Ying Liu¹ Zhiyong Yuan¹ Xiaoning Han¹ Kai Song² Jinyan Xing¹

Hamostaseologie 2023;43:171-178.

Address for correspondence Jinyan Xing, PhD, The Affiliated Hospital of Oinadao University, Wutaishan Road 1677, Qingdao, Shandong Province 266003, People's Republic of China (e-mail: xingjy@qdu.edu.cn).

Abstract

Background Unfractionated heparin is used to prevent coagulation activation in patients undergoing extracorporeal membrane oxygenation (ECMO) support. We designed this study to determine the preferable indicator for anticoagulation monitoring.

Methods We conducted a retrospective study and divided the patients into an activated coagulation time (ACT)-target group and an activated partial thromboplastin time (aPTT)-target group. The correlations between ACT, aPTT, and the heparin dose were explored.

Results Thirty-six patients were included (19 aPTT-target and 17 ACT-target patients); a total of 555 matched pairs of ACT/aPTT results were obtained. The correlation between the ACT and aPTT measurements was rs = 0.518 in all 555 pairs. The Bland-Altman plot showed data points outside the displayed range (51.2–127.7), suggesting that the agreement between ACT and aPTT was poor. The aPTT group had fewer heparin dose changes $(2.12 \pm 0.68 \text{ vs. } 2.57 \pm 0.64, p = 0.05)$ and a lower cumulative heparin dose (317.6 ± 108.5) vs. 396.3 \pm 144.3, p=0.00) per day than the ACT group. There was no difference in serious bleeding (9 vs. 5; p = 0.171) or embolism events (3 vs. 3; p = 1.0) or in the red blood cell and fresh frozen plasma transfusion volumes between the ACT- and aPTT-target groups. Similarly, there was no significant difference in the ECMO duration (9 [4-15] days vs. 4 [3–14] days; p = 0.124) or length of ICU hospitalization (17 [5–32] days vs. 13 [4–21] days; p = 0.451) between the groups.

Conclusion The correlation between ACT and aPTT and the heparin dose was poor. The aPTT group had fewer daily heparin dose changes and a lower cumulative heparin dose per day than the ACT group, with no more bleeding and thrombotic events. Therefore, we recommend aPTT rather than ACT to adjust heparin dose in the absence of better monitoring indicators.

Keywords

- ECMO
- thrombosis
- bleeding
- ACT
- aPTT

received September 20, 2021 accepted after revision March 11, 2022

DOI https://doi.org/ 10.1055/a-1796-8652. ISSN 0720-9355.

© 2022. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (https://creativecommons.org/ licenses/by-nc-nd/4.0/)

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

¹The Affiliated Hospital of Qingdao University, Qingdao, Shandong, People's Republic of China

² Oingdao University, Oingdao, Shandong, People's Republic of China

Introduction

Extracorporeal membrane oxygenation (ECMO) is a life-support method that provides respiratory and circulatory support for patients with respiratory failure, with or without heart failure. It is being increasingly used in the adult patient population. The management and technology of ECMO support have made significant progress in recent years. Nevertheless, mortality rates of patients with ECMO therapy remain as high as 38 to 42% in venovenous (VV)^{2,3} and 59 to 71% in venoarterial (VA) ECMO cohorts.²

During extracorporeal life support (ECLS), the exposure of the patient's blood to the artificial, nonendothelialized surfaces of an extracorporeal circuit leads to increased initiation of coagulation, cellular activation, and increased inflammation, which disrupts the normal homeostasis of patients who are already seriously ill. In addition, the shear stress and turbulence of this process further promote this activation, along with platelet or fibrin deposition at both high and low shear forces.⁴ Therefore, anticoagulation therapy is needed to keep the extracorporeal circuit unobstructed, without causing bleeding or thrombosis in the patients receiving ECMO support. Although other agents have been used, the overwhelming majority of international experience and data on ECMO have recommended the use of heparin anticoagulation for its advantages of low price, titratability, and reversibility.⁵

Despite the advances in the monitoring techniques and the treatment of abnormal coagulation cascades during ECLS, bleeding and thrombosis are still major complications that may be associated with morbidity and mortality related to ECMO. Approximately 27 to 60% of the ECMO patients experience hemorrhage, 6-8 while the true incidence of thromboembolic complications is unclear. Autopsy studies have suggested that the occurrence of these complications is underestimated. The most recent annual Extracorporeal Life Support Organization (ELSO) report indicated that nearly 13% of ECMO patients had clots that developed in the oxygenator. Central nervous system infarction was reported to occur in up to 3.5% of patients. 10

Nevertheless, the guidelines issued by the ELSO do not recommend any specific anticoagulation target for patients with VA or VV ECMO. Each ECMO program must develop a method to monitor the anticoagulant effect of unfractionated heparin to make it most effective for the patients at their own centers. Suggestions were made to monitor the effectiveness of heparin using activated coagulation time (ACT), with a target level of 180 to 200 seconds, or activated partial thromboplastin time (aPTT), with a prolongation of the target to 50 to 80 seconds. Recent Chinese guidelines indicate maintaining the ACT in the range of 140 to 220 seconds.

ACT and aPTT are the most commonly used metrics to assess anticoagulation during ECMO because of their ease of automation, accessibility, and relatively low cost. Unfortunately, the assays use different reagents and are affected by several biological factors that do not reflect the heparin activity. The main disadvantages include the constantly

fluctuating results, which necessitate multiple-dose adjustments and blood samples and delay the achievement of the treatment goals. ¹⁴ There are other indicators for monitoring the anticoagulant effects, including anti-factor Xa and thromboelastography, but they may have disadvantages in certain circumstances. The results from these assays can vary among the different research centers, among patients with different diseases, and even in the same patient at different times.

The clinical monitoring of heparin anticoagulation during ECMO has several important limitations. Most hospitals, including ours, can only monitor ACT and aPTT. Based on our observation and experience, monitoring ACT and aPTT may lead to different effects. Therefore, we designed a study to determine which indicator is preferable. The purposes of our study were (1) to verify the correlation between aPTT and ACT and the relationship of these two variables with the heparin dose and (2) to compare the risk of bleeding and embolism between aPTT and ACT monitoring.

Patients and Methods

Study Design

We conducted a retrospective study of 36 adult patients who received VV or VA ECMO treatment between October 2019 and October 2020 in a single center in Shandong Province, China. VV ECMO provides respiratory support for patients, while VA ECMO provides both respiratory and hemodynamic support. The study protocol was reviewed and approved by the Qingdao University Research Ethics Board (QYFYWZLL26348).

Patients were eligible for the study if they needed ECMO support, had not started taking heparin, and did not meet any of the following exclusion criteria: age under 16 years, death within 24 hours, pregnancy, refusal to have blood transfusions, any contraindication to heparin, or fewer than five pairs of corresponding ACT and aPTT measurements.

Before March 2020, we adjusted the heparin dosage for ECMO-treated patients to maintain an ACT of 160 to 180 seconds for VV ECMO and 180 to 200 seconds for VA ECMO patients. These values were lower than those that have been recommended by previous guidelines because we have observed that these values could maintain effective anticoagulation without bleeding. However, we observed that ACT was highly variable, even when the heparin dose was not changed. Therefore, after March 2020, we switched to a policy of maintaining the aPTT ratio at a target value of 2 to 3; we continued to monitor the ACT while monitoring the aPTT. On that basis, patients were placed into the ACT-target group or the aPTT-target group. In accordance with our protocol, ACT and aPTT were measured every 4 hours. When the circuit had changed or when the patient's clinical condition had changed, additional testing was required.

The ACT was obtained at the bedside using ACTALYKE MINI (Helena Laboratories, USA) containing an activator cocktail of glass particles, kaolin, and cellulite. The aPTT was measured in the laboratory Synth ASil (colloidal silica

and synthetic phospholipid activator) reagent on an ACL TOP700 CTS (Instrumentation Laboratory, Bedford, USA).

Complications Related to ECMO Anticoagulation **Treatments**

Bleeding events were defined according to the ELSO definition¹²: we defined an event as a bleeding event if there was clinically overt bleeding recorded in the medical and/or nursing charts in association with either the administration of two or more red blood cell (RBC) units within 24 hours or when there was a decrease in hemoglobin more than 2 g/L within 24 hours; if a patient developed a hemothorax, central nervous system or retroperitoneal bleeding; or if the bleeding required an intervention. If the same primary source continued to bleed during consecutive days, those days were considered part of the same bleeding event. When a patient had more than one bleeding source on the same day, this was also recorded.

Thromboembolic complications, including deep venous thrombosis, ischemic stroke, intracardiac thrombus, pulmonary embolism, and membrane circuit clotting requiring a membrane change, were collected from the medical records.

RBC transfusion was given to patients to maintain a hemoglobin concentration above 7 g/dL. Prophylactic blood products were not routinely given for coagulation abnormalities, with the exception of patients with severe thrombocytopenia (<50,000 platelets/mm³). In the case of bleeding, patients received platelets to maintain a platelet count of 80,000/mm³, fresh frozen plasma to maintain an international normalized ratio of less than 1.5 or a percentage prothrombin time greater than 70%, and cryoprecipitate or fibrinogen concentrate to maintain a fibrinogen plasma concentration of 1.5 g/L. The number of blood transfusions given to each patient was collected from our electronic medical record system.

Data Collection and Quality Control

The following data were obtained: (1) baseline characteristics-sex, age, APACHE II score, primary disease on ECMO treatment, and ECMO mode; (2) anticoagulation monitoring -aPTT, aPTT ratio, matched ACT and heparin doses, and other coagulation-related measurements (such as platelets, antithrombin III, and fibrinogen); (3) other treatment-antiplatelet drugs, renal replacement therapy, blood transfusion volume; (4) outcomes-bleeding events, thrombotic events, mechanical ventilation duration, length of ICU stay in days, length of hospital stay in days, ECMO duration, and mortality.

At each time point, we recorded the ACT and aPTT values and the corresponding heparin dose of each ECMO patient. We explored the correlations between ACT, aPTT, and heparin through all of the abovementioned data. All data were collected electronically on an electronic clinical report form.

Statistical Analysis

Descriptive statistics, including the medians and interquartile ranges (IQRs) or the counts and percentages, were calculated for all variables. Baseline comparisons were performed using chi-square tests (to test for equal proportions) for the categorical data, with independent t-tests for continuously normally distributed variables and with Wilcoxon's rank-sum tests in all the other data, with results reported as the n (%), mean (standard deviation), or median (IOR). We also performed a subgroup analysis of the VV and VA.

To investigate the correlations between ACT, aPTT, and heparin dose, the pairs for all of the patients were plotted on scatter plots, a bivariate analysis was carried out, and the Spearman productmoment correlation coefficient was calculated. Bland-Altman plots were constructed with the 95% confidence intervals (CIs) that are shown. All analyses were performed using SPSS 20.0. Statistical significance was defined as p < 0.05.

Results

Basic Characteristics of the Study Participants

A total of 36 patients were included in the study, including 28 male patients (77.8%). Twenty-six patients (72.2%) received VA ECMO therapy. Nineteen patients were in the aPTT-target group, and 17 patients were in the ACT-target group. There were no differences in sex, age, or the APACHE II score between the two groups (see Table 1).

Comparison of ACT and aPTT

Correlation between the ACT and aPTT and the Heparin

From the 36 patients included in the study (19 aPTT-target and 17 ACT-target patients), a total of 555 matched pairs of ACT and aPTT results were obtained, which were plotted on scatter plots, as shown in Fig. 1. A bivariate analysis was carried out, and the Spearman product-moment correlation coefficient was calculated.

The correlation between the ACT and aPTT measurements was rs = 0.518 in the overall set of 555 pairs. In the VV ECMO patients, 202 pairs were included, with a correlation coefficient of rs = 0.507. The correlation coefficient was rs = 0.511in the 353 matched pairs from the VA ECMO patients. The correlations between aPTT and heparin dosage were rs = 0.407, rs = 0.494, and rs = 0.316 in the overall, VV ECMO, and VA ECMO groups, respectively, which were stronger than those between the ACT and heparin dosage (Table 2).

To further directly compare the aPTT and ACT, a Bland-Altman plot was drawn from the mean and difference of the ACT and aPTT (shown in ► Fig. 2). The data points outside the displayed range suggest that the agreement between ACT and aPTT is poor.

Patient Outcomes

Comparison of the Heparin Dose between the Two Groups

We compared the times of the heparin dose changes per day between the two groups. The aPTT group had fewer changes than the ACT group (2.12 \pm 0.68 vs. 2.57 \pm 0.64, p = 0.05). The cumulative heparin dose per day between the two cohorts was also compared and was calculated as $U/kg \times d$. All of the data were collected except the bleeding period. The aPTT

Table 1 Baseline characteristics of the included patients

| Variables | All patients (n = 36) | ACT target (n = 17) | aPTT target (n = 19) | р |
|----------------------|-----------------------|---------------------|-------------------------|-------|
| VV ECMO | 10 | 6 | 4 | |
| VA ECMO | 26 | 11 | 15 | |
| Gender (male) | 28 | 14 (82.4%) | 14 (73.7%) | 0.414 |
| Antiplatelet therapy | 20 | 7 (41.2%) | 13 (68.4%) | 0.096 |
| CRRT | 22 | 11 (63.7%) | 11 (57.9%) | 0.470 |
| Age (years) | 55.89 ± 16.42 | 60.42 ± 14.65 | 50.82 ± 17.21 | 0.080 |
| APACHE II score | 20.69 ± 8.74 | 20.79 ± 6.40 | 22.18 ± 7.88 | 0.564 |

Abbreviations: ACT, activated coagulation time; APACHE II score, Acute Physiology and Chronic Health Evaluation II Score; aPTT, activated partial thromboplastin time; CRRT, continuous renal replacement therapy; VA ECMO, venoarterial extracorporeal membrane oxygenation; VV ECMO, venovenous extracorporeal membrane oxygenation.

Notes:

p refers to the difference between the ACT target and aPTT target cohorts, and the p-value was calculated by the chi-square test.

^{+/-}" refers to mean +/- standard deviation.

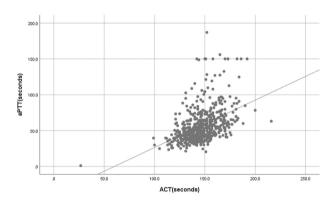


Fig. 1 Graph showing the relationship between activated coagulation time (ACT) and activated partial thromboplastin time (aPTT).

group took less heparin than the ACT group (317.6 \pm 108.5 vs. 396.3 ± 144.3 , p = 0.00; ►Table 3).

Bleeding and Thromboembolic Events in the ACT-Target and aPTT-Target Groups

Among the 36 patients included in the study, 14 patients experienced bleeding, and 6 patients experienced thromboembolic events. As bleeding events are more likely to occur in patients with a longer duration of ECMO, the data were presented as "bleeding events per day of ECMO." There was no difference between the ACT- and aPTT-target

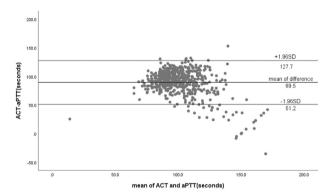


Fig. 2 Bland-Altman graph based on activated coagulation time (ACT) and activated partial thromboplastin time (aPTT). The y-axis shows the difference in ACT and aPTT, and the x-axis shows the mean of ACT and aPTT. The mean difference between ACT and aPTT was

groups in the incidence of bleeding or embolism events. However, the bleeding incidence of aPTT-target patients was lower than that of ACT-target patients (26.3 vs. 52.9%; **►Table 3**).

Gastrointestinal bleeding (6 patients) and retroperitoneal hematomas (4 patients) were the most common among the 14 patients with bleeding. One case of fatal brain hemorrhage occurred, and heparin was stopped in one patient because of severe puncture-site bleeding.

Table 2 Correlations between ACT, aPTT, and the heparin dosage

| | All n = 555 | | ACT target n = 262 | | aPTT target n = 293 | | VV ECMO n = 202 | | VA ECMO n = 353 | |
|-------------------------|-------------|-------|--------------------|-------|------------------------|-------|--------------------|-------|--------------------|-------|
| | r | р | r | р | r | р | r | р | r | р |
| ACT and aPTT | 0.518 | 0.000 | 0.485 | 0.000 | 0.536 | 0.000 | 0.507 | 0.000 | 0.511 | 0.000 |
| ACT and heparin dosage | 0.165 | 0.000 | 0.132 | 0.000 | 0.310 | 0.000 | 0.310 | 0.000 | 0.033 | 0.349 |
| aPTT and heparin dosage | 0.407 | 0.000 | 0.570 | 0.000 | 0.320 | 0.000 | 0.494 | 0.000 | 0.316 | 0.000 |

Abbreviations: ACT, activated coagulation time; aPTT, activated partial thromboplastin time; VA ECMO, venoarterial extracorporeal membrane oxygenation; VV ECMO, venovenous extracorporeal membrane oxygenation.

[&]quot;n" refers to numbers of subjects.

Table 3 Comparison of the outcomes between the two groups

| Variables | ACT target n = 17 | aPTT target n = 19 | р |
|-------------------------------------------|-------------------|-----------------------|-------|
| Times of heparin changes (time/day) | 2.57 ± 0.64 | 2.12 ± 0.68 | 0.050 |
| Cumulative heparin dose $U/(kg \times d)$ | 396.3 ± 144.3 | 317.6 ± 108.5 | 0.00 |
| Serious bleeding event ^a | 9 (0.049 ± 0.077) | 5 (0.018 ± 0.041) | 0.196 |
| Thrombotic events | 3 (17.6%) | 3 (15.8%) | 1.0 |
| In-hospital mortality | 4 (23.5%) | 5 (26.3%) | 0.577 |
| ECMO duration (days) | 10 (8, 15) | 7 (3, 14) | 0.083 |
| Mechanical ventilation duration (days) | 9 (4, 16) | 8 (3, 17) | 0.645 |
| ICU hospitalization (days) | 17 (10, 33) | 13 (8, 21) | 0.274 |
| Total hospitalization (days) | 22 (13, 42) | 20 (14, 29) | 0.303 |

Abbreviations: ACT, activated coagulation time; aPTT, activated partial thromboplastin time; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit.

Table 4 Transfusion and circuit data in the VA ECMO patients

| Variables | ACT target n = 11 | aPTT target n = 15 | р |
|----------------------------------------|---------------------|-----------------------|-------|
| RBC transfusion volume (U) | 10 (4.0–18.5) | 4.0 (1.5–16) | 0.297 |
| FFP transfusion volume (mL) | 2,040 (1,140–4,890) | 1,000 (0-2,560) | 0.113 |
| ECMO duration (days) | 9 (4–15) | 4 (3-14) | 0.124 |
| Mechanical ventilation duration (days) | 6 (3–13) | 4 (3-14) | 0.658 |
| ICU hospitalization duration (days) | 17 (5–32) | 13 (4–21) | 0.451 |
| Total hospitalization duration (days) | 22 (18–32) | 19 (16–28) | 0.938 |

Abbreviations: ACT, activated coaquiation time; aPTT, activated partial thromboplastin time; ICU, intensive care unit; FFP, fresh frozen plasma; RBC, red blood cell; VA ECMO, venoarterial extracorporeal membrane oxygenation.

RBC transfusion volume: the number of transfused red cell concentrates.

FFP transfusion volume: the volume of FFP.

Since the above values are not normally distributed, the interquartile range is shown in bracket.

Transfusion and Circuit Data in VA ECMO Recipients

In our study, there were no differences in the blood transfusion volume, ECMO duration time, mechanical ventilation time, or length of hospital stay between the two groups of VA ECMO recipients (see ►Table 4).

Discussion

ECMO is a key technology for the treatment of cases of severe heart failure and respiratory failure that are difficult to control with conventional strategies. Since the first ECMO patient in 2015, the number of cases has gradually increased. We routinely monitored ACT and aPTT when the patients were on anticoagulation therapy, and sometimes we measured the thromboelastography as needed. Anti-Xa is not routinely monitored due to its high cost and complicated techniques, which are available only in a few laboratories. The purpose of our research was to study the correlation

among ACT, aPTT, and heparin to evaluate the safety and effectiveness of ACT and aPTT monitoring.

In our study, despite a moderate degree of positive correlation between ACT and aPTT in the Spearman analysis, the Bland-Altman plots showed a large dispersion. There has always been controversy about the correlation between the two indicators. Cunningham et al¹⁵ reported a similar result as ours, with a moderate degree of positive correlation between APR and N-ACT (rs = 0.55). Simko et al considered that both the aPTT and ACT are clinically useful for the monitoring of heparin therapy and that the ACT is theoretically equally as useful as the aPTT, ¹⁶ In Smythe et al's study, ¹⁷ the correlation between the ACT and aPTT results ranged from r = 0.64 to 0.67, which was higher than our result. The different results may be related to the different conditions of the patients and anticoagulant targets. For instance, patients with respiratory failure may have different etiologies that lead to varying degrees of multiple-organ failure and

^aNine patients in the ACT-target group and five patients in the aPTT-target group experienced serious bleeding events. As bleeding events are more likely to occur in patients with a longer duration of ECMO, the data were presented as "bleeding events per day of ECMO" in brackets. Note: Since the above values (ECMO duration, mechanical ventilation duration, ICU hospitalization, and total hospitalization) are not normally distributed, the interquartile range is shown in brackets.

complications, such as sepsis. The additional levels of complexity lead to intra- and interindividual variation. 18 Changes in the blood composition, the platelet count and function, and the levels of coagulation and inflammatory factors also affect the monitoring results in a slightly different fashion. 19

Both the ACT and aPTT had a poor correlation with the heparin doses, although the heparin doses were more strongly correlated with aPTT than with ACT. These results are similar to those of previous studies. 17,20 In terms of the changes in the heparin dose, the aPTT-target group had fewer daily heparin dose changes and fewer cumulative daily heparin dosages, indicating that aPTT monitoring could achieve a more stable effect with a lower dose, while there were no significant increases in the number of complications of bleeding and embolism. Studies that have compared the heparin dose and adjustment in patients with ECMO are rare. Smythe et al showed that the clinical decisions that were guided by the ACT results differed more than one-third of the time from the clinical decisions that were guided by the aPTT results.¹⁷ This might be because ACT is a whole blood-based measurement technique that has no exclusive sensitivity to unfractionated heparin and is not capable of differentiating between the affecting variables.²¹ ACT was unable to differentiate between low and therapeutic levels of anticoagulation when using the aPTT as the reference.²⁰

Bleeding may occur in any part of the body, such as the intubation or catheter insertion site, the respiratory tract, the digestive tract, the urinary tract, the brain, the skin and mucous membranes, or a surgical incision. The rate of major bleeding in our study was 38.9%, which is higher than the 27% rate that was reported in a previous systematic review $(95\% \text{ CI}, 19-36\%; I^2=91\%).^{22} \text{ In Sy et al's study, major}$ bleeding requiring reoperation was the most commonly reported event, followed by intracranial hemorrhage and cannula-site bleeding. Otherwise, the most common bleeding sites in our study were gastrointestinal and retroperitoneal, and we found only one patient in which anticoagulation needed to be stopped due to bleeding at the puncture site, which may be related to the fact that all of our patients were internal medicine patients, and this study excluded those patients who had just undergone cardiopulmonary bypass surgery.

In our study, four patients developed retroperitoneal hematomas (RPH) that occurred a few days after ECMO initiation, but these events appeared unrelated to ECMO cannulation (one VV ECMO recipient and three VA ECMO recipients). A RPH during ECMO management is rarely reported. Anticoagulants, antiplatelet therapy, and chronic renal failure may be risk factors for a spontaneous RPH.²³ As reported by Yamamura et al,²⁴ one possible mechanism of RPH occurs when the patient has been in a restrained supine position for a long time, resulting in the compression of the posterior side of the affected muscle. Another possible mechanism is the iliopsoas muscle strain that occurs during routine patient care, and this is unknown to nurses and patients.²⁵

Thrombosis is one of the most common and dangerous complications during ECMO support. Deep vein thrombosis, ischemic cerebral infarction, and membrane circuit clotting are the most common embolic events; the true incidence is underestimated due to the invisibility of embolism. The majority of reported thrombosis cases in our study were deep vein thrombosis, possibly because it is relatively easy to detect. The oxygenators and tubes were changed for two patients, both of who were ACT-target patients, due to the presence of thrombosis in their oxygenators. One aPTT-target patient developed an intracardiac thrombosis with a size of approximately $10\,\mathrm{cm} \times 0.7\,\mathrm{mm}$. Fortunately, the thrombosis disappeared after active anticoagulant therapy, and the patient was weaned from ECMO at 2 weeks.

In our study, there were no differences in the blood transfusion volume, ECMO duration time, mechanical ventilation time, or length of hospital stay between the two groups. Mazzeffi et al reported that aPTT-guided anticoagulation therapy is associated with a reduction in the number of blood transfusions by approximately 30%. ²⁶ In a case series of adults and children, an increase in the use of blood products was an independent risk factor that affected the prognosis of patients. ^{27,28} We failed to reach this conclusion, probably because we had fewer data, fewer cases, and larger differences in the transfusion volume. In addition, patients in different medical conditions may have different thresholds for blood transfusion. For instance, in patients with hypoxia, their hemoglobin levels may be increased to 10 g/L or higher to improve their oxygen supply.

Limitations

Our research has some limitations. First, the sample size was small, making it difficult to draw conclusions about which anticoagulation program is safer and more effective. The data recorded before 2019 were incomplete and could not be included in the study. Second, this is a retrospective study, and further RCTs are needed to analyze the correlations between ACT, aPTT, and heparin, as well as their relationship with bleeding and embolism events. Third, anticoagulation, bleeding, and embolization events are affected by a variety of factors, including the platelet counts and function and AT3, and the influence of these factors cannot be excluded in our study.

Conclusion

In our study, the correlation between ACT and aPTT and the heparin dose was poor, but compared with ACT, patients who were monitored using aPTT had fewer daily heparin dose changes and fewer cumulative heparin doses per day. There was no difference between the ACT and aPTT monitoring in terms of bleeding, embolism events, blood transfusion volume, ECMO duration, mechanical ventilation time, or length of hospital stay. aPTT appears to be a more reliable indicator than ACT in the anticoagulant monitoring of ECMO patients in the absence of other better indicators.

Our results should be applied with caution when generalized for other ICUs or other settings. Centers should develop their own anticoagulation protocols based on individual differences.

What is known about this topic?

Bleeding and thrombosis are common complications of anticoagulant therapy in ECMO patients. Each monitoring method of heparin anticoagulation during ECMO has limitations. Each ECMO program must develop a method to monitor the anticoagulant effect of unfractionated heparin to make it most effective for patients at their own centers.

What does this paper add?

There was a moderate positive correlation between ACT and aPTT, both of which had a poor correlation with heparin dose. There was no difference between the two monitoring methods in complications such as bleeding and embolism.

Funding

This research did not receive any specific grants from funding agencies in the public, commercial, or not-forprofit sectors.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

- 1 Esper SA, Levy JH, Waters JH, Welsby IJ. Extracorporeal membrane oxygenation in the adult: a review of anticoagulation monitoring and transfusion. Anesth Analg 2014;118(04):731-743
- 2 Thiagarajan RR, Barbaro RP, Rycus PT, et al; ELSO Member Centers. Extracorporeal life support organization registry international report 2016. ASAIO J 2017;63(01):60-67
- 3 Vaquer S, de Haro C, Peruga P, Oliva JC, Artigas A. Systematic review and meta-analysis of complications and mortality of venovenous extracorporeal membrane oxygenation for refractory acute respiratory distress syndrome. Ann Intensive Care 2017;7 (01):51
- 4 Winkler AM. Managing the precarious hemostatic balance during extracorporeal life support: implications for coagulation laboratories. Semin Thromb Hemost 2017;43(03):291-299
- 5 Oliver WC. Anticoagulation and coagulation management for ECMO. Semin Cardiothorac Vasc Anesth 2009;13(03):154-175
- 6 Dalton HJ, Reeder R, Garcia-Filion P, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network. Factors associated with bleeding and thrombosis in children receiving extracorporeal membrane oxygenation. Am J Respir Crit Care Med 2017;196(06):762-771
- 7 Mazzeffi M, Greenwood J, Tanaka K, et al. Bleeding, transfusion, and mortality on extracorporeal life support: ECLS working group on thrombosis and hemostasis. Ann Thorac Surg 2016;101(02): 682-689

- 8 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(02):610-
- 9 Rastan AJ, Lachmann N, Walther T, et al. Autopsy findings in patients on postcardiotomy extracorporeal membrane oxygenation (ECMO). Int J Artif Organs 2006;29(12):1121-1131
- Murphy DA, Hockings LE, Andrews RK, et al. Extracorporeal membrane oxygenation-hemostatic complications. Transfus Med Rev 2015;29(02):90-101
- 11 The Extracorporeal Life Support Organization (ELSO), ELSO Anticoagulation Guideline . Ann Arbor, MI; 2014:17
- 12 Lorusso R, Whitman G, Milojevic M, et al. 2020 EACTS/ELSO/STS/ AATS Expert Consensus on post-cardiotomy extracorporeal life support in adult patients. Ann Thorac Surg 2021;111(01): 327-369
- 13 Chinese Society of Cardiothoracic and Vascular Anesthesiology, Chinese Society of Anesthesiology, Chinese Association of Anesthesiologists, et al. Expert consensus on the clinical application of adult extracorporeal membrane oxygenation under different conditions (2020 edition). Chinese Circulation J 2020; 35:1052
- 14 Samuel S, Allison TA, Sharaf S, et al. Antifactor Xa levels vs. activated partial thromboplastin time for monitoring unfractionated heparin. A pilot study. J Clin Pharm Ther 2016;41(05):
- Cunningham D, Besser MW, Giraud K, Gerrard C, Vuylsteke A. Agreement between ACT and aPTT during extracorporeal membrane oxygenation shows intra- and inter-individual variation. Perfusion 2016;31(06):503-507
- Simko RJ, Tsung FF, Stanek EJ. Activated clotting time versus activated partial thromboplastin time for therapeutic monitoring of heparin. Ann Pharmacother 1995;29(10):1015-1021, quiz 1061
- Smythe MA, Koerber JM, Nowak SN, et al. Correlation between activated clotting time and activated partial thromboplastin times. Ann Pharmacother 2002;36(01):7-11
- Selleng S, Malowsky B, Strobel U, et al. Early-onset and persisting thrombocytopenia in post-cardiac surgery patients is rarely due to heparin-induced thrombocytopenia, even when antibody tests are positive. J Thromb Haemost 2010;8(01): 30-36
- 19 Peek GJ, Firmin RK. The inflammatory and coagulative response to prolonged extracorporeal membrane oxygenation. ASAIO J 1999; 45(04):250-263
- 20 Atallah S, Liebl M, Fitousis K, Bostan F, Masud F. Evaluation of the activated clotting time and activated partial thromboplastin time for the monitoring of heparin in adult extracorporeal membrane oxygenation patients. Perfusion 2014;29(05): 456-461
- Wehner JE, Boehne M, David S, Brand K, Tiede A, Bikker R. Activated clotting time (ACT) for monitoring of low-dose heparin: performance characteristics in healthy adults and critically ill patients. Clin Appl Thromb Hemost 2020; 26:1076029620975494
- Sy E, Sklar MC, Lequier L, Fan E, Kanji HD. 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
- Hwang NK, Rhee H, Kim IY, et al. Three cases of spontaneous lumbar artery rupture in hemodialysis patients. Hemodial Int 2017;21(01):E18-E21
- Yamamura H, Morioka T, Yamamoto T, Kaneda K, Mizobata Y. Spontaneous retroperitoneal bleeding: a case series. BMC Res Notes 2014;7:659

- 25 Sugiura G, Bunya N, Yamaoka A, et al. Delayed retroperitoneal hemorrhage during veno-venous extracorporeal membrane oxygenation: a case report. Acute Med Surg 2019;6(02): 180–184
- 26 Mazzeffi MA, Tanaka K, Roberts A, et al. Bleeding, thrombosis, and transfusion with two heparin anticoagulation protocols in venoarterial ECMO patients. J Cardiothorac Vasc Anesth 2019; 33(05):1216–1220
- 27 Kumar TKS, Zurakowski D, Dalton H, et al. Extracorporeal membrane oxygenation in postcardiotomy patients: factors influencing outcome. J Thorac Cardiovasc Surg 2010;140(02):330–336.e2
- 28 Martucci G, Panarello G, Occhipinti G, et al. Anticoagulation and transfusions management in veno-venous extracorporeal membrane oxygenation for acute respiratory distress syndrome: assessment of factors associated with transfusion requirements and mortality. J Intensive Care Med 2019;34(08):630–639

Erratum: This article has been corrected, the Copyright in the bottom line must be © 2022. The Author(s).