Hemostatic Changes During Extracorporeal Membrane Oxygenation: A Prospective Randomized Clinical Trial Comparing Three Different Extracorporeal Membrane Oxygenation Systems

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Objective: Extracorporeal membrane oxygenation is a rescue therapy for patients with severe lung failure. Major complications caused by extracorporeal membrane oxygenation are bleeding, thrombosis, and hemolysis. The aim of this study was to compare the impact of different extracorporeal membrane oxygenation systems on blood hemostasis in adults during veno-venous extracorporeal membrane oxygenation therapy.

Design: Single center prospective randomized study.

Setting: University Hospital Regensburg, Germany.

Patients: Adult patients with severe acute respiratory distress syndrome requiring veno-venous extracorporeal membrane oxygenation therapy.

Interventions: None.

Measurements and Main Results: Three different extracorporeal membrane oxygenation systems: the Cardiohelp system (Maquet Cardiopulmonary AG), the Dideco ECC.O5 (Sorin Group), and the Deltastream system with Hilite 7000 LT + DP3 pumphead (Medos Medizintechnik AG) were compared. Therefore hemostasis, anticoagulation, hemolysis, and inflammatory parameters were monitored. Of the 54 patients included in the study, 18 patients each were randomly assigned to the three different extracorporeal membrane oxygenation systems. Exclusion criteria were acute renal failure, trauma, and surgery within 2 days. The median time on veno-venous extracorporeal membrane oxygenation support was 13.5 days (4–70 d). Median platelet count had dropped from 220.5 G/L before extracorporeal membrane oxygenation therapy to a minimum of 133 G/L by the last day of extracorporeal membrane oxygenation support. During the first 5 days of extracorporeal membrane oxygenation therapy, prothrombin fragment 1.2 (F1.2) (1.36–2.4 μM), thrombin-antithrombin complex (14.5–50 μg/L), and D-dimers (6.00–27.0 mg/L) increased, whereas fibrinogen values dropped from 5.8 to 4.1 g/L. The three different extracorporeal membrane oxygenation systems did not show any differences with regard to hemostasis, anticoagulation, hemolysis, and inflammatory parameters within the first 5 days of extracorporeal membrane oxygenation therapy.

Conclusions: Over time, miniaturized veno-venous extracorporeal membrane oxygenation therapy increasingly activates coagulation. The different types of membrane oxygenators and pumps did not significantly alter hemostasis. (*Crit Care Med* 2016; XX:00–00)

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Veno-venous extracorporeal membrane oxygenation (vvECMO) is a rescue strategy ensuring sufficient gas exchange in patients with severe acute respiratory distress syndrome (ARDS) who fail to respond to conventional therapy (1).

Recent years have seen numerous advances in circuit technology, including surface coatings, reduction in surface area and priming volume, and pump technology. Interest in vvECMO therapy has recently increased because of the promising results of the Conventional ventilatory support vs Extracorporeal membrane oxygenation for Severe Adult Respiratory failure trial, which showed both cost-effectiveness of ECMO and better survival rates of patients with severe reversible respiratory failure (2). Furthermore, matched pair analysis during the H1N1 influenza A pandemic showed a favorable outcome for patients referred for ECMO (3–5). Therefore, the number of medical centers introducing vvECMO programs is steadily on the rise.

Despite improved technology, bleeding, thrombosis, and hemolysis remain the most common causes of morbidity and mortality for patients receiving vvECMO therapy. These adverse effects have to be considered and should be monitored during ECMO therapy. Coagulation and inflammatory systems are immediately activated when blood comes in contact with the ECMO circuit, which necessitates systemic anticoagulation (6, 7).

The aim of this study was to monitor the influence of different vvECMO systems on hemostasis by analyzing markers for coagulation (including D-dimers, fibrinogen, antithrombin, thrombin-antithrombin complex, and prothrombin fragment 1.2), hemolysis, and inflammation.

METHODS

Study Population

The present trial was a prospective, randomized, parallel group, monocenter pilot study conducted at the University Medical Center Regensburg. From April 2011 to August 2013, 54 consecutive adult patients with acute respiratory failure receiving vvECMO therapy were enrolled in the study. The indication for vvECMO was fulfilled in the case of severe ARDS with a Murray lung injury score of 3 to 4 (8) and a Pa_{O_2}/fraction of inspired oxygen (F_{IO_2}) index less than 80 mm Hg despite optimized conservative therapy. A relative indication for vvECMO was given in the case of a Murray lung injury score of 2 to 3 and a Pa_{O_2}/F_{IO_2} index less than 150 mm Hg, severe respiratory acidosis (pH < 7.25), peak inspiratory pressure greater than 30 cm H_2O, or severe air leaks. Optimization of gas exchange followed an institutional protocol, including initial recruitment maneuvers, prone positioning, and inhalation of nitric oxide or iloprost in some patients. Patient baseline characteristics are specified in **Table 1**.

Exclusion criteria were trauma or surgery within 48 hours prior to ECMO initiation as well as requirement of renal replacement therapy because these confounding factors have a significant impact on target parameters. For inclusion into the study, written informed consent had been obtained from the legal proxy of each patient. The study was approved by the Ethics Committee of the University of Regensburg and conducted according to the guidelines of the Declaration of Helsinki.

Patients were randomly assigned (1:1:1) to one of the three groups. For allocation to each group, a blocked randomization list was used; each group consisted of 18 patients and received a different ECMO system.

A prespecified institutional transfusion guideline was followed that recommended RBC transfusion at a hemoglobin level less than 8 g/dL. Only in patients with hypoxemia despite ECMO was this threshold raised to 12 g/dL.

Technique of Extracorporeal Support

The systems applied in the study were the Cardiohelp system (Maquet Cardiopulmonary, Rastatt, Germany), the Dideco ECC.O5 (Sorin Group, Mirandola [MO], Italy), and the Deltastream system with Hilite 7000 LT + DP3 pumphead (Medos Medizintechnik, AG, Stolberg, Germany). All three systems use polymethylpentene fibers for the oxygenator membranes. The Sorin system has the smallest membrane surface area and is coated with phosphorylcholin. The Maquet and the Medos system are heparin coated. In Medos, an axial pump is used in contrast to the centrifugal pumps used in the other two systems. Technical data for all oxygenators are presented in the **supplementary data** (**Table S1**, Supplemental Digital Content 1, http://links.lww.com/CCM/B538). The filling volume of the complete system is between 500 and 700 mL, depending on the length of the tubing. Avalon Elite cannulas were used in 10 patients, the HLS cannulas (both Maquet Cardiopulmonary AG) in 41 patients, and the Novaport twin cannulas (Novalung, Heilbronn, Germany) in three patients. The choice of cannula was made by the medical staff responsible at the time of ECMO initiation and was not part of the study protocol.

Blood Samples and Laboratory Analysis

All patients had eight blood samples taken during this study; before ECMO initiation, every day during the first 5 days on the system, on the last ECMO day, and 1 day after explantation of the system. Because of the varying times on each oxygenator, we analyzed the time point before ECMO initiation on day 1 to 5 on the same oxygenator for better comparability of the applied systems. In addition, the last day on ECMO and 1 day after explantation of the system were analyzed separately to investigate changes in hemostasis without ECMO.

The daily routine blood values during ECMO therapy included a complete blood count, free hemoglobin (fHb), lactate dehydrogenase (LDH), creatinine kinase, creatinine, aspartate aminotransferase, a Quick Test (The "Quick" test, termed after the American physician Armand James Quick, is routinely used in Germany and measures the extrinsic system of the coagulation pathway; thus, this test is comparable with international normalized ratio), activated partial thromboplastin time (APTT), D-dimer, fibrinogen, antithrombin, C-reactive protein (CRP), and interleukin (IL)-6 and

TABLE 1. Baseline Characteristics of the Patients and Variables of Ventilation and Blood Values Before Veno-Venous Extracorporeal Membrane Oxygenation Initiation

	All ($n = 54$)	Cardiohelp ($n = 18$)	Hilite ($n = 18$)	ECC.O5 ($n = 18$)	p
Age (yr)	52 (41, 63)	50 (29, 60)	52 (44, 67)	57 (43, 68)	0.33, KW
Gender male/female	28/26	9/9	11/7	8/10	0.60, CS
Body mass index (kg/m^2)	29 (25, 33)	29 (25, 32)	28 (25, 32)	30 (25, 38)	0.69, KW
Sequential Organ Failure Assessment score	9 (7, 12)	9 (7, 13)	9 (8, 11)	8 (6,11)	0.40, CS
Lung injury score (Murray)	3.5 (3.3, 3.7)	3.5 (3.2, 3.8)	3.3 (3.0, 3.7)	3.5 (3.0, 3.7)	0.41, KW
Pulmonary/nonpulmonary acute respiratory distress syndrome	46/8	15/3	16/2	15/3	0.86, CS
Cannula used single/dual-lumen	44/10	16/2	15/3	13/5	0.42, CS
Fio_2	1.0 (0.9, 1.0)	1.0 (1.0, 1.0)	1.0 (0.8, 1.0)	1.0 (0.9, 1.0)	0.33, KW
Minute ventilation (L/min)	11.2 (8.5, 12.85)	12.0 (9.3, 13.3)	10.1 (7.3, 12)	12.1 (9.6,13.6)	0.17, KW
Tidal volume (mL)	483 (397, 577)	560 (403, 615)	483 (397, 539)	435 (309, 580)	0.32, KW
Peak inspiratory pressure (cm H_2O)	33 (30, 39)	32 (29, 40)	32 (30, 40)	34 (29, 38)	0.82, KW
Positive end-expiratory pressure (cm H_2O)	15.0 (12.0, 18.0)	15 (12.0, 17.5)	15 (13.0, 16.3)	15.5 (11.5, 19.3)	0.95, KW
Pao_2 (mm Hg)	64.0 (54.0, 75.0)	59.0 (52.0, 74.5)	70.5 (60.5, 93.0)	64.0 (54.8, 72.3)	0.14, KW
Pao_2/Fio_2 (mm Hg)	68 (54.0, 86.0)	59 (52.0, 81.3)	74 (60.5, 127.5)	65.5 (54.8, 91.3)	0.07, KW
$Paco_2$ (mm Hg)	59.0 (50.0, 82.0)	64.5 (55.3, 81.3)	54.5 (45.0, 98.0)	57.0 (49.5, 78.3)	0.66, KW
Arterial pH	7.26 (7.16, 7.37)	7.24 (7.12, 7.36)	7.32 (7.17, 7.38)	7.27 (7.18, 7.39)	0.46, KW
Lactate (mg/dL)	15.0 (9.5, 24.5)	14.5 (8.8, 23.8)	16.0 (11.0, 26.5)	12.0 (9.8, 21.3)	0.64, KW
Noradrenaline (mg/hr)	1.00 (0.40, 2.00)	1.50 (0.38, 2.13)	1.05 (0.50, 1.70)	0.70 (0.00, 2.00)	0.49, KW
Hemoglobin (g/dL)	10.5 (9.0, 12.8)	10.5 (9.4, 13.0)	10.8 (8.6, 13.0)	10.0 (8.2, 12.0)	0.35, KW
Creatinine (mg/dL)	1.0 (0.6, 1.6)	1.3 (0.7, 2.4)	1.1 (0.7, 1.6)	0.9 (0.5, 1.3)	0.20, KW
WBCs (g/L)	13.6 (8.0, 21.8)	15.5 (7.7, 23.0)	12.5 (6.7, 17.6)	14.5 (9.3, 25.0)	0.38, KW
Bilirubin (mg/dL)	0.7 (0.4, 1.2)	0.7 (0.4, 1.4)	0.7 (0.5, 1.1)	0.6 (0.4, 1.2)	0.67, KW

Cardiohelp = Cardiohelp system (Maquet Cardiopulmonary, Rastatt, Germany), Hilite = Deltastream system with Hilite 7000 LT + DP3 pumphead (Medos Medizintechnik, AG, Stolberg, Germany). ECC.O5 = Dideco ECC.O5 (Sorin Group, Mirandola, MO, Italy), KW = Kruskal-Wallis test, CS = chi-square test, arterial pH = pH in arterial blood.

Data show median (Q1, Q3) or absolute numbers.

IL-8. For this study, we additionally measured polymorphonuclear-elastase, factor XIII (FXIII), thrombin-antithrombin (TAT) complex, and prothrombin fragment 1.2 (F1.2). Platelet-poor plasma was obtained by centrifugation (12 min, 2,000 × *g*, 4°C) and stored in aliquots at –80°C until analysis. Platelet-poor plasma was used to determine the concentration of TAT complexes (ENZYGNOST TAT micro), F1.2 (ENZYGNOST F1 + F2, both Siemens Healthcare Diagnostics, Marburg, Germany), polymorphonuclear-elastase (Demeditec Diagnostics GmbH, Kiel, Germany), and FXIII (Date Behring, Marburg, Germany) according to the manufacturers' instructions. Enzyme-linked immunosorbent assays were done by a technician unaware of the patient's diagnosis and the type of ECMO therapy. Data were collected prospectively and transferred to the ECMO database (Regensburg ECMO Registry). Blood gas analysis, ventilatory parameters, hemodynamics, and vasopressor therapy were documented before ECMO initiation, 2 hours after initiation, thereafter once a day, before ECMO termination, and the day after ECMO termination.

Sample Size and Statistical Methods

This preliminary study was designed as an exploratory pilot study without any a priori sample size calculation based on a

primary endpoint. A sample size of 18 patients per group was considered feasible and expected to have enough power to discover clinically relevant differences between the systems.

The analysis population for comparing the ECMO systems was defined as all randomized patients receiving vvECMO for at least 5 days. Since none of the patients had a major protocol violation or changed the ECMO system, this analysis population represents both the intention-to-treat and the per-protocol population.

Continuous data are presented as median with interquartile range (IQR) and categorical data as absolute numbers (percentages). Due to the skewed distribution of the analyzed variables, nonparametric statistical methods were used for all analyses. Baseline characteristics were compared with the Kruskal-Wallis test for continuous variables and the chi-square test for dichotomous variables. Changes of laboratory values between the last day of ECMO support and 24 hours after discontinuation of ECMO therapy were analyzed with the Wilcoxon signed rank test. Effect estimates were computed according to Hodges-Lehmann (9) and accompanied by the corresponding 95% CIs. To analyze the impact of the ECMO systems and the course of time of the clinical parameters, we used linear mixed models based on ranks. The correlation structure of the repeated measurements was specified as unstructured in all mixed models. Because of the exploratory nature of our analyses, no adjustment for multiple testing was done. *p* values of less than 0.05 were considered statistically significant. All statistical tests were done using SAS 9.3 (SAS Institute, Cary, NC), Stata (version 12.1; StataCorp LP, College Station, TX), and Minitab (version 15.1.30; Minitab, State College, PA).

RESULTS

Study Population

Fifty-four patients were included in the study and randomized into three groups of 18 patients each. Each group was treated with a different vvECMO system. The major cause of lung failure in the study population was pneumonia with 85% ($n = 46$); other causes were trauma (trauma occurred > 48 hr before vvECMO initiation) ($n = 3$), sepsis ($n = 3$), pulmonary embolism ($n = 1$), and pulmonary edema of toxic origin ($n = 1$).

The three groups did not significantly differ in terms of patient demographics or severity of illness. All data are shown in Table 1.

The median time on vvECMO support was 13.5 days, ranging between 4 and 70 days. Forty-four of 54 patients (81%) survived ECMO therapy; 10 died during extracorporeal support and six patients (11%) died after weaning.

Anticoagulation

All but one patient received anticoagulation during extracorporeal assist with continuous infusion of unfractionated heparin. This patient of the Dideco ECC.O5 group received argatroban for anticoagulation because of suspected heparin-induced thrombocytopenia. This suspicion was ruled out after 2 days, and the patient was switched back to unfractionated heparin.

Doses of heparin and argatroban were adapted according to APTT measurements with a target APTT 50–60 seconds. Heparin infusion was started with 1,000 IE/hr, APTT was controlled every 4 hour until target values had been reached.

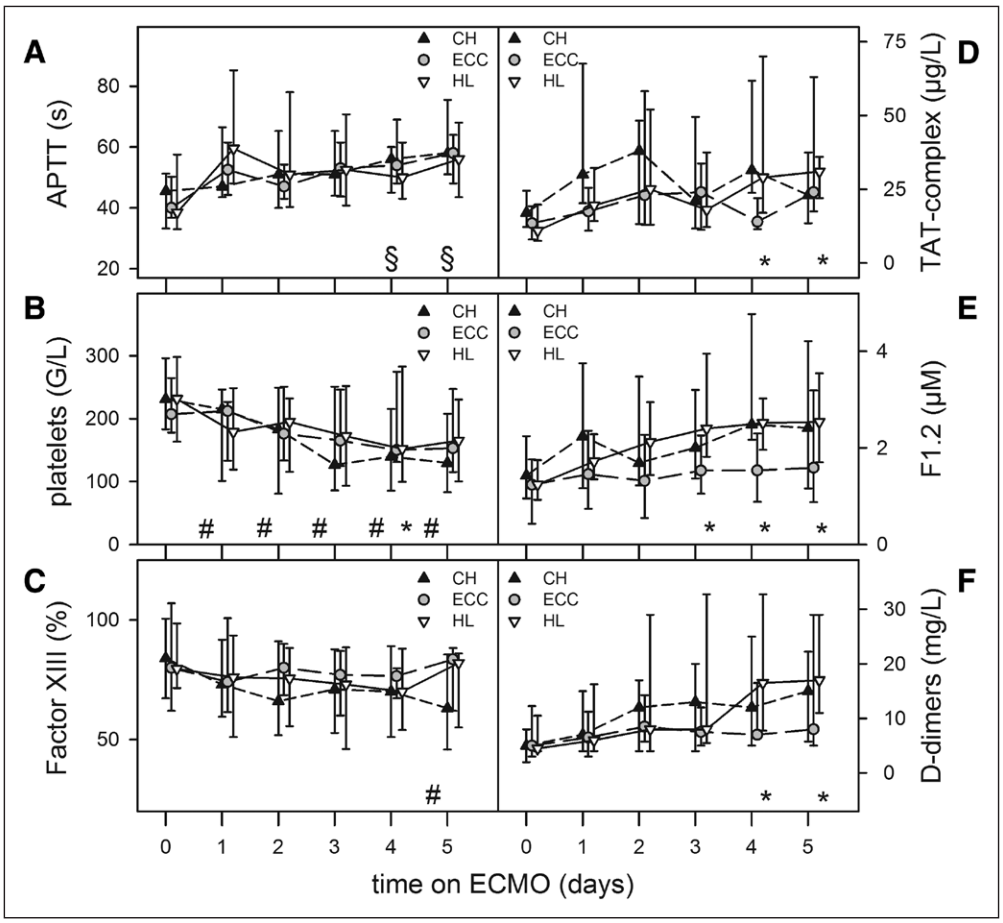

Figure 1. A–F, Medians of activated partial thromboplastin time (APTT) (**A**), platelet count (**B**), factor XIII (**C**), thrombin-antithrombin (TAT) (**D**), fragment 1.2 (F1.2) (**E**), and D-dimer (**F**) before extracorporeal membrane oxygenation (ECMO) initiation and the first 5 d on a system, subdivided for the different systems used. CH = Cardiohelp system (Maquet Cardiopulmonary, Rastatt, Germany), ECC = Dideco ECC.O5 (Sorin Group, Mirandola, MO, Italy), HL = Deltastream system with Hilite 7000 LT + DP3 pumphead (Medos Medizintechnik, AG, Stolberg, Germany). §Values for CH $p < 0.05$ compared with day 0. #Values for all three systems $p < 0.05$ compared with day 0. *Values for HL $p < 0.05$ compared with day 0. The *error bars* indicate the interquartile range.

Once target values were reached and if no signs of bleeding or worsening of the oxygenator membrane were present, APTT was controlled every 24 hours.

The values of APTT measurements during ECMO therapy are shown in **Figure 1*A***. None of the patients received antiplatelet drugs.

Coagulation

Platelet count plays a central role in coagulation. We measured a median of 221 g/L (IQR, 161–284 g/L) platelet count in all patients before vvECMO initiation. This number steadily dropped to 150 g/L (IQR, 101–236 g/L) ($p \leq 0.001$) on day 5 of vvECMO therapy. The time-dependent course for the individual system is illustrated in **Figure 1*B***. No differences were found between the three vvECMO systems. The comparison is depicted in Figure 1*B*.

The measurement of FXIII showed a decrease in plasma levels of FXIII over time; however, no difference between the systems was observed (**Fig. 1*C***).

All patients showed a significant increase in the median levels of F1.2 (1.36–2.4 µM), TAT complex (14.5–50 µg/L), and D-dimer (6.00–27.0 mg/L) within 5 days of ECMO therapy. The time-dependent course of each individual system is illustrated in **Figure 1**, ***D*–*F***. There were no significant differences between the ECMO systems (F1.2, $p = 0.137$; TAT complex, $p = 0.356$; and D-dimer, $p = 0.626$).

All patients showed a decrease in the median fibrinogen level within 5 days of ECMO therapy (before, 5.7 g/L [IQR, 3.8–to 7.7 g/L]; day 5, 4.4 g/L [IQR, 3.0–5.9 g/L]; $p < 0.001$). At the same time, antithrombin values increased from 70% (IQR, 57–85%) before ECMO to 90% (IQR, 75–106%) on day 5 ($p < 0.001$). As shown in **Figure 2**, ***A*** and ***B***, there was no difference between the systems (fibrinogen, $p = 0.311$; antithrombin, $p = 0.427$).

Hemolysis

Plasma levels of LDH and fHb were used to monitor hemolysis. The study population only showed small fluctuations in both LDH and fHb (LDH: before, 404 U/L [IQR, 287–574 U/L]; day 5, 425 U/L [IQR, 327–574 U/L); $p = 0.328$ and fHb: before, 48 mg/dL [IQR, 34–81 mg/dL]; day 5, 40 mg/dL [IQR, 27–61 mg/dL]; $p = 0.033$). As shown in **Figure 2**, ***C*** and ***D***, there was no difference between the ECMO systems (LDH, $p = 0.537$ and fHb, $p = 0.767$).

Inflammation

Because inflammation may activate coagulation, different inflammatory markers were analyzed in parallel (CRP, IL-6, IL-8, polymorphonuclear-elastase). All study patients showed a decrease in CRP, polymorphonuclear-elastase, IL-6, and IL-8 after ECMO therapy ($p \leq 0.001$ each). However, there was no difference between the systems (CRP, $p = 0.786$; polymorphonuclear-elastase, $p = 0.551$; IL-6, $p = 0.733$; IL-8, $p = 0.668$). Results are shown in **Figure 3**, ***A*–*D***.

Termination of ECMO Therapy

An additional goal of our study was to monitor changes in hemostasis, hemolysis, coagulation, and inflammation once ECMO therapy was terminated. Therefore, we compared all measured parameters of all patients between the last day on ECMO therapy and the day after explantation. The most pronounced changes were observed in coagulation parameters. F1.2, TAT, and D-dimers had dropped markedly within 24 hours. Antithrombin, platelet count, and fibrinogen stabilized once patients were weaned off the extracorporeal circuit. Hemolysis measured by fHb decreased. In contrast, inflammatory markers were not influenced by ECMO termination. All values are shown in **Table 2**.

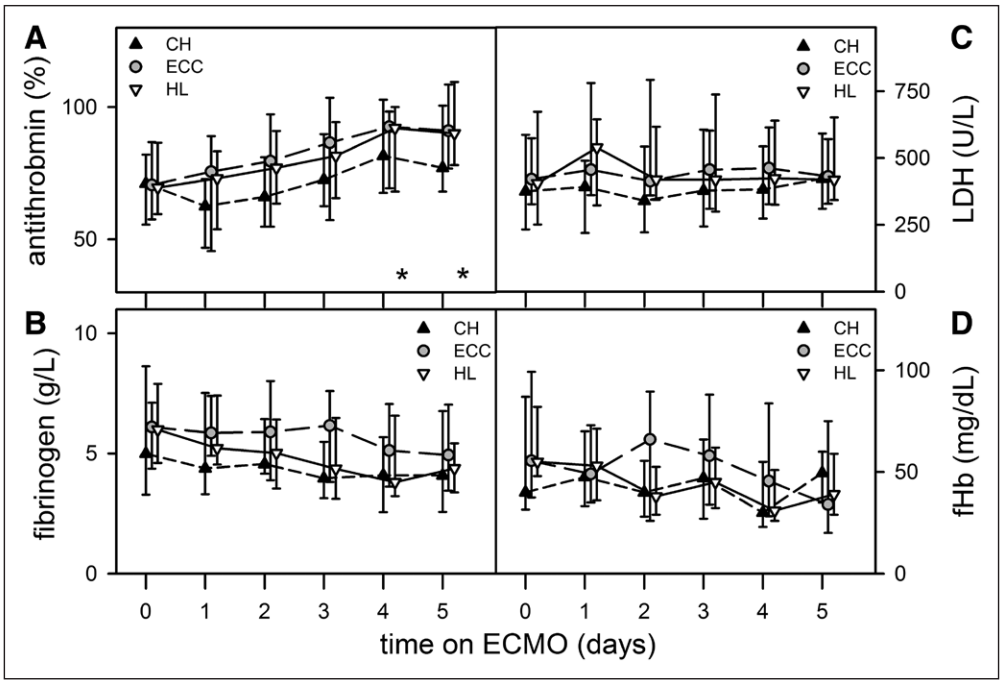

Figure 2. Medians of antithrombin (**A**), fibrinogen (**B**), lactate dehydrogenase (LDH) (**C**), and free hemoglobin (fHb) (**D**) before extracorporeal membrane oxygenation (ECMO) initiation and the first 5 d on a system, subdivided for the different systems used. CH = Cardiohelp system (Maquet Cardiopulmonary, Rastatt, Germany), ECC = Dideco ECC.O5 (Sorin Group, Mirandola, MO, Italy), HL = Deltastream system with Hilite 7000 LT + DP3 pumphead (Medos Medizintechnik, AG, Stolberg, Germany). *Values for HL $p < 0.05$ compared with day 0. The *error bars* indicate the interquartile range.

DISCUSSION

In this prospective observational study, three different commercially available adult ECMO systems with different biocompatible coatings, oxygenator surface areas, and

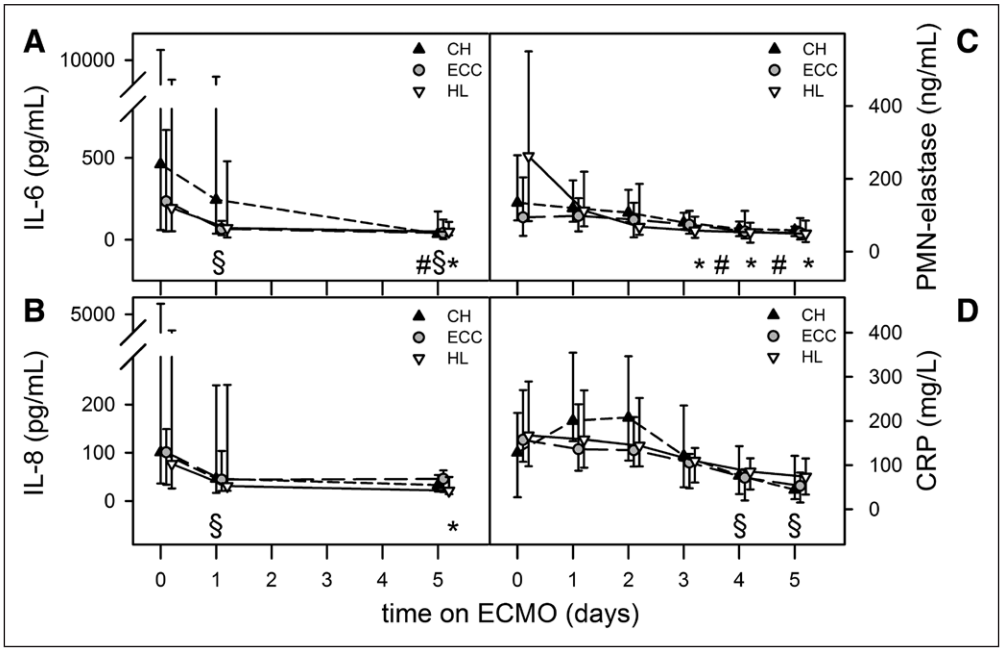

Figure 3 Medians of interleukin (IL)-6 (**A**), IL-8 (**B**), polymorphonuclear (PMN)-elastase (**C**), and C-reactive protein (CRP) (**D**) before extracorporeal membrane oxygenation (ECMO) initiation and the first 5 d on a system, subdivided for the different systems used. CH = Cardiohelp system (Maquet Cardiopulmonary, Rastatt, Germany), ECC = Dideco ECC.O5 (Sorin Group, Mirandola, MO, Italy), HL = Deltastream system with Hilite 7000 LT + DP3 pumphead (Medos Medizintechnik, AG, Stolberg, Germany). §Values for CH $p < 0.05$ compared with day 0. #Values for all three systems $p < 0.05$ compared with day 0. *Values for HL $p < 0.05$ compared with day 0. The *error bars* indicate the interquartile range.

pump speeds were compared for the first time with regard to activation of plasma coagulation and hemolysis. No differences were found between the systems with the blood flows applied in our study (**Table S2**, Supplemental Digital Content 2, http://links.lww.com/CCM/B539). Blood flows were adjusted to ensure sufficient gas exchange, but adjustments of the ventilator or ECMO device greatly vary among institutions. Therefore, we suggest that all three ECMO systems are equally recommendable for long-term use if the blood flow is comparable with our settings (< 3.5 L/min). Different results may be obtained with other parameters (e.g., higher blood flow or smaller cannulas) that can result in elevation of sheer stress to the blood.

Activation of coagulation pathways was assessed with D-dimer, TAT complexes, and F1.2 that have been shown to be sensitive markers (10). In our study, D-dimer, TAT, and F1.2 rose continuously during ECMO therapy. Our results indicate that monitoring only one marker (e.g., D-dimer) is probably sufficient for checking the activation of coagulation by a system. All three systems seem to be equal. In the absence of other pathological reasons, such as disseminated intravascular coagulation, pulmonary embolism, trauma, or major surgery, D-dimer has been shown to be an indicator for activating the coagulation cascade caused by ECMO systems (11, 12). Future studies could compare these markers with regard to predicting the need to exchange the oxygenator because of an ongoing thrombotic deposition.

Surveillance of platelet count during ECMO therapy is a necessity. In accordance with previous studies, platelet count in our patients had dropped by less than 25% over the first 5 days and almost by 40% at the end of ECMO therapy (13, 14). We show that this decrease is independent of the ECMO system applied. Possible causes for a rapidly decreasing platelet count that might result in serious bleeding are contact with the not only ECMO circuit and particularly the pump but also heparin-induced thrombocytopenia (15–17), sepsis, and toxic drug effects. Because no value for the need of platelet transfusions during ECMO therapy has yet been defined, we usually transfuse platelet concentrates in the case of bleeding or values less than 20 g/L.

Blood pumps are known to induce some degree of blood trauma. Hemolysis is caused by negative pressures within the centrifugal pump or cannula (18), and LDH and fHb is released from lysed erythrocytes. Daily monitoring of fHb and LDH values may help evaluate hemolysis caused by the ECMO circuit (19). On average, LDH or fHb values did not rise in our study population. LDH is a marker of low specificity because it may become elevated for numerous reasons. However, no elevation was observed in our patients during ECMO therapy. We believe that the surprising decrease in fHb values over the first 5 days on ECMO in our study was caused by abating sepsis but was not associated with the ECMO circuit. No major hemolysis or differences between the three blood pumps were observed.

The increase in antithrombin values can be interpreted as abating of the underlying sepsis in our patients. Decreasing antithrombin values on ECMO have so far only been described in pediatric patients (20), but coagulation in this population is fundamentally different from that in adults (21).

Inflammatory processes are known to be activated once blood has contact with extracorporeal circuits. Figure 3, *A* and *B* shows a significant decrease in IL-6 and IL-8 on day 1 of ECMO therapy. Similar findings have been published in the Xtravent study (22). This finding could be explained by the lower tidal volumes required by patients receiving ECMO, thus reducing pulmonary epithelial and endothelial injuries. Other hypotheses are resolution of the underlying infectious disease or reconstitution of normal pH, Po_2, and PCO_2. The decrease in polymorphonuclear-elastase over the first 5 days (Fig. 3*C*) can also be explained by abating sepsis.

Because the early days of vvECMO, bleeding, and thromboembolism have been major problems in the treatment of severe ARDS. The safety of ECMO has been improved by applying coated equipment, membranes, and tubings (23, 24).

TABLE 2. Laboratory Values on the Last Day of Extracorporeal Membrane Oxygenation Support Compared With Values 24 Hours After Discontinuation of Extracorporeal Membrane Oxygenation Support Therapy

Laboratory Value	Normal Reference Range	Last Day on ECMO	Post	Hodges-Lehmann Effect Estimate (95% CI)	*p*
Fragment 1.2 (μM) (*n* = 42)	0.4–1.2	3.1 (2.3, 4.7)	1.3 (1.0, 1.7)	−1.85 (−2.60, −1.32)	< 0.001
Thrombin-antithrombin III complex (μg/L) (*n* = 42)	< 0.3	41 (19, 87)	11 (9, 16)	42 (27, 64)	< 0.001
D-Dimer (mg/L) (*n* = 44)	< 0.5	32 (15, 35)	16 (9, 29)	9 (6, 12)	< 0.001
Polymorphonuclear (ng/mL) (*n* = 41)	19–78	43 (32, 69)	39 (24, 56)	8 (2, 14)	0.014
Factor XIII (%) (*n* = 42)	70–140	72 (53, 90)	69 (55, 91)	−2 (−7, 3)	0.364
C-reactive protein (mg/L) (*n* = 15)	< 3.0	66 (30, 138)	78 (40, 116)	0 (−21, 21)	0.955
WBCs (g/L) (*n* = 44)	4.23–9.1	11 (8, 16)	11 (8, 16)	0 (−1, 1)	0.704
Lactate dehydrogenase (U/L) (*n* = 42)	< 250	390 (317, 528)	366 (303, 520)	19 (−7, 41)	0.167
Free hemoglobin (mg/dL) (*n* = 44)	< 50	54 (35, 85)	38 (27, 67)	8 (0.5, 16)	0.039
Quick (%) (*n* = 44)	> 70	80 (69, 97)	85 (79, 98)	−6 (−10, −2)	0.003
Activated partial thromboplastin time (s) (*n* = 44)	25.9–36.6	52 (45, 63)	38 (33, 51)	10 (7, 15)	< 0.001
Fibrinogen (g/d) (*n* = 44)	2.1–4.0	4.2 (2.6, 5.6)	4.4 (3.2, 5.6)	−0.4 (−0.6, −0.2)	0.001
Antithrombin (%) (*n* = 44)	79.4–111.5	90 (74, 110)	95 (79, 108)	−3 (−6, −0,5)	0.023
Platelet count (g/L) (*n* = 44)	163–337	133 (95, 212)	154 (118, 236)	−15 (−23, −6)	0.003

Data show median (Q1, Q3).

Nowadays, most membrane oxygenators available are made of polymethylpentene microfibers, offering low resistance to blood flow, high gas-transfer capability, and high leak-proof performance. Certified ECMO oxygenators thereby facilitate long-term use (25). The three adult ECMO systems applied use the same polymethylpentene membrane OXYPLUS (Membrana, Wuppertal, Germany) but differ in priming volumes, membrane, and heat-exchanger surface area, the type of pump, and biocompatible coatings (Table S1, Supplemental Digital Content 1, http://links.lww.com/CCM/B538). Nonetheless, the ECMO systems applied in our study did not show any differences in activating coagulation and hemolysis.

In our center, anticoagulation therapy is routinely administered with continuous infusion of unfractionated heparin. Regular monitoring is done with APTT because this test is the most commonly used tool for assessing anticoagulation during adult ECMO therapy (26). We aim at APTT values of 50–60 seconds. However, most thromboembolic complications occur despite APTT values being within the target range (6).

Our study subjects received ECMO therapy for a median of 13.5 days. Because ECMO always involves activation of coagulation and some degree of hemolysis, the duration of this therapy should be as short as possible. We compared three different systems over the first 5 days of therapy. Because with increasing duration of the therapy, oxygenators or even the entire ECMO system had to be exchanged in some patients, we could not compare the different systems over a longer period of time. The data of all study patients showed that the changes in plasma coagulation (D-dimer, F 1.2, and TAT) had stabilized within 1 day after ECMO termination (**Table 2**). Furthermore, the decrease in fHb and LDH values and the increase in the fibrinogen, antithrombin, and platelet count after ECMO termination indicate the large influence of this therapy on hemostasis.

The main limitation of our study is that all our conclusions cannot be generalized because they are subject to our settings of blood flow, pump speed, and cannula selection.

A further limitation is that we did not monitor actual heparin levels by measuring anti-Xa levels; this can be of

importance in ECMO patients as the APTT in contrast to anti-Xa is sensitive to fibrinogen levels. Furthermore, we did not monitor platelet function or von Willebrand factor multimers, which are influenced by ECMO circuits. Our results apply only to adults.

CONCLUSIONS

Our data show the influence of long-term vvECMO therapy on hemostasis. All our patients showed continuous activation of coagulation and slight hemolysis. The different pump types and membrane oxygenators used in our study showed comparable results. All devices tested are suitable for long-term use. After termination of ECMO therapy, changes in plasmatic coagulation had stabilized within 1 day.

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