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Hemorrhagic complications during extracorporeal membrane oxygenation – The role of anticoagulation and platelets

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ABSTRACT

Purpose: Hemorrhagic complications during extracorporeal membrane oxygenation are frequent and have a negative impact on outcome. We studied the association between activated partial thromboplastin time or platelet count and the occurrence of hemorrhagic complications. The secondary objective was to determine risk factors for hemorrhagic complications.
Methods: Retrospective cohort study in a single-center Dutch university hospital. We included all adult patients on extracorporeal membrane oxygenation admitted to the intensive care unit between 2010 and 2017.
Results: We included 164 consecutive patients of which 73 (45%) had a hemorrhagic complication. The most prevalent hemorrhagic complications were surgical site (62%) and cannula site bleeding (18%). Survival to discharge was 67% in the patients without a hemorrhagic complication and 33% in the patients with hemorrhagic complications ($p < .01$). A higher activated partial thromboplastin time in the 24 h prior was associated with the occurrence of hemorrhagic complications (adjusted hazard ratio per 10 s increase 1.14; (95% CI 1.05–1.24). Venoarterial extracorporeal membrane oxygenation, duration of support, and higher activated partial thromboplastin time were risk factors for the occurrence of hemorrhagic complications.
Conclusions: Higher activated partial thromboplastin time is associated with the occurrence of hemorrhagic complications.

1. Introduction

Extracorporeal membrane oxygenation (ECMO) is used to support critically ill patients with cardiorespiratory dysfunction when conventional treatments have failed. Data from the Extracorporeal Life Support Organization (ELSO) registry show that the use of ECMO is increasing over the last decades with an overall weaning success of 70%, and 58% survival to hospital discharge [1].

Complications of ECMO can be patient-related or of mechanical nature, that is the ECMO circuit components including the cannulas. Exposure of blood to the nonbiologic surfaces of an extracorporeal circuit initiates a complex inflammatory response involving the intrinsic and extrinsic coagulation pathway, complement systems, endothelial cells, leucocytes and platelets [2]. The most feared complication is a thromboembolic stroke due to clotting related to the ECMO circuit. Anticoagulation is necessary to prevent thrombosis. The most used anticoagulant in this setting is unfractionated heparin. Unfortunately, titrating the intensity of anticoagulation to prevent the ECMO circuit from clotting without inducing bleeding risk remains a major challenge. Hemorrhagic and thrombotic complications, including intracranial hemorrhagic and ischemic stroke, surgical bleeding, and circuit thrombosis occur frequently [1]. Both hemorrhagic and thromboembolic complications have a significant impact on morbidity and mortality although the impact varies between studies and seems to be stronger during venoarterial (VA) ECMO support [3-5]. Some studies suggest that instead of the occurrence of a serious bleeding event, the transfusion of red blood cells (RBC) is an independent risk factor for mortality [5,6]. The transfusion of platelets during venovenous (VV) ECMO was also identified as independent risk factor of in-hospital mortality [5].

Finding the balance between preventing clotting due to the circuit without inducing the risk for hemorrhagic complications is pivotal. A comprehensive guideline for the use and monitoring of anticoagulation during ECMO therapy may be found on the ELSO website (https://www.elso.org/Resources/Guidelines.aspx), but this guideline stops short of any one mandate, given the lack of evidence in favor of most of the practices reviewed [7]. Rigorous evaluations of anticoagulation use in ECMO patients are therefore urgently needed [8,9]. Recently the first pilot

Abbreviations: aPTT, activated partial thromboplastin time; ECMO, Extracorporeal membrane oxygenation; ELSO, Extracorporeal Life Support Organization; HR, hazard ratio; ICU, intensive care unit; RBC, red blood cells; VA, venoarterial; VV, venovenous.

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study was published in order to support a large randomized controlled trial comparing therapeutic heparin with a low dose heparin protocol [10].

The primary objective of the current study was to evaluate the association between activated partial thromboplastin time (aPTT) or platelet count and the occurrence of hemorrhagic complications. The secondary objective was to determine risk factors for hemorrhagic complications.

2. Materials and methods

This retrospective observational study was approved by the institutional review board, written informed consent was waived (METc2018/327).

The University Medical Center Groningen, the Netherlands, is a referral hospital for ECMO including bridge to heart- or lung transplantation in. The closed format adult intensive care unit (ICU) has a capacity of 40 beds with over 3000 admissions per year. All consecutive patients treated with ECMO between 2010 and 2017 in our ICU were included in the study. As occasionally minors are treated on our adult ICU we excluded patients if they were under the age of 16 years. Data were extracted from the medical records. The date, time and type of bleeding were meticously recorded. We also evaluated transfusions (red blood cell, platelet, fresh frozen plasma), duration of ECMO support, ICU and hospital length of stay, and in-hospital mortality.

All patients were treated with the Cardiohelp device (Maquet-Getinge) with dedicated ECMO cannulas and circuits (HLS Set Advanced 7.0). All patients received a bolus of unfractionated heparin (2500–5000 U) at the time of cannulation followed by a continuous infusion for the duration of ECMO therapy, although this may be withheld for 24 h in patients with recent surgery. The aim was to maintain aPTT between 50 and 70 s regardless of the mode of cannulation. APTT was measured every 6 h according to standard ICU care or more frequent if the heparin dosage was adjusted or circumstances warrants more frequent control. If the aPTT was out of range, the infusion rate of heparin was changed per protocol. Heparin was tapered or withheld in patients who had significant bleeding if conservative measures to stop the bleeding failed.

There was no strict protocol on platelet transfusion; in general platelet transfusion was given to maintain platelets ≥20 $\times$ 10^9 cells/L while transfusion threshold was adapted to maintain platelet count ≥50 $\times$ 10^9 cells/L in case bleeding occurred. Hemoglobin was maintained ≥4.3 mmol/L (6.9 g/dl), except in patients bridged to organ transplant for which a somewhat lower hemoglobin level was accepted if tolerated

Hemorrhagic complications were registered according to the ELSO definitions. Major bleeding was defined as clinically overt bleeding with a decrease in hemoglobin of at least 1,24 mmol/L (2 g/dl)/24 h, or a transfusion requirement of 1 or more 10 ml/kg RBC transfusions over that same time period. Retroperitoneal bleedings, pulmonary or bleedings that involves the central nervous system or require surgical intervention were also considered as major bleeding [7].

2.1. Statistical analysis

The primary analysis was performed using the mean aPTT during the 24 h prior to the event and the last known platelet count prior to the moment of the complication, because platelet count was usually not measured more than once daily. For the patients without a hemorrhagic complication the aPTT and platelet count from the median day of the first hemorrhagic complication (day 3) was used for analyses if the patient was still on ECMO, otherwise the measurements at the last full day of ECMO were used for comparison. Comparisons between patients with and without hemorrhagic complications were done with a Fisher exact test for categorical variables and with a Mann-Whitney *U* test for continuous variables. Cox regression analyses were used to study if aPTT or platelets were associated with hemorrhagic complications yielding crude hazard ratio's (HRs) with corresponding 95% confidence interval. We assessed the influence of adjustment of the crude HRs using clinically meaningful variables from in Table 1 in the subsequent multivariable analyses. To assess risk factors for hemorrhagic complications during ECMO support, we performed a stepwise Cox regression with the backward method. The full model consisted of the same clinically meaningful variables from Table 1. A p value < .05 (two sided) was considered to be statistically significant. Statistical analyses were conducted using the IBM SPSS Statistics version 23.0 software package.

3. Results

During the study period 164 consecutively patients were treated with ECMO and included in the analyses. Demographic data are presented in Table 1. Seventy-three patients (45%) had a hemorrhagic complication, 16 (10%) patients had more than one hemorrhagic complication. The most prevalent hemorrhagic complications were surgical site and cannula site bleeding (Table 2). The median time to the first hemorrhagic complication was on day 1(IQR: 0–5 days) after initiation of ECMO. Lethal hemorrhagic stroke occurred in four patients, in three patients on the fifth day of treatment and in one case the bleeding was on day 19. Of these four patients, one patient had a severe thrombocytopenia, therefore heparin was already withheld before the hemorrhagic stroke occurred, in one patient platelet count was 103 $\times$ 10^9 cells/L, but the aPTT was above range (100–120 s) for >12 h before the event, while in the remaining two patients both the aPTT and platelet count were within range. There were 2 patients with a thromboembolic

Table 1
Baseline characteristics of patients with and without hemorrhagic complication.

Demographic data	All (n = 164)	Without hemorrhagic complication, (n = 91, 55%)	With hemorrhagic complication (n = 73, 45%)	p
Age, years, median (IQR)	51 (39–60)	51 (39–60)	51 (40.5–60.5)	0.75
Female sex, n (%)	78 (48%)	34 (44%)	44 (56%)	0.87
Body mass index, kg/m^2 median	24.8 (21.9–27.7)	26.6 (22.4–27.6)	24.9 (21.6–28.3)	0.92
APACHE II score, median (IQR)	22 (17–27)	21 (17–27)	23 (17–28)	0.61
Patient category				0.01
Respiratory, bridge to recover	37 (23%)	31 (84%)	6 (16%)	
Respiratory, bridge to transplant	28 (17%)	12 (43%)	16 (57%)	
Cardiac, bridge to recover	22 (13%)	12 (54.5%)	10 (45.5%)	
Cardiac bridge to bridge of transplant	6 (4%)	3 (50%)	3 (50%)	
Cardiac, Postcardiotomy	59 (36%)	27 (46%)	32 (54%)	
ECPR	12 (7%)	6 (50%)	6 (50%)	
Mode of ECMO, veno-arterial, n (%)	101 (61%)	48 (48%)	53 (52%)	0.01
Mode of cannulation, peripheral, n (%)	100 (61%)	63 (63%)	37 (37%)	0.03
Any surgical procedure, n (%)	100 (61%)	51 (51%)	49 (49%)	0.19
ECMO implanted directly after surgical procedure, n (%)	64 (39%)	31 (48%)	33 (52%)	0.15

IQR: interquartile range, ECPR: extracorporeal cardiopulmonary resuscitation, ECMO: extracorporeal membrane oxygenation.

Table 2
Type hemorrhagic complications during ECMO treatment.

Site of bleeding	First complication	Median day (IQR)	Second complication	Median day (IQR)
Total	73	1 (0–5)	16	4 (1−10)
Surgical site bleeding, n (%)	45 (62)	0 (0–2)	12 (75)	3 (1–8)
Cannula site bleeding, n (%)	13 (18)	3 (0–7)	0	
Pulmonary hemorrhage, n (%)	6 (8)	7 (2−11)	0	
Gastrointestinal hemorrhage, n (%)	3 (4)	1	1 (6)	7
Intracranial hemorrhage, n (%)	2 (3)	4	2 (13)	12 (5–19)
Other bleeding, n (%)	4 (5)	7 (2–18)	1 (6)	44

IQR: interquartile range.

stroke, that occurred on the 10th (aPTT was 90 s in 24 h prior) and 19th (aPTT was 54 s in 24 h prior) day of ECMO treatment both after having had a previous hemorrhagic complication. There was one patient with confirmed heparin induced thrombocytopenia who was switched to argatroban treatment.

Outcome parameters are shown in Table 3. In the group with hemorrhagic complications hospital survival was half (33%) as in the group without hemorrhagic complications (67%) ($p = .003$). The majority of patients ($n = 139$, 85%) had one or more RBC transfusions and 71 patients (43%) received platelets during ECMO support. Patients with hemorrhagic complications received more blood products than patients without hemorrhagic complications. The median number of RBC units or thrombocytes transfused while on ECMO was not significantly different between VA and VV mode, but the median number of plasma units transfused was significantly higher in the VA group (5 units) compared with the VV group (0 units; p 0.01). Furthermore, central cannulation was associated with higher requirements of total blood products (median 28 units) compared to peripheral cannulation (median 13 units, $p = .08$) and this was solely due to more plasma transfusions (median 10 vs. 0; p 0.001). The median number of RBC units transfused while on ECMO was higher in the patients who died regardless of ECMO mode.

A higher aPTT was associated with the occurrence of hemorrhagic complications (adjusted HR per 10 s increase 1.14; (95% CI 1.05–1.24). The adjusted hazard ratio per 10×10^9 platelets cells/L increase for the occurrence of hemorrhagic complications was 0.97 (95% CI 0.94–1.01) (Table 4). With the stepwise backward regression analyses we found that VA ECMO, duration of ECMO support, and higher aPTT were independent risk factors for the occurrence of hemorrhagic complications (Table 5). Platelets were not a statistical significant risk factor for the occurrence of hemorrhagic complications (hazard ratio 0.96, 95% CI 0.93–1.01).

4. Discussion

The main finding of our study is that mean aPTT in the 24 h prior is associated with the occurrence of a hemorrhagic complication in patients with ECMO support. Platelet count was not associated with hemorrhagic complications. Risk factors for the occurrence of hemorrhagic complications are a higher aPTT, duration of ECMO, and VA ECMO of which the latter is the most important. Another finding is that the occurrence of hemorrhagic complications during ECMO support is frequent and has a negative impact on hospital survival. Reducing the risk for hemorrhagic complications may therefore improve outcome of ECMO treatment. Aiming for lower aPTT targets seems the most potential modifiable factor to achieve this.

Strong points of our study are that we have complete data including a precise time to event, established ELSO definitions of bleeding, and supporting laboratory measurements in a large cohort that includes both VV and VA ECMO patients.

The high occurrence of hemorrhagic complications in our cohort is most likely caused by the overrepresentation of postcardiotomy patients, which makes it difficult to compare our results to previous reported incidences as most studies include a specific ECMO modality (VA or VV). According to the ELSO registry the incidence of surgical site bleeding is 10.5–20.2%, bleeding from the cannula site 13.2–18.5% and hemorrhagic stroke 2.2–3.9% [1,11]. In a study with predominant patients on VV ECMO 80% had a bleeding event, but only a few major bleeding events occurred [4]. In a systematic review and meta-analysis on anticoagulation in VV ECMO totaling 18 studies ($n = 646$) the overall rate of hemorrhagic complications was 29% while major bleeding across all studies was 10–16% [9,12]. In several studies of adult patients on ECMO for cardiogenic shock the incidence for hemorrhagic complications varied between 15 and 63%. [5,13-15]. In a systematic review and meta-analysis on anticoagulation in VA ECMO totaling 26 studies (1496 patients) the summary prevalence of major bleeding was 27% (95% CI 18%–35%), with considerable between-study heterogeneity. Major bleeding requiring reoperation was the most common hemorrhagic complication [15]. The diversity in incidence may be due to the different definitions of (major) bleeding and the mode of ECMO support used in the studies. However, analysis of studies performed after 2010 showed a declining rate of thromboembolic complications and a stable rate of hemorrhagic complications [15]. Therefore, the

Table 3
Outcome parameters for patients with and without hemorrhagic complication.

Outcome parameters	All patients, n = 164	Patients without hemorrhagic complication, n = 91 (55%)	Patients with hemorrhagic complication N = 73 (45%)	*p*
Duration of ECMO, days	4.4 (1.6–8.7)	3.04 (1.4–7.6)	6.06 (2.0–14.4)	0.001
Duration of mechanical ventilation, days	10.6 (3.2–20.7)	8.7 (2.6–16.5)	12.5 (5.7–27.6)	0.183
Length of ICU stay, days	15 (5–30)	14 (4–28)	17 (6–34)	0.332
Length of hospital stay, days	29 (11–63)	30 (11–63)	28 (9–62)	0.892
Successful weaning of ECMO, yes	98 (60%)	62 (63%)	36 (37%)	0.017
Survival to hospital discharge or transfer, n (%)	80 (49%)	54 (67%)	26 (33%)	0.003
aPTT 0-24 h before complication (seconds)	62 (47–80)	60 (45–72)	63 (49–90)	0.088
Platelets prior to complication (x 10^9 cells/L)	103 (64–165)	125 (74–176)	84 (54–145)	0.007
Total blood products/ECMO run, median	8 (3−22)	4 (1–8)	22 (11–41)	<0.001
Total RBC/ECMO run, median	6 (2–16)	3 (1–6)	16 (6–29)	<0.001
Total FFP/ECMO run, median	0 (0–5)	0 (0–2)	4 (0–15)	<0.001
Total platelets/ECMO run, median	0 (0–2)	0 (0)	2 (0–4)	<0.001

Data are shown as absolute values and percentages of the study population or their respective median and interquartile range.
ECMO: extracorporeal membrane oxygenation, ICU: intensive care unit, aPTT: activated partial thromboplastin time, RBC: red blood cells, FFP: fresh frozen plasma.

Table 4
Chance for hemorrhagic complications for aPTT and platelet count.

Variable	Crude hazard ratio (Confidence Interval 95%)	Adjusted hazard ratio[a] (Confidence Interval 95%)
Mean aPTT 24 h prior (per 10 s)	1.13 (1.04–1.23)	1.14 (1.05–1.24)
Platelets on day of event (10×10^9/L)	0.95 (0.92–0.98)	0.97 (0.94–1.01)

aPTT: activated partial thromboplastin time.
[a] Adjusted for age, sex, APACHE II, mode of ECMO support, ECMO duration, and platelet count or aPTT.

improved design of ECMO systems and cannula's in recent years may also have had a large impact on the occurrence of thromboembolic complications, but not on hemorrhagic complications as anticoagulation targets pretty much remained unchanged.

Several factors have been postulated to be associated with the occurrence of hemorrhagic complications during ECMO support, including higher aPTT on the day prior to the complication, a higher APACHE III score at ICU admission, and post-surgical ECMO [3]. Fungal pneumonia as indication for ECMO support was also postulated as risk factor for a hemorrhagic complication [4]. Finally, loss of high-molecular-weight von Willebrand factor multimers occurs in patients on ECMO. This acquired von Willebrand's disease might also play a role in the bleeding tendency [16].

Of these risk factors only administration of heparin as reflected by the level of anticoagulation (aPTT target) is modifiable. Since strict guidelines are lacking, there are huge differences in daily practice regarding the level of anticoagulation. In an international survey on anticoagulation during ECMO support the aPTT target varied between 40 and 80 s for 80% of the participating centers, with the majority using 60–80 s for VA-ECMO and 40–60 s for VV-ECMO [17]. Given the association between aPTT and hemorrhagic complications the higher aPTT target during VA ECMO support may in part explain the higher incidence of hemorrhagic complications we and others found when using this ECMO mode. Our findings are in line with a retrospective cohort of 149 patients, mostly supported by VA ECMO, in two centers in which the highest aPTT quartile on the day prior to the bleeding event was shown to be an independent risk factor. In both groups platelet count was above 100×10^9/L. [5]. In a retrospective analysis of 59 patients (83% on VV ECMO) there was no significant difference in aPTT on days with a bleeding event compared to days without [4]. A single center study in which 123 patients undergoing VV ECMO were retrospectively reviewed compared three sequential eras of anticoagulation strategy: activated clotting time (ACT: 160–180 s), high aPTT (60–80 s), and low aPTT (45–55 s). Both major bleeding and thromboembolic events were statistically significantly lower with a low aPTT target compared to the two other strategies [18]. The pilot study, endorsed by the international ECMO network, randomizing patients between therapeutic heparin (aPTT 50–70 s) to a low dose heparin protocol (aPTT <45 s) showed that it was possible to achieve a significant difference in daily aPTT and anti-Xa levels during the ECMO run. After subgroup analyses the difference in anticoagulation targets was only accomplished in patients on VV ECMO. In this small study ($n = 32$) there was no difference in bleeding [10].

Table 5
Risk factors for hemorrhagic complications based on stepwise backward Cox regression.

Variable	Hazard ratio (CI 95%)	p
ECMO mode of support, VA	2.89 (1.66–5.04)	<0.001
Mean aPTT 24 h prior (per 10 s)	1.11 (1.04–1.23)	0.003
Duration of ECMO, days	0.97 (0.94–0.99)	0.037

Variables entered on step 1: Sex, Age, APACHE II, ECMO mode of support, Duration of ECMO, Mean aPTT 24 h prior, Platelets on day of event.
CI: confidence interval, ECMO: extracorporeal membrane oxygenation, VA: venoarterial, aPTT: activated partial thromboplastin time.

In a small open label randomized study in 10 patients on VV ECMO evaluating a non-titrating, weight-based heparin scheme to a standard titration regime it was shown that the weight-based schema appeared to be safe in preventing circuit thrombotic complications. The median aPTT was significantly lower 38 vs. 48 s but did not result in a differences in transfused RBC's or documented bleeding complications [19]. In a study evaluating conventional ACT (180–220 s) vs. lower ACT (140–160 s) in a group with both VA and VV ECMO patients lower ACT targets led to significantly less transfusion of blood products, less major bleeding events and less bleeding-related deaths. However, the corresponding aPTT' s were 129.1 vs. 79.7 s, which are very high targets in our opinion [20].

Our study has several limitations. First, this is a single-center retrospective study. So we can only explore the association between risk factors and hemorrhagic complications. However, our data are very detailed on timing of hemorrhagic complications and the corresponding aPTT and platelet count without missing values. Although our study involves more patients than previous reports, given the heterogeneity among patients on ECMO support it is still a relatively small population. In our hospital the mode of ECMO does not lead to a different anticoagulation target which might limit generalizability to centers that do have different targets for VV and VA ECMO. We do not have information on the amount of heparin infused because it is not documented automatically in our hospital we cannot extract this information reliably for this study. Also we do not routinely use anti Xa, platelet function analysis, rotational thromboelastometry or thromboelastography in our ICU, which might have provided additional information. Several authors suggest using a more comprehensive assessment of clot dynamics. The rotational thromboelastometry and platelet function analysis was used in a small prospective study in VAD and ECMO patients. This study showed that decreased maximum clot firmness in rotational thromboelastometry was associated with bleeding [21]. However another study using the rotational thromboelastometry did show that VV ECMO leads to a continuous increase in clotting time and a decrease in maximum clot firmness the longer ECMO lasts, but bleedings events could not be predicted [22]. In our center we did not measure parameters of von Willebrand factor or give von Willebrand factor concentrate so its contribution to hemorrhagic complications could not be estimated. We did not look systematically at thrombotic events other than thromboembolic stroke in our cohort. There were only two patients with a thromboembolic stroke but this may be underestimated in case of sedated patients with discrete symptoms. Furthermore, we did not take oxygenator exchanges into account, but we did not have any acute pump stops or emergency oxygenator exchanges in this cohort.

5. Conclusions

Higher aPTT is associated with the occurrence of hemorrhagic complications in patients on ECMO. Besides aPTT, risk factors for the development of hemorrhagic complications are VA-ECMO mode and duration of ECMO support. A prospective study must answer the question if reduced anticoagulation targets diminish hemorrhagic complications without an increase in thromboembolic complications or a negative impact on outcome.

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Availability of data

The dataset supporting the conclusions of this article is available at request to the corresponding author.

Declaration of Competing Interest

The authors have disclosed that they do not have any conflicts of interest.

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References

[1] Thiagarajan RR, Barbaro RP, Rycus PT, et al. Extracorporeal life support organization registry international report 2016. ASAIO J 2017;63:60–7.
[2] Millar JE, Fanning JP, McDonald CI, et al. The inflammatory response to extracorporeal membrane oxygenation (ECMO): a review of the pathophysiology. Crit Care 2016;20:387.
[3] Aubron C, DePuydt J, Belon F, et al. Predictive factors of bleeding events in adults undergoing extracorporeal membrane oxygenation. Ann Intensive Care 2016;6:97.
[4] Lotz C, Streiber N, Roewer N, et al. Therapeutic interventions and risk factors of bleeding during extracorporeal membrane oxygenation. ASAIO J 2017;63 (624-0).
[5] Aubron C, Cheng AC, Pilcher D, et al. Factors associated with outcomes of patients on extracorporeal membrane oxygenation support: a 5-year cohort study. Crit Care 2013;17:R73.
[6] Mazzeffi M, Greenwood J, Tanaka K, et al. Bleeding, transfusion, and mortality on extracorporeal life support: ECMO working group on thrombosis and hemostasis. Ann Thorac Surg 2016;101:682–9.
[7] Lequier L, Annich G, Al-Ibrahim O, et al. ELSO Anticoagulation Guidelines 2014. Available from: https://www.elso.org/Resources/Guidelines.aspx. [Accessed December 1, 2018].
[8] Combes A, Brodie D, Chen YS, et al. The ICM research agenda on extracorporeal life support. Intensive Care Med 2017;43:1306–18.
[9] Sklar MC, Sy E, Lequier L, et al. Anticoagulation practices during venovenous extracorporeal membrane oxygenation for respiratory failure. A systematic review. Ann Am Thorac Soc 2016;13:2242–50.
[10] Aubron C, McQuilten Z, Bailey M, et al. Low-dose versus therapeutic anticoagulation in patients on extracorporeal membrane oxygenation: a pilot randomized trial. Crit Care Med 2019. https://doi.org/10.1097/CCM.0000000000003780.
[11] Paden ML, Conrad SA, Rycus PT, et al. Extracorporeal life support organization registry report 2012. ASAIO J 2013;59:202–10.
[12] Vaquer S, de Haro C, Peruga P, et al. Systematic review and meta-analysis of complications and mortality of veno-venous extracorporeal membrane oxygenation for refractory acute respiratory distress syndrome. Ann Intensive Care 2017;7:51.
[13] Cheng R, Hachamovitch R, Kittleson M, et al. Complications of extracorporeal membrane oxygenation for treatment of cardiogenic shock and cardiac arrest: a meta-analysis of 1,866 adult patients. Ann Thorac Surg 2014;97:610–6.
[14] Zangrillo A, Landoni G, Biondi-Zoccai G, et al. A meta-analysis of complications and mortality of extracorporeal membrane oxygenation. Crit Care Resusc 2013;15:172–8.
[15] Sy E, Sklar MC, Lequier L, et al. Anticoagulation practices and the prevalence of major bleeding, thromboembolic events, and mortality in venoarterial extracorporeal membrane oxygenation: a systematic review and meta-analysis. J Crit Care 2017;39:87–96.
[16] 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 2015;120:730–6.
[17] Esper SA, Welsby IJ, Subramaniam K, et al. Adult extracorporeal membrane oxygenation: an international survey of transfusion and anticoagulation techniques. Vox Sang 2017;112:443–52.
[18] Shah A, Pasrija C, Kronfli A, et al. A comparison of anticoagulation strategies in venovenous extracorporeal membrane oxygenation. Crit Care Med 2016;44(12):93.
[19] Deatrick KB, Galvagno SM, Mazzeffi MA, et al. Pilot study evaluating a non-titrating, weight-based anticoagulation scheme for patients on veno-venous extracorporeal membrane oxygenation. Perfusion 2019. https://doi.org/10.1177/0267659119850024 [May 23. [Epub ahead of print].
[20] Yeo HJ, Kim DH, Jeon D, Kim YS, Cho WH. Low-dose heparin during extracorporeal membrane oxygenation treatment in adults. Intensive Care Med 2015;41(11):2020–1.
[21] Laine A, Niemi T, Suojaranta-Ylinen R, et al. Decreased maximum clot firmness in rotational thromboelastometry (ROTEM®) is associated with bleeding during extracorporeal mechanical circulatory support. Perfusion 2016;31:625–33.
[22] Hellmann C, Schmutz A, Kalbhenn J. Bleeding during veno-venous ECMO cannot reliably be predicted by rotational thrombelastometry (ROTEM™). Perfusion 2018;33:289–96.