Artificial
Organs

Comparison of Coagulation Parameters, Anticoagulation, and Need for Transfusion in Patients on Interventional Lung Assist or Veno-Venous Extracorporeal Membrane Oxygenation

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Abstract: Clinical data on anticoagulation needs of modern extracorporeal membrane oxygenation (ECMO) and its impact on coagulation are scarce. Therefore, we analyzed coagulation-related parameters, need for transfusion, and management of anticoagulation in adult patients with severe acute respiratory failure during treatment with either pumpless interventional lung assist (iLA) or veno-venous ECMO (vv-ECMO). Sixty-three patients treated with iLA and 192 patients treated with vv-ECMO at Regensburg University Hospital between January 2005 and May 2011 were analyzed. Data related to anticoagulation, transfusion, and coagulation parameters were collected prospectively by the Regensburg ECMO registry. Except for a higher, sequential organ failure assessment (SOFA) score in the ECMO group (12 [9–15] vs. 11 [7–14], $P = 0.007$), a better oxygenation, and a lower dosage of vasopressors in the iLA patients, both groups had similar baseline characteristics. No difference was noted in terms of outcome and overall transfusion requirements. Factors of the plasmatic coagulation system were only marginally altered over time and did not differ between groups. Platelet counts in ECMO-treated patients, but not in those treated with iLA, dropped significantly during extracorporeal support. A more intense systemic anticoagulation with a mean activated partial thromboplastin time (aPTT) > 53 s led to a higher need for transfusions compared with the group with a mean aPTT < 53 s, whereas the average durability of membrane oxygenators was not affected. Need for red blood cell (RBC) transfusion was highest in patients with extrapulmonary sepsis (257 mL/day), and was significantly lower in primary pulmonary adult respiratory distress syndrome (ARDS) (102 mL/day). Overall, 110 (0–274) mL RBC was transfused in the ECMO group versus 146 (41–227) mL in the iLA group per day on support. The impact of modern iLA and ECMO systems on coagulation allows comparatively safe long-term treatment of adult patients with acute respiratory failure. A moderate systemic anticoagulation seems to be sufficient. Importantly, platelets are more affected by vv-ECMO compared with pumpless iLA. **Key Words:** Extracorporeal membrane oxygenation—Interventional lung assist—Extracorporeal circulation—Anticoagulation—Transfusion.

Adult respiratory distress syndrome (ARDS) represents a syndrome of acute lung failure caused by different diseases, which shares common clinical features and results in severe hypoxemia (1). Since the first description in 1967 (2), substantial progress in treatment and improved survival have been achieved. By pursuing a protective ventilation strategy, ventilation-associated lung damage could be reduced, with a major impact on survival (3,4). Nevertheless, in the most severe forms of ARDS, mortality remains high. Maintaining both a lung-protective ventilation strategy and attaining sufficient oxygenation and/or carbon dioxide removal at the same time are sometimes impossible in these patients. The predominant clinical problem may be

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limited to either oxygenation or, in some patients, to severe hypercapnia with acidosis (5). Thus, use of an extracorporeal device to support lung function had been investigated for decades to serve both as a tool to ensure gas exchange and to enable a lung-protective ventilation strategy concomitantly. Since the first application of extracorporeal membrane oxygenation (ECMO) in an adult patient with severe lung failure after a motor vehicle accident in the early 1970s (6), the procedure became a standard treatment in newborn severe respiratory failure during the next 20 years (7). In adults with ARDS, ECMO had only been considered a rescue therapy in selected patients, because early randomized trials failed to demonstrate a benefit in comparison with conventional therapy (8,9). Among ECMO-related complications, both clotting and bleeding contributed to the majority of unfavorable events in neonatal or pediatric cases (10) as well as in adult patients (11). Transfusions of large amounts of blood products had been necessary in almost every patient on ECMO, limiting a safe prolonged continuation (12,13).

Technical progress during the last 10 years may have reduced these complications. In 2000, a pumpless extracorporeal lung assist was introduced into clinical practice, today termed "interventional Lung Assist" (iLA). The system consists of an artificial arterio-venous shunt in combination with a low-resistance membrane oxygenator. Because arterial blood passes through the device, effective CO_2 elimination is possible, but O_2 transfer is marginal (14). Therefore, iLA can be considered a suitable tool in patients with stable hemodynamics and predominantly hypercapnic lung failure. With new oxygenators available, miniaturized pump-driven ECMO systems for long-term extracorporeal oxygenation have been introduced and applied in pediatric patients (15), and patients with cardiogenic shock (16) and ARDS (17). Veno-venous ECMO (vv-ECMO) effectively removes CO_2 and significantly improves oxygenation in patients with severe lung failure who cannot be stabilized by conventional means. Modern pump-driven as well as pumpless lung assist devices require only low-dose anticoagulation, which may contribute to a reduction of severe bleeding.

Although there are some data concerning coagulation management on ECMO in pediatric patients (18,19), data on adult patients are limited. To our knowledge, there is no current study investigating the need for anticoagulation and related complications with modern lung assist devices. In the present study we performed a detailed analysis of coagulation-related parameters, management of anticoagulation, and need for transfusion during treatment with either iLA or veno-venous ECMO, and tried to delineate differences between both.

PATIENTS AND METHODS

Patients

Between January 2005 and May 2011, 91 adult patients were treated with pumpless arterio-venous iLA and 201 patients with vv-ECMO due to severe respiratory failure. Patients on veno-arterial ECMO and patients switched from one treatment modality to another (16 patients) were not included in the analysis. Moreover, 21 patients enrolled in the Xtravent Trial (NCT00538928) (20) between September 2007 and January 2011 were excluded. Final analysis was performed in 63 patients on iLA and 192 patients on ECMO. Patients were considered eligible for extracorporeal support if lung failure was judged potentially reversible. Treatment with extracorporeal lung devices was initiated after failure of conservative treatment options to improve oxygenation and ventilation (PEEP-trial, recruitment maneuvers, prone position, inhaled prostaglandins or nitric oxide). At a PaO_2/FiO_2 ratio < 80 mm Hg and/or persistent respiratory acidosis (pH < 7.25) despite invasive mechanical ventilation (positive inspiratory pressure > 32 cm H_2O, $FiO_2 > 0.9$, TV > 8 mL/kg BW), conventional treatment was declared ineffective.

ECMO/iLA

The technique of extracorporeal support devices has been described in detail elsewhere (14,17). Cannulae were implanted using the Seldinger technique, and cannula size was chosen according to individual vessel diameter measured by ultrasound and expected need for flow. For iLA, 15–17 Fr cannulae were implanted into the proximal femoral artery for blood delivery; venous cannulae (17–21 Fr) were placed in the contralateral femoral vein for blood return (NovaLung GmbH, Heilbronn, Germany). For ECMO outflow, usually long 21 Fr or 23 Fr cannulae (Maquet Cardiopulmonary, Rastatt, Germany) were placed through the right femoral vein into the inferior caval vein. Reinfusion cannulae (15–21 Fr) were mainly implanted into the right jugular vein. Since April 2009, 23 Fr, 27 Fr, and 31 Fr double-lumen bi-caval cannulae introduced through the right jugular vein (Maquet Cardiopulmonary) were also used if applicable (21). Double-lumen cannulae have opening ports for blood delivery both in the superior and inferior caval veins, and return the

blood via a port into the right atrium. Only polymethyl-pentene membrane oxygenators with a surface area of 1.8–1.9 m^2 and a priming volume of about 275 mL (PLS Quadrox, Cardiohelp, all Maquet Cardiopulmonary; Medos-Hilite LT7000, Medos Medizintechnik, Stolberg, Germany) were used in combination with a centrifugal pump (Rotaflow/Cardiohelp, Maquet Cardiopulmonary or Deltastream III, Medos Medizintechnik). For iLA, smaller oxygenators with a surface area of 1.3 m^2 and a priming volume of 175 mL (iLA-MV or NovaBreath, NovaLung GmbH) were used. After a bolus application (1000–5000 IE heparin according to impairment of coagulation), systemic anticoagulation was continued with unfractionated heparin aiming at an activated partial thromboplastin time (aPTT) of 50 s in both devices, but heparin was withheld if significant bleeding occurred. According to preset standards, red blood cells (RBCs) were substituted at a hemoglobin concentration below 8 g/dL, with the exception of patients with borderline oxygenation despite ECMO, in whom hemoglobin concentration was kept above 12 g/dL. Platelets were transfused below a count of 20/μL, or in case of diffuse bleeding, fresh frozen plasma (FFP) was substituted if bleeding due to DIC (disseminated intravascular coagulation) occurred or in the course of plasmapheresis.

An exchange of the membrane oxygenator was done, if gas exchange capability decreased rapidly, trans-membrane pressure increased considerably, or extensive clotting was visible with concomitant thrombocytopenia, high D-dimers, or hyperfibrinolysis.

Data collection and statistical analysis

All data from patients treated with iLA or ECMO were collected prospectively in a large database (Regensburg ECMO Registry). The first measurement was taken before extracorporeal lung assist was initiated and once daily thereafter. Due to its retrospective and anonymized design, for this study need for informed consent was waived by the Ethics Committee of the University of Regensburg. Statistical analysis was performed with PASW Statistics 18 (SPSS Inc., Chicago, IL, USA). The Kolmogorov–Smirnov test was applied to test for normal distribution of baseline parameters. Most parameters were not distributed normally; thus, median and 25/75 percentile (interquartile range [IQR]) were given. Paired analysis of parameters without normal distribution was performed using the Wilcoxon signed-rank test; for normally distributed parameters, the paired *t*-test was used. Mann–Whitney *U*-tests and chi-square tests were used for intergroup differences. Significance was assumed for a P value <0.05.

RESULTS

Patient characteristics and outcome

Baseline data and patient characteristics, collected before the initiation of extracorporeal support, are shown in Table 1. The ECMO group had a higher sequential organ failure assessment (SOFA) score and a higher mean body mass index (BMI). Whereas the proportion of patients with ARDS of primary pulmonary origin ("pulmonary ARDS") was similar in both groups, there were more patients with posttraumatic ARDS in the iLA group and slightly more patients with ARDS due to extrapulmonary sepsis ("extrapulmonary ARDS") in the ECMO group. Patients classified as "other" in the ECMO group consisted of a mixed group of patients with near drowning, pulmonary bleeding, or terminal lung disease awaiting transplantation. Hypoxemia in ECMO-treated patients was more severe, corresponding to the capability of vv-ECMO to improve oxygenation. Vasopressors (mainly noradrenaline) were used in both groups, but this need was less pronounced in iLA-treated patients. According to the ISTH-DIC (International Society on Thrombosis and Haemostasis—disseminated intravascular coagulation) Score, which involves fibrinogen, platelet count, international normalized ratio (INR), and D-dimers (22), 12% of ECMO-treated patients fulfilled the criteria defining DIC, whereas no patient in the iLA group met these criteria at baseline.

Outcome data are given in Table 2. Weaning from the device was possible in approximately two-thirds of patients (ECMO 67.7%, iLA 63.5%). In-hospital mortality showed no statistically significant difference between ECMO- and iLA-treated patients (45.3% vs. 55.6%, $P = 0.33$).

Laboratory parameters of coagulation

An overview of coagulation-related laboratory parameters in the course of treatment is depicted in Fig. 1A–F. Expectedly, aPTT rose significantly after initiation of treatment and decreased after termination of extracorporeal support, which is attributable to systemic anticoagulation (A). The "Quick," commonly used in Germany and termed after the American physician Armand James Quick, measures the extrinsic system of the coagulation pathway and is comparable with INR. "Quick" values showed a trend for improvement over time, although were mostly within the normal range (70–100%), and increased significantly after termination of extracor-

TABLE 1. *Baseline characteristics*

	ECMO (n = 192)	iLA (n = 63)	P value
Male	133 (69.3)	51 (81.0)	—
Female	59 (30.7)	12 (19.0)	—
Age in years (SD)	48.5 (± 16.3)	49.9 (± 15.5)	0.50
BMI (kg/m^2) (IQR)	27.8 (24.6–33.8)	26.3 (23.5–31.1)	0.03
SOFA score (IQR)	12 (9–15)	11 (7–14)	0.007
Diagnosis n (%)			
Pulmonary ARDS	132 (68.8)	40 (63.5)	—
Extrapulmonary ARDS	27 (14.1)	7 (11.1)	—
Traumatic ARDS	14 (7.3)	13 (20.6)	—
Other	19 (9.9)	3 (4.8)	—
Respiratory parameters			
PaO_2 mm Hg (IQR)	63 (50–77)	82 (76.5–99)	<0.001
$PaCO_2$ mm Hg (IQR)	64 (53–78)	70 (55–84)	0.16
PaO_2/FiO_2 mm Hg (IQR)	66 (50–88)	92.5 (66.0–152.9)	<0.001
pH (IQR)	7.23 (7.15–7.31)	7.23 (7.16–7.33)	0.51
PIP cm H_2O (IQR)	36.0 (32.0–40.0)	34.5 (31.0–38.3)	0.30
PEEP cm H_2O (IQR)	17 (14–22)	17 (13–20)	0.53
Noradrenaline (mg/h)	1.5 (0.6–3.5)	1.0 (0.2–1.7)	<0.001
ISTH-DIC score			
Score median (IQR)	3 (2–4)	2 (2–3)	0.23
Score < 5 n (%)	111 (88.1)	7 (100)	—
Score ≥ 5 n (%)	15 (11.9)	0 (0)	—
Total	126	7	—

Most data are presented as median and interquartile range.

PEEP, positive endexpiratory pressure; PIP, peak inspiratory pressure; SD, standard deviation.

poreal support (B). Although there were 15 patients in the ECMO group who fulfilled ISTH criteria for DIC, average fibrinogen values were in the normal range in both groups at baseline. Fibrinogen slightly decreased over the next days, reaching statistical significance compared with baseline on day 2 in the iLA group and on day 3 in the ECMO group. On average, values remained within the normal range (C). D-Dimers were comparably low in both groups at baseline and did not rise during the initial days of treatment. After a gradual increase during treatment, values at the end of treatment were usually higher in the ECMO group, but not in the iLA group. Cessation of extracorporeal circulation led to a significant drop of D-dimers in the ECMO group (D). Antithrombin-III was below normal in the ECMO group and in the lower normal range in the iLA group at baseline, mirroring a higher percentage of cases with severe sepsis in the ECMO group. After initiation of extracorporeal lung support, antithrombin-III values in both groups rose significantly during the first days and were within the normal range around day 3 (E). Platelet count as a parameter of cellular coagulation was in the lower normal range in both groups at baseline. In the iLA group, platelet counts remained stable, except for a slight decrease on day 1, whereas platelet counts in the ECMO group dropped significantly during the first days of treatment, remained low, and recovered only after cessation of therapy (F).

Need for transfusion

Overall, daily transfusion requirements were not different in both groups (Table 3): median need for RBC substitution per day on assist was moderate in the ECMO group as well as in the iLA group (110 [0–274] mL vs. 146 [41–227] mL). Platelet concentrates had to be given to a minority of patients, result-

TABLE 2. *Final outcome*

	ECMO n = 192	iLA n = 63	P value
Outcome			
Weaning from device, n (%)	130 (67.7)	40 (63.5)	P = 0.53
Death within 30 days, n (%)	72 (37.5)	30 (47.6)	—
Death overall, n (%)	87 (45.3)	35 (55.6)	—
Survival to discharge, n (%)	105 (54.7)	28 (44.4)	P = 0.33
Days on extracorporeal support median (IQR)	9 (6–15)	7 (4–10)	P = 0.31

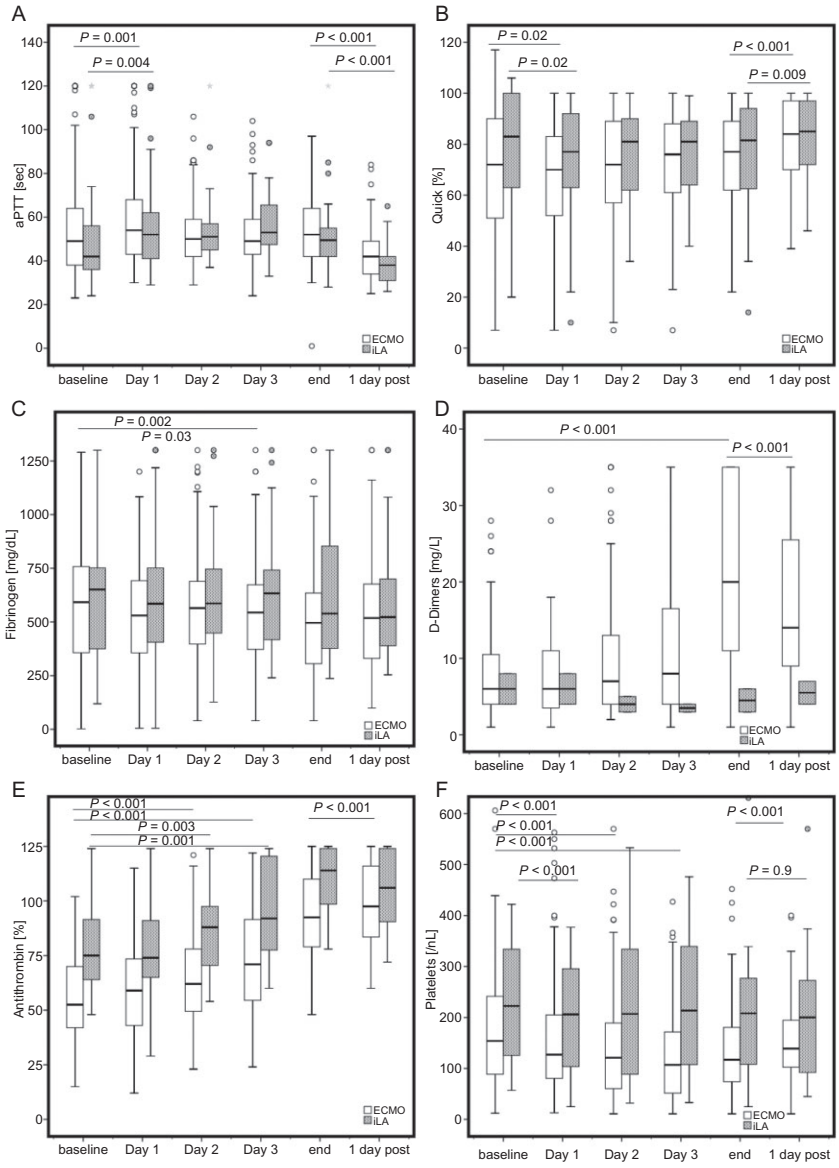

FIG. 1. Laboratory parameters of plasmatic coagulation and platelet count before initiation, on days 1–3, at the end of treatment (end) and 1 day after the end of treatment of extracorporeal lung support. The following parameters are shown: aPTT (A), "Quick" (B), fibrinogen (C), D-dimers (D), antithrombin-III (E), and platelet count (F). Boxplots indicate median and 25–75 percentile; whiskers represent smallest and largest values, not classified as outliers.

ing in a median of 0 (0–17) mL for platelet concentrates. Similarly, the median need for transfusion of FFP was 0 (0–140, ECMO and 0–124, iLA) mL in both groups. Therapeutic plasmapheresis with its procedure-related substitution of large amounts of plasma had a major impact on the overall volume of FFP used. Excluding the five patients in the ECMO group and the one in the iLA group requiring plasmapheresis still resulted in no difference between both groups.

To evaluate the effect of a more pronounced anticoagulation on the need for transfusions, we separately analyzed the subgroup of all patients, who were supported for 7 days or more with the assist device (n = 110 for ECMO, n = 24 for iLA). In those, the mean aPTT of all measured aPTTs during the first week was calculated to determine the average anticoagulation. Fifty percent of all patients had an average aPTT below 53 s, whereas the other half was above this value. In the ECMO group, patients with a higher mean aPTT had a higher need for RBC transfusions compared with those with an aPTT below 53 s (112 [25–259] mL/day vs. 93 [0–255] mL/day, P = 0.006). This difference was not observed in the iLA group (110 [77–193] mL/day vs. 99 [39–174] mL/day).

Exchange rate of oxygenators

Intensity of anticoagulation may influence the durability of the membrane oxygenator, which is predominantly determined by the extent of thrombosis on its surface. In our patients, the need for substitu-

TABLE 3. *Need for transfusion*

		ECMO (n = 192)			iLA (n = 63)			P value
I.	Transfusions in mL/day, (median [IQR])							
	RBC concentrates*	110 (0–274)			146 (41–227)			P = 0.41
	Platelet concentrates*	0 (0–17)			0 (0)			P = 0.06
	Fresh frozen plasma, all patients*	0 (0–140)			0 (0–124)			P = 0.68
	Fresh frozen plasma, excluding patients with plasmapheresis	0 (0–120)			0 (0–119)			P = 0.76
	Patients requiring plasmapheresis	5			1			—
II.	Transfusions in mL/day according to diagnosis (median [IQR])							
		RBC	FFP	Platelets	RBC	FFP	Platelets	
	Pulmonary ARDS	102 (0–250)	0 (0–98)	0 (0–0)	174 (87–303)	0 (0–236)	0 (0–0)	—
	Extrapulmonary ARDS	257 (0–566)	140 (0–616)	0 (0–222)	132 (33–165)	100 (0–224)	0 (0–0)	—
	Traumatic ARDS	85 (0–1320)	0 (0–1773)	0 (0–125)	138 (0–174)	0 (0–0)	0 (0–0)	—
	Other	126 (0–330)	0 (0–43)	0 (0–0)	0 (0–85)	0 (0–0)	0 (0–0)	—
III.	Transfusion of RBC in mL/day according to mean anticoagulation (median (IQR))		n = 110**			n = 24**		
	aPTT mean > 53 s		112 (25–259)			110 (77–193)		
	aPTT mean ≤ 53 s		93 (0–255)			99 (39–174)		

* ECMO group: 129 of 192 patients received at least one RBC, 72 of 192 at least one FFP, and 53 of 192 at least one platelet concentrate. ILA group: 51 of 63 patients received at least one RBC, 21 of 63 at least one FFP, and 10 of 63 at least one platelet concentrate. Section III of the table includes only patients who were treated with extracorporeal support for at least 7 days; this group is broken down into subgroups with a mean aPTT above or below 53 s.

** Only patients with extracorporeal treatment of at least 7 days' duration.

Demand of transfusions is given as milliliters per day on extracorporeal support. The first part of the table depicts the need according to the type of blood product; the second part shows need for transfusion according to diagnosis.

tion of the oxygenator was not common, and 75% of all patients did require only one oxygenator. "Operating time" of an oxygenator was mainly limited by the actual need for extracorporeal support without necessity to exchange the oxygenator. Patients supported for more than 1 week did not require an exchange of the oxygenator more often if they had an average aPTT below 53 s compared with those with an aPTT above 53 s (Table 4). In total, there were 50 patients in the ECMO group and 13 patients in the iLA group who were treated for more than 7 days and had at least one exchange of the oxygenator due to clotting.

DISCUSSION

The use of extracorporeal lung assist to support adult patients with acute respiratory failure, in particular use of vv-ECMO, became popular worldwide during the last years due to the development of new miniaturized devices and the H1N1 epidemic in 2009/2010 (23,24). Although there is only one recent randomized trial comparing modern ECMO with conventional therapy (25), evidence increases that the use of ECMO may be beneficial in patients with severe ARDS (24). Both iLA and miniaturized ECMO systems have been shown to provide sufficient extracorporeal gas transfer to maintain a protective ventilation (17,26). However, in the past, the positive effects of a more protective ventilation may have been neutralized by device-related complications—especially thrombosis, bleeding, and necessity of large amounts of transfusions (12,13). Although events of thrombosis and bleeding have been mentioned in some reports (14,27), there has

TABLE 4. *Number of membrane oxygenators used and impact of anticoagulation on their durability*

	ECMO	iLA
I. Membrane oxygenators used (n (%))		
1	139 (72.4)	45 (71.4)
2	36 (18.8)	13 (20.6)
3	11 (5.7)	3 (4.8)
4	5 (2.6)	1 (1.6)
5	0	1 (1.6)
6	1 (0.5)	0
II. Durability of membrane oxygenators (days (SD))	n = 50*	n = 13*
aPTT > 53 s	9.48 (3.4)	6.49 (2.0)
aPTT ≤ 53 s	9.85 (4.0)	5.32 (1.7)

* Only patients requiring more than one MO and extracorporeal support for at least 7 days. Section I of the table depicts the number of patients who needed one or more membrane oxygenators. Section II of the table presents the average durability of the membrane oxygenators in days. It includes only patients who required more than one membrane oxygenator and were treated with extracorporeal support for at least 7 days; this group is broken down into subgroups with a mean aPTT above or below 53 s.

SD, standard deviation.

been no current systematic analysis of the impetus of modern lung support devices on parameters of coagulation and need for transfusion.

In patients on extracorporeal lung support, both risk of thrombosis and risk of bleeding depend on a variety of contributing and interacting factors, which can be broadly discriminated into disorder-related and therapy-related. For example, ARDS in the course of sepsis with multiple organ failure may be accompanied by disseminated intravascular coagulation, and severe trauma leading to ARDS can be associated with altered coagulation parameters in case of significant blood loss and massive transfusion. Therapy-related factors can be due to exposure of blood to the nonbiologic surface of the device with a strong impact on platelets, plasmatic factors, and the complement system (18,28,29). In addition, systemic anticoagulation is routinely needed to avoid/reduce clotting of the device.

An important finding of our study is that key factors of plasmatic coagulation were not substantially compromised by the initiation of extracorporeal support. Fibrinogen slightly decreased initially, and antithrombin-III values normalized over time. Most likely, this reflects overall stabilization of our patients, as acute septic shock was controlled by the initiated treatment. Lower values in the ECMO group at baseline probably result from the fact that more patients with severe sepsis were in this group. D-Dimers commonly increased according to length of treatment, but not during the first days. In all probability, this is related to ongoing clotting within the oxygenator, as exchange of the device often normalized D-dimers. Approximately 25% of our patients required at least one exchange of the oxygenator. Interestingly, on average the increase in D-dimers was more pronounced in ECMO patients compared with iLA patients, which may reflect a stronger fibrin deposition in pump-driven devices.

Platelet counts significantly dropped and remained low in patients treated with ECMO, but not in those treated with iLA. The latter finding is consistent with a small cohort of iLA-treated adult patients from Korea (30). During vv-ECMO, platelets decreased on average within 4 days to 60% of pre-ECMO values, and remained stable thereafter. Transfusion of platelets was necessary in 53 of 192 patients. A possible explanation for thrombocytopenia in some cases can be that ECMO-treated patients were sicker at baseline, tended to have a higher SOFA score, and more often met criteria for prevalent DIC (15 patients on ECMO vs. no patient on iLA). However, plasmatic coagulation improved in both groups, rendering thrombocytopenia solely due to ongoing DIC unlikely. For years, thrombocytopenia in ECMO-treated infants has been a common complication (29,31) and has been particularly attributed to the prolonged exposure of blood to foreign surfaces (32). Nowadays, heparin coating and a reduced foreign surface may contribute to a reduced platelet activation, but shear stress caused by high flow velocity remains an important issue (33). Depending on cannula size and mean arterial blood pressure, blood flow through iLA systems reaches about 1.5 L/min (27), which accounts for only about half of the average flow obtained in vv-ECMO in our patients (17). Therefore, it can be assumed that thrombocytopenia in ECMO-treated patients correlates with pump velocity, flow resistance of the system, and the amount of shear stress generated. Shear stress may predominantly occur with high negative outflow pressures. As we did not measure outflow pressures routinely, we cannot prove this assumption. Thus, the often observed drop of platelets in ECMO may be a pump-related problem, and iLA, despite its known limitations of low oxygen transfer and need for arterial cannulation, may have the advantage of less platelet consumption in comparison with vv-ECMO.

The need for blood cell transfusion on extracorporeal support has not been analyzed systematically. In the beginning, treatment with ECMO was associated with a high need for substitution of blood components, which accumulated to more than 2 L per day (8,9). Butch et al. found a need for transfusion of more than 15 000 units of blood components in 74 adult patients treated with ECMO for up to 53 days; the high amount of blood products was mainly caused by the substitution of platelets (34). Ang et al. described an average daily need for 2 units of RBC, 3 units of platelets, and 0.6 units of FFP (35). The current study reports a significantly lower need for transfusions, which seems to depend mainly on the disease causing ARDS and is highest in extrapulmonary sepsis. Overall, there was no difference in the amount of transfusions between the iLA and ECMO group, but patients with traumatic as well as extrapulmonary ARDS had a higher need for transfusions than those with primary pulmonary ARDS. Our data prove that despite an increased risk of bleeding and a somewhat higher need for transfusions, which may also be attributable to continuing surgical procedures, extracorporeal support is possible in the subgroup of traumatic lung failure (36).

In critically ill patients, it is difficult to separate effects of systemic anticoagulation on the need for transfusion from those caused by the underlying disorder. In our cohort, patients with a mean aPTT

above the median of 53 s required more transfusions of RBC than those with an aPTT below 53 s. Importantly, the average durability of membrane oxygenators, which is essentially defined by the extent of clotting on the membrane, did not differ in both groups. Therefore, it has become standard in our center to aim for an aPTT of about 50 s to minimize need for transfusions.

Yet it should be kept in mind that the time of implantation and times of decreased flow probably have a higher risk of clotting, which may require stronger anticoagulation. During implantation, generally a bolus of heparin is given. During weaning, we reduce blood flow to a minimum of 1.5 L/min and do not increase anticoagulation (see Fig. 1A). We cannot exclude that device clotting is accelerated, which is less relevant in clinical practice, as the patient is weaned from extracorporeal support. In iLA, lower flows are probably tolerable, as the surface area of the oxygenator is significantly smaller. Most oxygenators had to be changed after more than 7 days' treatment, which is not depicted in Fig. 1.

This study has several limitations. Data, which were collected prospectively in a large registry, were retrospectively analyzed. We compared two groups, which were different in sample size, gender ratio, and BMI. iLA is effective in carbon dioxide elimination, but hardly supports oxygen transfer in contrast to ECMO. Therefore, both devices have different indications for use, which is mirrored in different severity of disease (Table 1). Taking this fact into account, we concentrated on the longitudinal course of parameters in both groups. A comparison of our results with other reports may be hampered by the fact that treatment standards influence results. For example, it is obvious that the hemoglobin threshold for transfusion largely influences the amount of RBCs substituted. Also, it must be kept in mind that we analyzed groups of patients, and means do not represent the individual patient. Uncommon complications, like bacterial contamination of the oxygenator, may massively alter parameters of plasmatic coagulation (37).

Deep vein thrombosis related to cannulated vessels seems to be a common complication of vv-ECMO (38,39). Based on our experience, thrombosis in a jugular or caval vein is diagnosed in a relevant percentage of patients, and may be underestimated especially in patients on long-term ECMO. The impact of anticoagulation and preset goals for aPTT on the incidence of thrombo-embolic complications on ECMO have not been investigated yet. There was no systematic screening for deep vein thrombosis in our patients in the past. Therefore, at present we cannot give a recommendation on the best level of anticoagulation on miniaturized ECMO devices, before the amount of concurrent deep vein thrombosis is known. The dilemma of anticoagulation necessary to avoid the risk of thrombosis or clotting of the device versus anticoagulation increasing the risk of bleeding complications faces all ECMO therapies and will require an individual response in every patient. Bleeding complications were not fully documented in our database in the past. Therefore, we cannot give an accurate information on individual bleeding complications in relation to the level of anticoagulation. This important topic requires further investigation.

CONCLUSION

To our knowledge, this study is the first report comparing coagulation-related parameters in two large cohorts of adult patients with respiratory failure treated with different modalities of extracorporeal lung support. Our data attest that modern extracorporeal membrane oxygenation and interventional lung assist systems both allow a prolonged respiratory support without major impairment of the coagulation system. In vv-ECMO, but not in iLA, thrombocytopenia is common, but rarely requires platelet transfusions. Despite critical illness, there is usually no relevant consumption of coagulation factors if sepsis can be treated effectively, and most coagulation-related parameters normalized over time. In comparison with ECMO devices of the first generation, a lower systemic anticoagulation is possible without increased incidence of clotting within the device and a clearly reduced need for transfusion.

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