation or facilitating extubation in patients suitable for lung transplant, providing lung protective ventilation in acute respiratory distress syndrome (ARDS), and preventing right-sided heart failure in persistent hypercarbia. With approval by the local ethics committee (EK 26/2013), demographic and specific laboratory details of the patients prospectively were anonymously collected in a registry provided by the manufacturer. According to departmental standards for diagnosis and treatment of ECMO patients, comprehensive laboratory analyses and rotation thrombelastography were performed regularly. Intensive care unit staff prospectively monitored and documented clinical bleeding signs three times a day. The local ethics committee approved the analysis and publication of the data and confirmed that no specific patient's consent was necessary because of the anonymous and observational design of the study (EK 557/15).

ECCO2R System

The Hemolung RAS has been specifically described earlier.[18,19] It consists of one unit in which blood is accelerated as well as gas exchange takes place. Inside this unit, blood flows centrally into a rotating core and is radially pumped through a stationary annular fiber bundle. The rotor is magnetically connected to the motor and the control console. The system is connected to the patient with a dual-lumen 15.5 Fr catheter placed either jugular or femoral into the superior or inferior vena cava. The oxygenator surface area is 0.59 m^2. CO_2 is washed out by a sweep gas flow sucked along the hollow fibers generated by a vacuum pump within the console. Depending on the hematocrit, resulting blood flow is 300–600 ml/min with a maximum rotation speed of 1,400 rpm.

Blood and Coagulation Tests

Blood cell count, INR, and aPTT were determined daily. Patients received unfractionated heparin aiming for an aPTT of 40–50 seconds according to the manufacturer's recommendation. Until the desired aPTT level was achieved, analyses were performed 8 hourly. Rotation thrombelastography was conducted at the time of implantation and at least on days 6 and 8 after implantation and—if possible—after discontinuation of the RAS. On Mondays and Wednesdays, additionally, factor XIII and VWF analyses were performed. Lactate dehydrogenase (LDH) and if available serum-free hemoglobin were determined.

VWF Analyses

Basic analysis was performed by measuring von Willebrand factor activity (VWF:A) and von Willebrand factor antigen (VWF:Ag) and calculating the VWF:A/VWF:Ag ratio.

The comprehensive analyses for diagnosis of AVWS including collagen-binding capacity and separation of HMW VWF multimers have been described earlier.[16] An AVWS was diagnosed if HMW multimers were missing and the VWF collagen-binding capacity (VWF:CB)/VWF:Ag ratio was below the normal range.

Transfusion

Threshold for transfusion of red blood cells (RBCs) was plasma hemoglobin less than 7 g/dl.

Statistical data were collected in Microsoft Excel (Microsoft, Redmond, Washington, DC). Statistical analysis was performed using SigmaPlot for Windows Version 11 (Systat Software Inc., San Jose, CA). Data were analyzed for normal distribution with Shapiro–Wilk test. For the differences between platelet count and Rotem at different time points, a one-way repeated-measures analysis of variance test was applied. To isolate the time points that differ from each other, a pairwise multiple comparison procedure following the Student–Newman–Keuls method was executed. For the before–after analysis of LDH and haptoglobin levels, a paired t-test was applied. A p value of less than 0.05 was chosen as level of significance. Statistical dispersion is presented as interquartile range (IQR) between first and third quartiles.

Results

Eight patients received the RAS. One was excluded because of death within the first 24 hours of treatment caused by unforeseen multiorgan failure. Overall, 52 days of therapy have been observed. Details can be found in **Table 1**.

Patients

In three patients, before potential lung transplant (two with pulmonary fibrosis and one with exacerbated COPD), RAS was implanted because of respiratory acidosis despite noninvasive ventilation. Intubation was prevented in these cases. Two patients had a prolonged weaning after coronary bypass surgery (one of them with COPD stadium gold IV), and RAS was implanted because of persistent respiratory acidosis during lung-protective ventilation. One patient had undergone lobectomy because of pulmonary cancer and had to be reintubated several days later because of muscular weakness despite noninvasive ventilation. Extracorporeal CO_2 removal was initiated to lower the ventilation pressure because of bronchopleural fistula. In one patient, with postaspiration ARDS, RAS was applied to facilitate lung-protective ventilation during prone positioning. One patient was referred to our center with massive bronchial obstruction caused by influenza infection. With invasive ventilation, severe respiratory acidosis persisted and ECCO2R was consecutively initiated.

Table 1. Demographic Details of ECCO2R Group

Demographic Details	Results
Male, n (%)	2 (29)
Female, n (%)	5 (71)
Age (years), median (IQR)	55 (14)
Body weight (kg), median (IQR)	60 (22)
SAPS II, median (IQR)	39 (17.75)
Duration of extracorporeal therapy (days), median (IQR)	8 (5.25)
Duration of ICU therapy (days), median (IQR)	19 (20.5)
Cannulation, n (%)	
Jugular	6 (85)
Femoral	1 (15)
Died during extracorporeal therapy, n (%)	2 (29)
Indication, n (%)	
Bridge to lung transplant or lung transplant evaluation	3 (43)
Respiratory failure after thoracic surgery	3 (43)
Influenza A H2N3	1 (14)

ECCO2R, extracorporeal CO_2 removal; ICU, intensive care unit; IQR, interquartile range; SAPS, simplified acute physiology score.

Hemolung RAS Data

Motor speed was always set to 1,400 rpm. A median blood flow of 496 ml/min (IQR 52) was generated within all days of therapy. The median sweep gas flow was 10 l/min (0.95). The median CO_2 removal rate was 104 ml/min (IQR 19).

Clinical Bleeding Symptoms

In four of seven patients (57%), clinical bleeding was observed: three patients showed abnormal bloody bronchial secretion, two of them also presented with unexpected large hematoma after venous puncture, and one developed tamponade of the urinary bladder because of spontaneous macrohematuria.

Standard Coagulation Parameters and Platelet Count

Median INR and median aPTT of all patients during RAS therapy was 1.05 (IQR 0.16) and 45 (11) seconds, respectively. For anticoagulation, a median of 18.4 thousand IU unfractionated heparin/day (IQR 14.7 thousand) was necessary. Six patients had regular values for platelet count before implantation of the RAS. One already suffered from idiopathic thrombocytopenia. Heparin-induced thrombocytopenia had been ruled out in his case. See **Table 2** for daily details. In all patients, platelets decreased continuously during therapy. This trend is demonstrated in **Figure 1**. Platelet count within all patients showed a normal distribution so means were used in the figure to better demonstrate the platelet drop. The difference of means between the time points days 2, 4, 6, and 8 was significant in each case compared with the mean value before implantation of RAS ($p < 0.001$). There also was a statistical significant difference of each mean value at every time point compared to the former time point calculated with the Student–Newman–Keuls method ($p < 0.001$).

Acquired von Willebrand Syndrome

In five patients, VWF:A and VWF:Ag were determined and VWF:A/VWF:Ag ratio was calculated. All of them developed pathologic values less than 0.73, hinting to AVWS during RAS therapy.

To confirm this, in three of them, additionally comprehensive diagnostics including VWF:CB and multimer analysis were performed before implantation, during, and after explantation of the RAS. They all had a normal VWF:CB/VWF:Ag ratio at the beginning of the extracorporeal therapy and dropped far below 0.7 during the therapy. In combination with a loss of HMW VWF multimers, AVWS was diagnosed. One patient died during the extracorporeal therapy from right-sided heart failure; the other two patients recovered from AVWS within the first day after discontinuation of the RAS. As an example, we demonstrate the course of VWF:CB/VWF:Ag ratio of patient no. 8 in **Figure 2**.

Table 2. Median Values (IQR) of Coagulation Parameters, Days 1–11

	Patients (n)	Platelets (×1,000/µl)	INR	aPTT (seconds)
Before	7	260 (299)	1.04 (0.17)	34 (11)
Day 1	7	219 (191)	1.1 (0.16)	45 (18)
Day 2	7	198 (144)	1.07 (0.13)	48 (8)
Day 3	6	181 (118)	1.05 (0.13)	42 (8)
Day 4	6	179 (62)	1.07 (0.13)	50 (8)
Day 5	5	164 (74)	1.03 (0.15)	49 (18)
Day 6	5	138 (123)	1.07 (0.15)	54 (14)
Day 7	5	152 (146)	1.09 (0.08)	45 (3)
Day 8	5	157 (136)	1.09 (0.08)	47 (6)
Day 9	4	109 (98)	1.00 (0.06)	45 (11)
Day 10	3	156 (75)	0.98 (0.01)	45 (18)
Day 11	2	154 (69)	0.99 (0.0)	49 (2)

IQR, interquartile range.

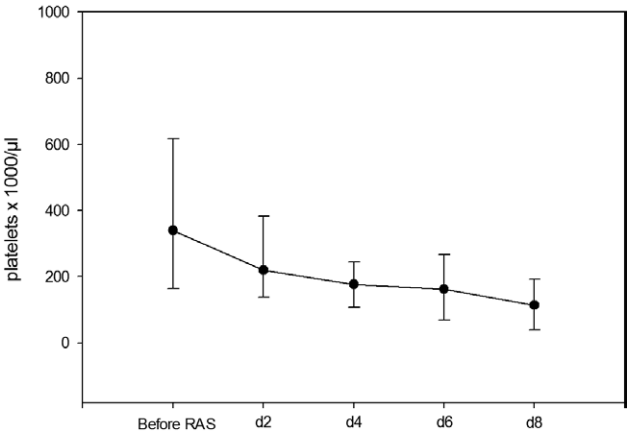

Figure 1. Mean platelet count (IQR) during ECCO2R therapy. $P < 0.001$ for differences of each time point *versus* "before RAS." ECCO2R, extracorporeal CO_2 removal; IQR, interquartile range; RAS, respiratory assist system.

Factor XIII Deficiency

In six patients, factor XIII activity was determined. Median factor XIII activity at the start of the extracorporeal therapy was 66.5% (IQR 9). Four patients (67%) developed factor XIII activity values below 60%, two of them even below 50%. One patient was substituted with factor XIII concentrate (Fibrogammin, CSL Behring, Marburg, Germany) because of clinical bleeding.

Rotem Analysis

Repeated Rotem analysis did not significantly show differences in clot formation between days 1, 5/6, and 8/9. In addition, no case of relevant fibrinogen deficiency or

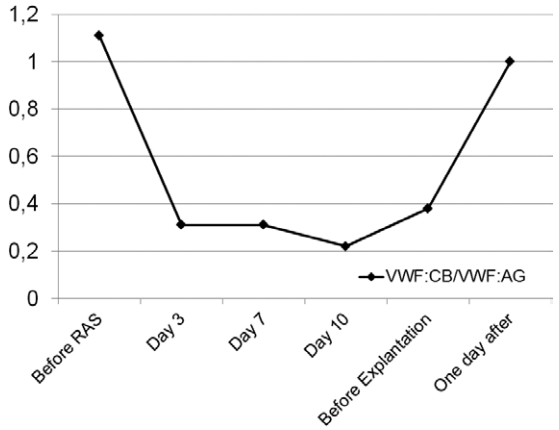

Figure 2. Trend of VWF:CB/VWF:Ag ratio in patient no. 8. VWF:Ag, von Willebrand factor antigen; VWF:CB, VWF collagen-binding capacity.

hyperfibrinolysis was detected. None of the patients received fibrinogen concentrate. Detailed parameters can be found in **Table 3**.

Hemolysis

In five patients, haptoglobin serum levels have been determined. Median haptoglobin was 191 mg/dl (IQR 96) before implantation of the RAS. In all patients, haptoglobin dropped below the limit of detection (< 5 mg/dl) within the first 2 days of therapy.

Median LDH was 428 IU/l (IQR 162) on the first day of RAS therapy and 842 IU/l (IQR 575) before explanting the system. For the differences of haptoglobin (p = 0.06) and LDH (p = 0.133) levels before implantation compared with a time point just before explantation, no statistical significance could be demonstrated because of the small patient groups. In two patients, we repetitively measured free hemoglobin serum levels. One had 0.4 mg/dl (reference: < 5 mg/dl) before RAS and developed values up to 16 mg/dl during the therapy. In the other patient, baseline levels for hemoglobin serum levels were not measured before RAS; however, increased values were found (up to 65 mg/day) during the therapy. All these findings are hinting to hemolysis.

Transfusion

One of seven patients did not need transfusion of blood products. The other six patients received a total of 19 units of RBCs during 43 days of therapy (0.44 units/day). One patient with preexisting thrombocytopenia also received 2 units of platelet concentrates because of clinical bleeding during the therapy. No plasma or fibrinogen concentrate was transfused. For detailed amount of transfused blood products, please see **Table 4**.

Discussion

This observational prospective study for the first time evaluates blood cell injury and acquired coagulation disorders during ECCO2R therapy.

The main findings are that ECCO2R leads to hemolysis, thrombocytopenia, and AVWS (including loss of HMW VWF multimers) as well as factor XIII deficiency. Clinical bleeding symptoms and transfusion are common during ECCO2R therapy.

Blood cell damage and acquired coagulation disorders have been described in high-flow venovenous ECMO therapy. It is well known that ECMO leads to thrombocytopenia and thrombocytopathia,[20–22] fibrinogen and factor XIII deficiency,[23] and AVWS with loss of HMW VWF multimers.[16,23] Bleeding is still the main problem in (high-flow) ECMO patients and is associated with worse survival,[14] and it can hardly be predicted using standard coagulation parameters. There is incomplete data for bleeding during ECCO2R. Braune *et al.*[3] report 11 major and 10 minor bleeding events in 25 COPD patients treated with the iIA activve (Novalung, Heilbronn, Germany) with a mean blood flow of 1.3 l/min. Fanelli *et al.*[2] in their 15 ARDS patients treated with the Hemolung RAS simply do not report bleeding but had a relevant stake of patients transfused with RBCs. In four of seven ECCO2R patients in this study (57%), relevant clinical bleeding was observed. We confirm that the same coagulation disorders known from ECMO appear in ECCO2R and may be responsible for the clinical bleeding.

This finding shows that the quantity of blood flow is not necessarily the main factor for blood injury. We stated earlier that rather contact to the artificial surface per se and negative pressure phenomena, shear stress, and turbulences caused by the design of the extracorporeal system lead to the abovementioned coagulation disorders.[24]

Blood Cell Injury

Negative pressure phenomena, nonlinear flow, and shear stress cause damage to erythrocytes and platelets. In this study, a decrease of platelet count as well as the development of low haptoglobin levels in conjunction with elevated LDH and plasma free hemoglobin levels was observed. This confirms that ECCO2R causes relevant hemolysis.

Acquired Coagulation Disorders

Acquired von Willebrand syndrome has been described to increase the risk of bleeding complications in patients with ventricular assist devices[25] and venoarterial as well as

Table 3. Median Values (IQR) *of All Patients* in Rotation Thrombelastography on Days 1, 5/6, and 8/9

Test	Parameter	Before	Day 5/6	Day 8/9	Standard Value
Intem	CT	190 (197)	212 (64)	232 (22)	100–240 s
	CFT	55 (25)	49 (25)	51 (11)	30–110 s
	A10	70 (5)	69 (2)	68 (8)	44–66 mm
	MCF	75 (4)	75 (25)	74 (6)	50–72 mm
	ML	3.5 (4.8)	1 (0.5)	3 (1)	0–15%
Extem	CT	91 (51)	82 (30)	83 (27)	38–79 s
	CFT	49 (23)	46 (3.5)	49 (12)	34–159 s
	A10	75 (7)	70 (4)	69 (7)	43–65 mm
	MCF	79 (3)	75 (3)	73 (4)	50–72 mm
	ML	3 (5.5)	1 (1.5)	2 (0.5)	0–15%
Fibtem	CT	67 (45)	77 (33)	79 (29)	n.a.
	CFT	54 (53)	54 (16)	50 (15)	n.a.
	A10	40 (15)	39 (8)	34 (10)	7–23 mm
	MCF	45 (16)	41 (10)	37 (11)	9–25 mm
	ML	0 (5.5)	2 (2.5)	0 (2.5)	0–15%

A10: clot firmness after 10 min; CFT, clot formation time; CT, clotting time; IQR, interquartile range; MCF, maximum clot firmness; ML, median lysis; n.a., not applicable.

Table 4. Individualized Amount of Transfused Red Packed Blood Cell Units (RBC) and Platelet Concentrates

				Hemoglobin	
	Runtime (days)	RBC	Platelet Concentrates	Before Implantation	After Explantation
Patient 1	10	7	—	10.7	9.4
Patient 2	2	4	—	9.1	11.8
Patient 4	8	2	2	9.7	8.8
Patient 5	13	2	—	9.3	8.2
Patient 6	6	2	—	9.5	8.6
Patient 7	4	2	—	6.6	7.9
Patient 8	9	0	—	10.7	8.4

Hemoglobin levels (g/dl) before implantation and after explantation of RAS. Patient no. 3 had been ruled out.
RAS, respiratory assist system.

venovenous ECMO.[16,26,27] Acquired von Willebrand syndrome results from increased shear stress caused by turbulent flow within extracorporeal systems. Because of shear stress, VWF is unfolded and subsequently cleaved by the metalloprotease A disintegrin and metalloprotease with thrombospondin-1-like domains 13 (ADAMTS-13).[25,28–30] This results in the loss of the HMW multimers and consecutively decreased binding of VWF to collagen.

As basic tests, VWF:A and VWF:Ag were measured in five of seven patients. Decreased VWF:A/VWF:Ag ratios were found in all of them within 1–3 days of RAS therapy. Comprehensive testing in three of them showed VWF:CB/VWF:Ag ratios between 0.1 and 0.3 and loss of HMW multimers, confirming the diagnosis of severe AVWS. Results were similar to those found in high-flow ECMO.[16,31]

Factor XIII deficiency can be responsible for severe bleeding events in the peri-interventional and perioperative setting, and this pathology cannot be detected by usual coagulation tests such as aPTT or INR.[32,33]

In this study, almost 70% of the patients developed factor XIII deficiency, 28% with factor XIII activity below 50%. In high-flow ECMO, values below 50% are found in 80–90% of patients. Fibrinogen deficiency is reported with an incidence of up to 40% in ECMO patients. In this study, thrombelastography revealed no case of relevant fibrinogen deficiency or fibrinogen clot destabilization. We assume that the relatively small membrane surface of the RAS with 0.59 m^2 may be responsible for this finding: in high-flow ECMO, surface area is relevantly larger (*e.g.*, 1.8 m^2 in the Maquet Quadrox-i-Oxygenator, Maquet Holding, Rastatt, Germany, or 1.2 m^2 in the Sorin-EOS-Oxygenator, Sorin Group, Mirandola, Italy). We did not observe a case of relevant hyperfibrinolysis. Neither standard coagulation tests like INR and aPTT nor rotation thrombelastography were helpful to determine hemorrhagic diathesis.

Transfusion

Only one of seven patients did not require a transfusion of RBCs during ECCO2R therapy. Six patients received a total of 19 units of RBCs during 43 days of therapy (0.44 units/day). There are different reasons why patients suffer from anemia during critical care treatment: alterations in hematopoiesis because of critical illness, hemolysis, blood sample collection for laboratory analyses, and bleeding. In one patient with macrohematuria, the blood loss might have been a relevant cofactor, and for the other patients, hemolysis may be responsible for the increased requirement of RBC transfusion.

Indications for ECCO2R and Setting

The idea of ECCO2R is interesting and technically it works. Nevertheless, this procedure is still missing its clear indication. Recently, ECCO2R was evaluated to facilitate ultraprotective ventilation in patients with moderate ARDS,[2] but of 15 patients included, only 6 were still treated with ECCO2R at the third day of therapy. With a 28 day mortality rate of 48%, outcome in moderate ARDS was not better than in studies without extracorporeal treatment. Extracorporeal CO_2 removal also was applied to avoid intubation in 25 patients with exacerbated COPD.[11] Eleven of them needed intubation during ECCO2R, seven of them because of hypoxemia. Two more patients had to be intubated after explantation of the system.

Two patients developed relevant hypoxic failure during ECCO2R therapy in our study. One had chronic pulmonary disease and it turned out that he was not suitable for lung transplant. Therapy was deescalated and the patient died in due course. The other had to be switched to high-flow venovenous ECMO. Extracorporeal membrane oxygenation cannulation was complicated because the right jugular vein—our preferred location to implant a double-lumen ECMO cannula—was already obstructed by the Hemolung cannula.

Study Limitation

The experience with ECCO2R is still poor. Only 10 of 239 French ICUs used venovenous systems for CO_2 removal.[6] In addition, eight ICUs practiced ECCO2R with two catheters instead of one double-lumen cannula. Some of them had only one patient treated so far.

This single-center study therefore is the largest consecutive observation of the influence of ECCO2R on coagulation with the Hemolung RAS in one of the most experienced ECMO centers in Germany. With only seven patients included, however, future studies including more patients with Hemolung support are needed to give more comprehensive insights on the development of acquired bleeding disorders during ECCO2R support. In our study, we regulated anticoagulation with heparin using the aPTT. It would have been better to monitor antifactor Xa levels as this is a more precise testing than aPTT.[34]

Conclusion

The idea of CO_2 removal with low blood flow rate is interesting, although patient groups taking advantage of this therapy are still not clearly identified. The assumption that ECCO2R

is "less invasive" cannot be supported by the findings of this study: even in the low-flow area of extracorporeal lung support, relevant injury to the blood is traceable. Thrombopenia, hemolysis, factor XIII deficiency, and AVWS with consecutive blood product transfusion are common. In future studies evaluating ECCO2R, these parameters should be taken into concern. From our point of view, it is too early to appraise these systems as "safe." For now, ECCO2R should exclusively be applied in ICUs experiencing hemostaseologic disorders during ECMO therapy.

References

1. Terragni P, Maiolo G, Ranieri VM: Role and potentials of low-flow CO(2) removal system in mechanical ventilation. *Curr Opin Crit Care* 18: 93–98, 2012.
2. Fanelli V, Ranieri MV, Mancebo J, *et al*: Feasibility and safety of low-flow extracorporeal carbon dioxide removal to facilitate ultra-protective ventilation in patients with moderate acute respiratory distress syndrome. *Crit Care* 20: 36, 2016.
3. Braune S, Sieweke A, Brettner F, *et al*: The feasibility and safety of extracorporeal carbon dioxide removal to avoid intubation in patients with COPD unresponsive to noninvasive ventilation for acute hypercapnic respiratory failure (ECLAIR study): multicentre case-control study. *Intensive Care Med* 42: 1437–1444, 2016.
4. Abrams DC, Brenner K, Burkart KM, *et al*: Pilot study of extracorporeal carbon dioxide removal to facilitate extubation and ambulation in exacerbations of chronic obstructive pulmonary disease. *Ann Am Thorac Soc* 10: 307–314, 2013.
5. Bonin F, Sommerwerck U, Lund LW, Teschler H: Avoidance of intubation during acute exacerbation of chronic obstructive pulmonary disease for a lung transplant candidate using extracorporeal carbon dioxide removal with the Hemolung. *J Thorac Cardiovasc Surg* 145: e43–e44, 2013.
6. Deniau B, Ricard JD, Messika J, Dreyfuss D, Gaudry S: Use of extracorporeal carbon dioxide removal (ECCO2R) in 239 intensive care units: results from a French national survey. *Intensive Care Med* 42: 624–625, 2016.
7. Gattinoni L, Kolobow T, Tomlinson T, *et al*: Low-frequency positive pressure ventilation with extracorporeal carbon dioxide removal (LFPPV-ECCO2R): an experimental study. *Anesth Analg* 57: 470–477, 1978.
8. Müller T, Lubnow M, Philipp A, *et al*: Extracorporeal pumpless interventional lung assist in clinical practice: determinants of efficacy. *Eur Respir J* 33: 551–558, 2009.
9. Bein T, Weber-Carstens S, Goldmann A, *et al*: Lower tidal volume strategy (approximately 3 ml/kg) combined with extracorporeal CO2 removal versus 'conventional' protective ventilation (6 ml/kg) in severe ARDS: the prospective randomized Xtravent-study. *Intensive Care Med* 39: 847–856, 2013.
10. Gattinoni L, Pesenti A, Mascheroni D, *et al*: Low-frequency positive-pressure ventilation with extracorporeal CO2 removal in severe acute respiratory failure. *JAMA* 256: 881–886, 1986.
11. Braune S, Sieweke A, Brettner F, *et al*: The feasibility and safety of extracorporeal carbon dioxide removal to avoid intubation in patients with COPD unresponsive to noninvasive ventilation for acute hypercapnic respiratory failure (ECLAIR study): multicentre case-control study. *Intensive Care Med* 42: 1437–1444, 2016.
12. da Rocha AC, da Silva AB, de Brito AB, *et al*: Virulence factors of avian pathogenic Escherichia coli isolated from broilers from the south of Brazil. *Avian Dis* 46: 749–753, 2002.
13. Amilien V, Ponthus JP, Ngasseu P, *et al*: Feasibility of the implementation of a technic of extra-corporeal Co2 removal (ECCO2R) in an intensive care unit which doesn't use ECMO and its real utilization. *Intensive Care Med Exp* 3 (suppl 1): A505, 2015.
14. Zangrillo A, Landoni G, Biondi-Zoccai G, *et al*: A meta-analysis of complications and mortality of extracorporeal membrane oxygenation. *Crit Care Resusc* 15: 172–178, 2013.
15. Kalbhenn J, Wittau N, Schmutz A, Zieger B, Schmidt R: Identification of acquired coagulation disorders and effects of target-controlled coagulation factor substitution on the incidence and severity of spontaneous intracranial bleeding during veno-venous ECMO therapy. *Perfusion* 30: 675–682, 2015.
16. Kalbhenn J, Schmidt R, Nakamura L, Schelling J, Rosenfelder S, Zieger B: Early diagnosis of acquired von Willebrand Syndrome (AVWS) is elementary for clinical practice in patients treated with ECMO therapy. *J Atheroscler Thromb* 22: 265–271, 2015.
17. Panigada M, Artoni A, Passamonti SM, *et al*: Hemostasis changes during veno-venous extracorporeal membrane oxygenation for respiratory support in adults. *Minerva Anestesiol* 82: 170–179, 2016.
18. Batchinsky AI, Jordan BS, Regn D, *et al*: Respiratory dialysis: reduction in dependence on mechanical ventilation by veno-venous extracorporeal CO2 removal. *Critical Care Med* 39: 1382–1387, 2011.
19. Burki NK, Mani RK, Herth FJ, *et al*: A novel extracorporeal CO(2) removal system: results of a pilot study of hypercapnic respiratory failure in patients with COPD. *Chest* 143: 678–686, 2013.
20. Konkle BA: Acquired disorders of platelet function. *Hematology Am Soc Hematol Educ Program* 2011: 391–396, 2011.
21. Görlinger K, Bergmann L, Dirkmann D: Coagulation management in patients undergoing mechanical circulatory support. *Best Pract Res Clin Anaesthesiol* 26: 179–198, 2012.
22. Plötz FB, van Oeveren W, Bartlett RH, Wildevuur CR: Blood activation during neonatal extracorporeal life support. *J Thorac Cardiovasc Surg* 105: 823–832, 1993.
23. Kalbhenn J, Wittau N, Schmutz A, Zieger B, Schmidt R: Identification of acquired coagulation disorders and effects of target-controlled coagulation factor substitution on the incidence and severity of spontaneous intracranial bleeding during veno-venous ECMO therapy. *Perfusion* 30: 675–682, 2015.
24. Kalbhenn J: Hemostasis and extracorporeal membrane oxygenation: bleeding cannot be seen in aliquots. *Crit Care Med* 44: e591–e592, 2016.
25. Nascimbene A, Neelamegham S, Frazier OH, Moake JL, Dong JF: Acquired von Willebrand syndrome associated with left ventricular assist device. *Blood* 127: 3133–3141, 2016.
26. Heilmann C, Geisen U, Beyersdorf F, *et al*: Acquired von Willebrand syndrome in patients with extracorporeal life support (ECLS). *Intensive Care Med* 38: 62–68, 2012.
27. Heilmann C, Geisen U, Beyersdorf F, *et al*: Acquired Von Willebrand syndrome is an early-onset problem in ventricular assist device patients. *Eur J Cardiothorac Surg* 40: 1328–1333, 2011; discussion 1233.
28. Baldauf C, Schneppenheim R, Stacklies W, *et al*: Shear-induced unfolding activates von Willebrand factor A2 domain for proteolysis. *J Thromb Haemost* 7: 2096–2105, 2009.
29. Federici AB, Rand JH, Bucciarelli P, *et al*: Acquired von Willebrand syndrome: data from an international registry. *Thromb Haemost* 84: 345–349, 2000.
30. Mohri H: Acquired von Willebrand syndrome: features and management. *Am J Hematol* 81: 616–623, 2006.
31. Tauber H, Ott H, Streif W, *et al*: Extracorporeal membrane oxygenation induces short-term loss of high-molecular-weight von Willebrand factor multimers. *Anesth Analg* 120: 730–736, 2015.
32. Korte W: F. XIII in perioperative coagulation management. *Best Pract Res Clin Anaesthesiol* 24: 85–93, 2010.
33. Gödje O, Gallmeier U, Schelian M, Grünewald M, Mair H: Coagulation factor XIII reduces postoperative bleeding after coronary surgery with extracorporeal circulation. *Thorac Cardiovasc Surg* 54: 26–33, 2006.
34. Vandiver JW, Vondracek TG: Antifactor Xa levels versus activated partial thromboplastin time for monitoring unfractionated heparin. *Pharmacotherapy* 32: 546–558, 2012.