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Satisfactory outcome with low activated clotting time in extracorporeal membrane oxygenation

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Optimal anticoagulation is critical for successful extracorporeal membrane oxygenation (ECMO) to counterbalance the activation of the coagulation system initiated by the blood-biosurface reaction and mechanical stresses. Systemic anticoagulation is achieved mainly with unfractionated heparin (UFH). Activated clotting time (ACT) is a widely used laboratory parameter to monitor anticoagulation. The therapeutic range of ACT is 180–220 s. We investigated the effect of a lower target ACT (<150 s) during ECMO on safety and outcomes and compared it with those of a conventional target ACT (180–200 s). In this single-center, retrospective study, we reviewed 72 adult patients treated with ECMO from March 2017 to October 2019. We included 43 patients after applying the exclusion criteria and divided them into the low ACT group (<150 s, n = 14, 32.6%) and conventional ACT group (≥150 s, n = 29, 67.4%). There was no difference in the successful weaning from ECMO support (50% vs. 62.1%, $p = 0.452$) and discharge (50% vs. 41.4%, $p = 0.594$) rates between the groups. One patient in the conventional ACT group had intracranial hemorrhage. There was one thromboembolic complication case with an intra-circuit thrombus. To date, anticoagulation remains a challenge during ECMO. Our results suggest that a lower target ACT does not necessarily increase the thromboembolic risk during ECMO management. Clinicians may consider anticoagulation with lower ACT target for some patients with careful assessment and close monitoring. Further prospective trials are warranted to validate these results.

Keywords

Extracorporeal membrane oxygenation; Extracorporeal cardiopulmonary resuscitation; Anticoagulation; Activated clotting time; Complication; Discharge survival

1. Introduction

Extracorporeal membrane oxygenation (ECMO) is a supportive therapy that is increasingly being used for patients with acute respiratory or cardiocirculatory failure refractory to medical therapy. However, high mortality and morbidity rates are noted among patients receiving ECMO, partly due to device-related complications. Adverse outcomes, such as bleeding and thromboembolism, are expected due to the nature of the ECMO circuit components. As blood comes into constant contact with non-endothelial biosurfaces, the coagulation cascade, complement system, platelets and von Willebrand factor, and the fibrinolytic system are activated. Also, the shear stresses of the circuit pump contribute to hemolysis [1]. Continuous anticoagulation monitoring is crucial during ECMO, and a fine balance must be maintained between potential risks of bleeding and thromboembolism.

Unfractionated heparin (UFH) remains the mainstay for continuous anticoagulation therapy. The activated clotting time (ACT) and activated partial thromboplastin time (aPTT) are most commonly used to monitor heparin level. Although therapeutic anticoagulation during ECMO is defined by an ACT of 180–220 s [2], there is no consensus presently regarding the ACT target and the guidelines vary across different centers [3]. In cases of active bleeding and thrombocytopenia, the heparin dose is typically modified, which may lead to favorable outcomes [4–11]. In this study, we investigated the effect of a lower ACT target (<150 s) during ECMO management on safety and outcomes and compared the effects of lower ACT with those of a conventional target ACT (180–200 s) during ECMO.

2. Methods

This is a retrospective study at a single center. After institutional review board approval (2020AS0038), the data were retrospectively collected from the electronic medical records. Patients aged >18 years who received veno-venous (VV) or veno-arterial (VA) ECMO support from March 2017 to October 2019 were initially included. Because this study aimed to investigate the effect of low ACT (<150 s) on the outcomes of ECMO, to reduce bias we excluded some patients with possibly unstable coagulation systems. The other exclusion criteria were cardiopulmonary bypass weaning failure in the operating room leading to postoperative ECMO support, ECMO support duration <24 h, and non-availability of ACT data (only aPTT was monitored). The primary outcomes were thromboembolism and bleeding event, and the secondary outcomes were the rate of successful weaning from ECMO support and survival to discharge.

We used two different sets of ECMO circuits. One circuit comprised of a poly-methyl-pentene membrane oxygenator (PLS Quadrox, Maquet Cardiopulmonary, Hirrlingen, Germany), a centrifugal pump (Rotaflow, Maquet Cardiopulmonary, Hirrlingen, Germany), and recombinant human albumin and heparin-coated tubes (Bioline, Maquet

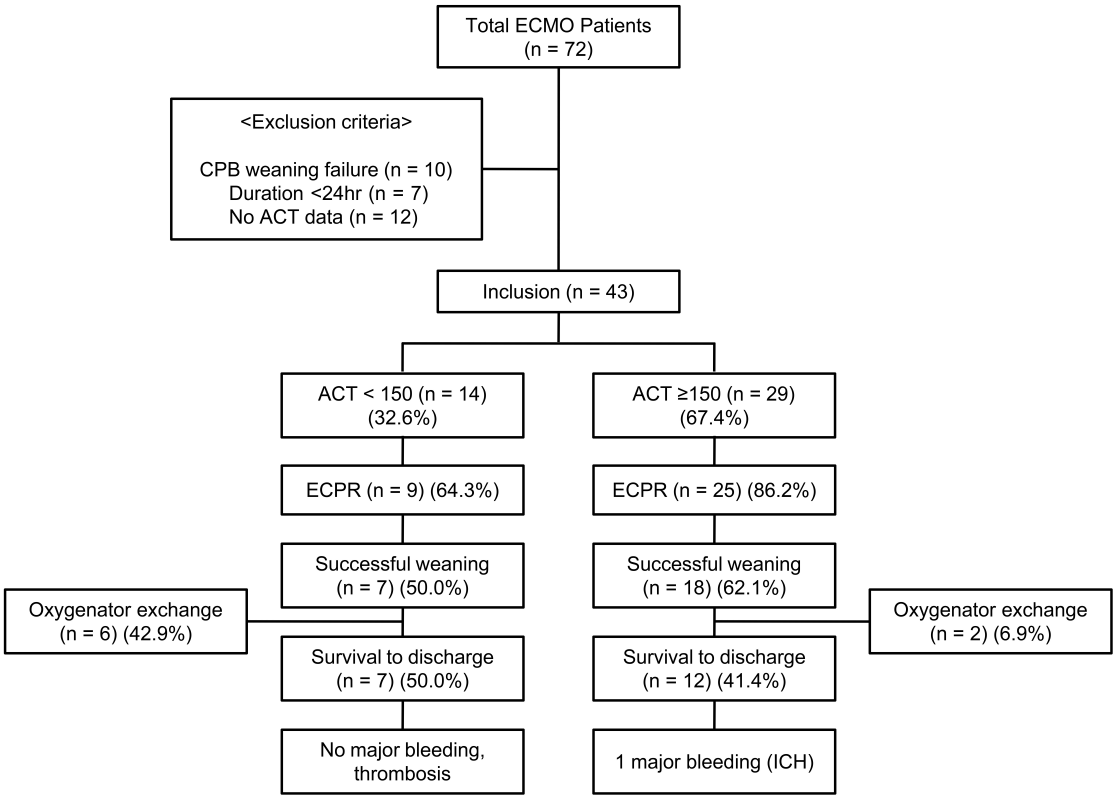

Fig. 1. Flow chart showing the inclusion and exclusion criteria for the study population. ACT, activated clotting time; CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; ICH, intracranial hemorrhage.

Cardiopulmonary, Hirrlingen, Germany). The other circuit comprised of a poly-methyl-pentene membrane oxygenator (Terumo CAPIOX EBS, Japan), a centrifugal pump (SL 45, Terumo CAPIOX EBS, Japan), and biocompatible hydrophilic polymer surface coated tubes (Xcoating, Terumo, Japan).

During cannulation, a heparin bolus (30–50 units/kg body weight) was administered at the discretion of the attending clinician. The ACT was measured at the bedside using a portable Hemochron 401 device (Hemochron, ITC Medical, Edison, NJ, USA) with HRFTCA510 tubes. After ECMO, the ACT was measured to be in the guideline range of 180–220 s. The circuit was then managed either without heparin or with low-dose continuous intravenous UFH. If the ACT was >200 s (secondary to CPR-related hypothermia, deteriorating coagulopathy, or previous intake of platelet inhibitors); or if there were significant bleeding diatheses (e.g., cannulation site bleeding, mucosal bleeding, or bloody nasogastric drainage) UFH was not initiated. A low ACT was maintained unless the oxygenator showed a visual clot, and left ventricular thrombus or spontaneous echo contrast was observed on echocardiography. An ACT point-of-care test was performed every hour until stabilization, and then the interval was increased to every 2–4 hours. Besides the ACT, laboratory measures, such as aPTT (measured every 6 hours) and fibrinogen, d-dimer, and antithrombin III levels were also monitored on a daily basis. We did not routinely perform thromboelastography or anti-factor Xa assay. If the patient developed bleeding complications despite maintaining low ACT levels, anticoagulation therapy was stopped. To resume anticoagulation therapy, either bleeding complications should resolve or the risk of thrombosis should outweigh the hemorrhagic conditions. The circuit was routinely checked for any visible clot formation. Plasma-free hemoglobin levels were monitored and post-oxygenator blood gas analysis was performed to assess the efficacy of the oxygenator. The oxygenator was changed if inadequate post-oxygenation blood gas analyses results were obtained or gross hematuria or clot larger than 5 mm at infusion side of circuit was detected in the oxygenator. The target ACT range varied according to the patient's condition and the clinician's preference (ACT goal 130–200 s). The patients were divided into two groups, namely, the low ACT or conventional ACT groups, according to a cut-off ACT of 150 s for comparison. We used the median ACT observed on ECMO day 2 when the intravenous UFH dose had been titrated and ACT stabilized in the desired range. The blood products were transfused to reach a target hemoglobin concentration >9.0 g/dL, platelet count >50,000/mm^3, international normalized ratio (INR) <1.5, and fibrinogen concentration >200 mg/dL. The whole process from ECMO cannulation to weaning was performed and supervised by three cardiothoracic surgeons and a perfusionist.

Continuous variables are expressed as median and range or mean and standard deviation. The descriptive statistics are expressed as count and percentage. The chi-square test or Fisher's exact test was used to compare the categorical variables. The Student's *t*-test or Mann-Whitney U-test was used to compare the continuous variables. Univariate and multivariate logistic regression analyses were used to identify the risk factors for successful weaning from ECMO support and survival until discharge. The results were considered statistically significant if the *p*-value was <0.05. SPSS software version 18.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis.

3. Results

A total of 43 ECMO cannulations performed from March 2017 to October 2019 were included in the study. There were 14 patients with ACT <150 s (low ACT group) and 29 patients with ACT ≥150 s (conventional ACT group). In the low ACT and the high ACT group, the mean ACT was 139.8 ± 6.8 s and 181.4 ± 22.6 s, respectively ($p = 0.001$) (Figs. 1,2).

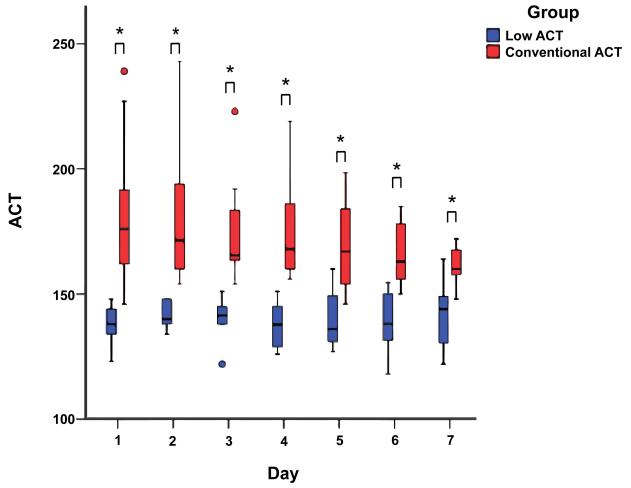

Fig. 2. Difference in the mean ACT between the low ACT and conventional ACT groups from ECMO day 1 to 7. ACT, activated clotting time; ECMO, extracorporeal membrane oxygenation. * indicated $p < 0.05$.

There were no significant differences in the baseline characteristics of the two groups before ECMO (Table 1). There was a predominance of male patients in each group. The comorbidities included dyslipidemia (most common), hypertension, diabetes mellitus, chronic kidney disease, history of percutaneous coronary intervention (PCI), and history of cerebrovascular accident (CVA).

Table 2 shows the ECMO factors in each group. The VA and VV ECMO rates did not differ in the low ACT and conventional ACT groups (9:5 vs. 22:7, $p = 0.428$). The proportion of patients receiving extracorporeal cardiopulmonary resuscitation (ECPR) in the low ACT and conventional ACT groups was 64.3% (n = 9) and 86.2% (n = 25), respectively ($p = 0.098$). The frequency of use of the PLS and EBS machines

Table 1. Baseline characteristics of the two groups before ECMO.

Variables	Low ACT (n = 14)	Conventional ACT (n = 29)	*p*-value
Age (years)	59.6 ± 10.4	57.2 ± 16.2	0.611
Male (n)	8 (57.1%)	18 (62.1%)	0.757
Comorbidities (n)			
Hypertension	9 (64.2%)	12 (41.4%)	0.159
DM	3 (21.4%)	12 (41.4%)	0.198
CKD	1 (7.1%)	2 (6.9%)	0.976
Dyslipidemia	9 (64.3%)	15 (51.7%)	0.437
h/o PCI	3 (21.4%)	7 (24.1%)	0.844
h/o CVA	3 (21.4%)	5 (17.2%)	0.741

ACT, activated clotting time; CKD, chronic kidney disease; CVA, cerebral vascular accident; DM, diabetes mellitus, ECMO, extracorporeal membrane oxygenation; PCI, percutaneous coronary intervention.

was similar between the low ACT and conventional ACT groups (7:7 vs. 14:15, $p = 0.916$). The duration of ECMO support in the low ACT and conventional ACT groups was 17.5 ± 7.7 days and 20.7 ± 5.6 days, respectively ($p = 0.102$). The average flow rates were also similar between the low ACT and conventional ACT groups (2.7 ± 1.3 vs. 2.9 ± 1.1 L/min, $p = 0.819$).

Of the 14 patients in the low ACT group, 7 (50%) were weaned off ECMO support, and all patients survived until discharge without further complications. Of the 29 patients in the conventional ACT group, 18 (62.1%) were successfully weaned off ECMO support and 12 (41.3%) survived until discharge. The cause of death was septic shock (n = 5) and intracranial hemorrhage (ICH; n = 1). There was no significant difference in the weaning rate ($p = 0.452$) and survival until discharge rate ($p = 0.594$) between the two groups. We also investigated patient outcomes according to ECMO support type (VA vs. VV) (Table 3). There were no differences between the two groups, except for ECPR frequency (100% vs. 25%, $p = 0.001$, respectively) and initial ACT time (205.4 s vs. 164.8 s, $p = 0.007$, respectively).

Of the 9 patients receiving ECPR in the low ACT group, 6 (66.6%) were weaned-off from ECMO support uneventfully, and patients of which all survived until discharge. Among the 25 patients receiving ECPR in the conventional ACT group, 16 (64.0%) were successfully weaned off and 10 (40.0%) survived to discharge. There was no significant difference in the weaning rate ($p = 0.866$) and survival until discharge rate ($p = 0.169$; Table 4).

The ECMO-related complications, such as oxygen exchange rate, intra-circuit clot formation, cannulation site bleeding or hematoma, gastrointestinal bleeding, and cerebrovascular accident (either ischemic or hemorrhagic) events, were assessed. The oxygenator exchange rate was significantly higher in the low ACT group than in the conventional ACT group (6 patients vs. 2 patients, $p = 0.009$). Five oxygenators were electively replaced due to decreased oxygen exchange capability which was calculated by measuring pre-oxygenator blood gas value minus the

Table 2. ECMO-related factors of the two groups.

Variables	Low ACT (n = 14)	Conventional ACT (n = 29)	*p*-value
ECMO type (VA/VV) (%)	9 (64.3)/5 (35.7)	22 (75.9)/7 (24.1)	0.428
ECPR (%)	9 (64.3)	25 (86.2)	0.098
ECMO duration (days)	17.5 ± 7.7	20.7 ± 5.6	0.102
ECMO machine (PLS/EBS) (%)	7 (50.0)/7 (50.0)	14(48.3)/15 (51.7)	0.916
Average flow rate (L/min)	2.7 ± 1.3	2.9 ± 1.1	0.819
Initial ACT (s)	176.0 ± 52.0	202.8 ± 65.9	0.190
Mean ACT (s)	139.8 ± 6.8	181.4 ± 22.6	0.001
Successful weaning (%)	7 (50.0)	18 (62.1)	0.452
Survival to discharge (%)	7 (50.0)	12 (41.4)	0.594
ECMO-related complications			
Oxygenator exchange	6	2	0.009
Circuit clot	1	0	0.145
Cannulation site bleeding	1	0	0.145
Oral cavity bleeding	0	1	0.145
Intracranial hemorrhage	0	1	0.482

ACT, activated clotting time; ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; VA, veno-arterial; VV, veno-venous.

Table 3. Patients' outcomes according to ECMO support type.

Variables	VA ECMO (n = 31)	VV ECMO (n = 12)	*p*-value
ACT <150 sec (%)	9 (29.0)	5 (41.7)	0.482
ECPR (%)	31 (100)	3 (25)	0.001
ECMO duration (days)	8.0 ± 7.5	10.5 ± 16.4	0.498
ECMO machine (PLS/EBS) (%)	13 (41.9) /18 (58.1)	8 (66.6)/4 (33.3)	0.185
Average flow rate (L/min)	2.9 ± 0.9	3.3 ± 1.0	0.309
Initial ACT (s)	205.4 ± 68.8	164.8 ± 24.8	0.007
Mean ACT (s)	167.6 ± 25.5	168.3 ± 30.6	0.785
Successful weaning (%)	20 (64.5)	5 (41.7)	0.301
Survival to discharge (%)	16 (51.6)	3 (25)	0.174
ECMO-related complications			
Oxygenator exchange	5	3	0.585
Circuit clot	0	1	0.279
Cannulation site bleeding	0	0	1.000
Oral cavity bleeding	1	0	1.000
Intracranial hemorrhage	1	0	1.000

ACT, activated clotting time; ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; VA, veno-arterial; VV, veno-venous.

Table 4. Comparison of the ECMO weaning and survival rates among the patients receiving ECPR between the two groups.

Variables	Low ACT (n = 9)	Conventional ACT (n = 25)	*p*-value
Successful weaning (%)	6 (66.6)	16 (64.0)	0.866
Survival to discharge (%)	6 (66.6)	10 (40.0)	0.169

ACT, activated clotting time; ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation.

post-oxygenator. The other one was replaced due to a thrombus visible inside the oxygenator without change in the ECMO flow. Bleeding occurred in 3 patients in the conventional ACT group (preexisting heel wound, n = 1; oral cavity, n = 1; ICH, n = 1) and in 1 patient in the low ACT group (femoral artery cannulation site) who was permitted voluntary movement before heart transplantation 19 days after ECMO.

4. Discussion

Optimal anticoagulation is critical for successful ECMO support. To the best of our knowledge, there are no randomized controlled studies on adequate anticoagulation strategies in patients at a high risk of bleeding during ECMO. According to the Extracorporeal Life Support Organization (ELSO) guidelines, the therapeutic anticoagulation range is defined as an ACT of 160–220 s, variable according to the analyzers.

This is, however, not universally agreed upon. The guidelines suggest UFH titration and adjustment of the ACT goal range based on factors including patient bleeding, circuit clotting, or the measured anti-factor Xa level [2]. According to a recent international survey, the target ACT for VA and VV ECMO ranged from 140 to 220 s. The majority of the institutions used an ACT between 160 s and 200 s [3]. In this study, we report the safety and efficacy of a lower ACT in patients on ECMO support.

The rate of weaning from ECMO support and survival until discharge did not show a significant difference between the low and conventional ACT groups. All patients in the low ACT group and two-thirds of the patients in the high ACT group who were successfully weaned from ECMO support were discharged to home. A majority of the patients who did not survive after weaning died from septic shock. A patient in the high ACT group developed ICH during ECMO and died, despite being successfully weaned from ECMO support even after normalization of the coagulation status. Another patient with diabetes mellitus in the high ACT group had bleeding from the heel of the foot, which required electrocauterization. In the low ACT group, no major thromboembolic event, such as stroke, pulmonary thromboembolism, or mesenteric ischemia was observed. A patient in the low ACT group developed cannulation site bleeding after 7 days of ECMO support. This patient was allowed awakening without mechanical ventilation and the arterial cannula site bleeding occurred while moving in bed. The bleeding finally stopped after heart transplantation and ECMO support was terminated after 19 days.

The oxygenator exchange rate was significantly higher in the low ACT group. Six patients required oxygenator replacement. A grossly visible clot formed inside the VV-ECMO circuit in one patient. In the remaining 5 patients, there was decreased oxygenation capability on post-oxygenator blood gas analysis. This may be due to the formation of microthrombi that affect the fibers of the oxygenator membrane.

Improvements in the ECMO equipment, including centrifugal pumps, poly-methyl-pentene membrane oxygenators, and heparin-coated circuits aid in reducing the incidence of thrombosis during and after heparin discontinuation. With these improvements, systemic heparinization during ECMO may be reduced or stopped as long as the blood flow is maintained at a high rate [4–11]. In our study, the average flow rate was 2.7 ± 1.3 and 2.9 ± 1.1 L/min in the low ACT and high ACT groups, respectively, and was not significantly different ($p = 0.819$). If the ECMO flow decreases for $<$15 min, extensive thrombosis may develop in the four heart chambers, even when the ACT is high ($>$170 s) [12–15].

The concept of maintaining ECMO in cases of multiple trauma with severe bleeding and ICH with heparin-free or heparin-sparing strategies is evolving [4, 5, 16, 17]. This concept is being accepted by most intensivists presently. However, there are only a few reports on the feasibility of low ACT during VA ECMO [7, 9]. ECPR is usually associated with hypothermia, metabolic acidosis-induced coagulopathy, anti-platelet medication, like clopidogrel or ticagrelor-induced platelet dysfunction before PCI, and mechanical chest wall massage-induced bleeding, like sternal or rib fracture or intra-pericardial bleeding. Sometimes, it is accompanied by a cannulation site and mucosal bleeding and bloody nasogastric tube drains. We attempted to maintain a lower ACT during ECPR because of the higher tendency for bleeding. When initiating ECPR, we usually administer a heparin bolus (30–40 units/kg) and check the ACT every hour until it reaches ~140 s before continuous intravenous infusion of heparin is initiated. If the bleeding persists and there is unstable ECMO flow, we usually do not initiate heparin infusion even when ACT is ~120–130 s. After bleeding is stopped, we initiate intravenous heparin with caution to prevent re-bleeding. As thrombocytopenia and platelet dysfunction are common in ECMO patients [18], especially those treated with aspirin and clopidogrel, we attempted to maintain a platelet count of $>50{,}000/mm^3$.

Compared with other studies [4–11, 16, 17], our study did not include multiple trauma patients on VV ECMO support. In the low ACT group, all VA ECMO supports were performed with ECPR. According to Shoskes *et al.* [19], the rate of acute brain injury appeared to be higher in VA ECMO patients than VV ECMO. Among described studies, ischemic stroke was most prevalent, and rates were significantly higher in VA ECMO patients. ICH showed no significant difference between modes of ECMO. The mechanism of ischemic stroke in VA ECMO may be considered due to thromboembolism, which is more likely than in VV ECMO because of arterial cannulation [19]. Thus, systemic anticoagulation protocol should be designed accordingly in different modes of ECMO. In our study, there were no significant differences in complication outcomes in VA vs. VV ECMO groups (Table 3). Since our result showed that all VA ECMO patients in low ACT group were comprised of ECPR patients, the predisposition to bleeding in these patients is believed to have played a role against thromboembolism. ECMO component exchange due to clotting can be quickly performed when the ICU team is well-trained; however, major bleeding is harmful and difficult to treat [8]. In our series, oxygenator exchange was more common in the low ACT group, but the incidence of serious bleeding and thrombosis was not observed more commonly. Although we could not identify any risk factor for ECMO weaning, dyslipidemia was a risk factor for survival until discharge. A low ACT was not a risk factor for weaning and survival.

This study has several limitations. First, this is a retrospective analysis of a relatively small sample population at a single center without protocolized approach among the clinicians. Second, the lower target value of ACT ($<$150 s) is somewhat arbitrary as it was chosen by the median value of the study population. Third, we did not compare other anticoagulation monitoring methods, like analysis of the aPTT,

thromboelastography and anti-factor Xa assay. Lastly, we did not separate our protocols according to the modes of ECMO, and further study is required.

5. Conclusions

Improvements in the ECMO circuits aid in reducing the incidence of thrombosis and systemic heparinization may be reduced or stopped in patients at a high risk of bleeding. In our study, a lower target ACT (<150 s) was not associated with an increased thromboembolic risk, weaning failure, and mortality during ECMO management. A lower ACT may be considered for patients with ongoing bleeding or who are at a high risk of hemorrhagic complications. Further randomized controlled and multicenter studies are required to validate our study results.

Abbreviations

ECMO, extracorporeal membrane oxygenation; ECLS, extracorporeal life support; ECPR, extracorporeal cardiopulmonary resuscitation; UFH, unfractionated heparin; ACT, activated clotting time; aPTT, activated partial thromboplastin time; VV, veno-venous; VA, veno-arterial; PCI, percutaneous coronary intervention; CVA, percutaneous coronary intervention; CPR, cardiopulmonary resuscitation; INR, international normalized ratio; ICH, intracranial hemorrhage.

Author contributions

JIH and HJS designed the study. JIH and JH performed the study. JIH and HJS wrote the manuscript. HJS and JH reviewed the drafts. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All participants provided informed consent for inclusion before participating in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Korea University Ansan Hospital (approval number: 2020AS0038).

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Conflict of interest

The authors declare no conflict of interest.

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