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Thromboembolic Complications in Continuous Versus Interrupted Anticoagulation During Venovenous Extracorporeal Membrane Oxygenation: A Multicenter Study

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OBJECTIVES: Continuous, therapeutic anticoagulation is the standard of care for patients on extracorporeal membrane oxygenation (ECMO). The risks of hemorrhage exacerbated by anticoagulation must be weighed with the thrombotic risks associated with ECMO. We hypothesized increased thrombotic events in patients who had interrupted (vs. continuous) anticoagulation during venovenous ECMO.

DESIGN: This is a retrospective, observational study.

SETTING: Enrollment of individuals took place at three adult ECMO centers in Minnesota from 2013 to 2022.

PATIENTS: This study consists of 346 patients supported with venovenous ECMO.

INTERVENTIONS: Anticoagulation administration was collected from electronic health records, including frequency and duration of anticoagulation interruptions (IAs) and timing and type of thrombotic events, and data were analyzed using descriptive statistics.

MEASUREMENTS AND MAIN RESULTS: A total of 156 patients had IA during their ECMO run and 190 had continuous anticoagulation. Risk adjusted logistic regression demonstrated that individuals in the IA group were not statistically more likely to experience a thrombotic complication (odds ratio [OR], 0.69; 95% CI, 0.27–1.70) or require ECMO circuit change (OR, 1.36; 95% CI, 0.52–3.49). Subgroup analysis demonstrated greater frequency of overall thrombotic events with increasing frequency and duration of anticoagulation being interrupted ($p = 0.001$).

CONCLUSIONS: Our multicenter analysis found a similar frequency of thrombotic events in patients on ECMO when anticoagulation was interrupted vs. administered continuously. Further investigation into the impact of the frequency and duration of these interruptions is warranted.

KEYWORDS: acute respiratory distress syndrome; anticoagulation; extracorporeal membrane oxygenation

Extracorporeal membrane oxygenation (ECMO) has been established as an effective intervention for severe cardiac and pulmonary failure (1). However, several factors related to ECMO have been reported to impair intrinsic anticoagulative properties of the body, including the underlying critical nature of patients, patient comorbidities, and interactions with the ECMO circuit itself (2). Therefore, while beneficial, ECMO may predispose patients to a high risk of thrombosis with a prevalence of 22.9% in venovenous and venoarterial ECMO patients without continuous systemic anticoagulation (2). Venovenous

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KEY FINDINGS

Question: Do patients undergoing venovenous extracorporeal membrane oxygenation (ECMO) who have anticoagulation held at any point experience increased thrombotic events?

Findings: Risk adjusted logistic regression demonstrated that individuals with intermittent anticoagulation were not more likely to experience a thrombotic complication.

Meanings: Clinicians should consider the length and extent to which anticoagulation is held during a venovenous ECMO run.

and venoarterial ECMO have also been associated with increased risk of ischemic stroke, intracardiac thrombus, and deep vein thrombosis (DVT) (3).

Given the established risk of thrombotic complications, the Extracorporeal Life Support Organization (ELSO) guidelines for anticoagulation currently recommend anticoagulating ECMO patients at cannulation and continuously throughout the ECMO course (4). Clinicians have several anticoagulant drug choices for patients on ECMO, although the ideal anticoagulation agent remains the subject of debate in the literature (5). While unfractionated heparin is the most frequently used for patients on ECMO, direct thrombin inhibitors are increasingly being used off-label for ECMO patients due to pharmacokinetic considerations and to remove the risk of heparin-induced thrombocytopenia (HIT) (4). Anticoagulation best practice remains a current field of active investigation (6–9).

Major bleeding is a frequent complication of ECMO and a cause of patient morbidity and mortality. The coagulopathy during ECMO seems to be multifactorial, relating the underlying acuity of patients and the mechanical disruption of hemostatic domains (10, 11). Past studies have demonstrated the risk of bleeding in ECMO patients to be between 10% and 29% (3, 12), with severe complications including bleeding at the cannula site, retroperitoneal, pulmonary, and potentially devastating neurologic bleeding.

While continuous anticoagulation (CA) is the current standard of care for patients on ECMO, there are instances where it must be interrupted. These include catastrophic bleeding and before procedures like tracheostomy placement. Past studies in venoarterial ECMO patients have reported an increased risk of thrombosis when not utilizing CA (13, 14). However, there is limited data analyzing the complications of interrupting anticoagulation during venovenous ECMO (15, 16). Therefore, the purpose of this study is to use our multicenter registry to investigate the effects of interrupting anticoagulation in venovenous ECMO patients. Based on existing studies, we hypothesize that interrupting anticoagulation during ECMO would be associated with a greater risk of thrombotic events than uninterrupted anticoagulation.

MATERIALS AND METHODS

This was a retrospective, observational cohort study of patients supported with venovenous ECMO at three adult ELSO-certified Centers of Excellence in Minnesota including University of Minnesota MHealth Fairview (n = 158 from 2013 to 2022), Hennepin County Medical Center (n = 77 from 2015 to 2022), and Abbott Northwestern Hospital (n = 111 from 2013 to 2022). This study was approved by the institutional review board of each participating site—for more information, see **Supplemental Digital Content** (http://links.lww.com/CCX/B427). Research was performed in accordance with the ethical standards of the study institutional review board and with the Helsinki Declaration of 1975. The registry includes patient who require venovenous ECMO for any indication and excludes patients receiving venoarterial or venoarteriovenous ECMO. Patients requiring left or right ventricular assist devices during their course are also excluded from the registry. The institutional review boards at each site approved this study with a waiver of informed consent.

Data were extracted from the electronic medical record at each site by trained investigators as part of the construction of the Minnesota ECMO Consortium Registry maintained with Research Electronic Data Capture data tools (17). Variables used for this study included patient demographics, comorbidities, indication for ECMO, details of ECMO configuration, hospital and ICU length of stay, length of ECMO run, in-hospital mortality, and complications. Thrombotic complications included CNS infarction, HIT, myocardial infarction, pulmonary embolism, DVT, and limb ischemia. We also examined circuit changes as these are often performed because of circuit component thrombosis. Anticoagulation specific

variables included type of anticoagulation used, timing and duration of gaps in anticoagulation, reason anticoagulation was interrupted, and number of times anticoagulation was interrupted. We defined an interruption as any gap in anticoagulation that was not due to inherent dosing schedule or supratherapeutic levels.

Baseline characteristics were compared using chi-square test for categorical variables and *t* test and Mann-Whitney *U* test for continuous variables, as appropriate. Patients were organized into groups based on whether anticoagulation was interrupted at least once or not interrupted (administered continuously). In the interrupted anticoagulation group, stratified analysis was performed according to the total duration and the discrete number of anticoagulation interruptions (IAs). Logistic regression models were developed to determine differences in thrombotic events between groups, adjusting for age, indication for ECMO, Respiratory ECMO Survival Prediction (RESP) score, COVID-19 status, tobacco use, alcohol use, bivalirudin usage, and total time spent on extracorporeal life support (ECLS). These were expressed as odds ratios (ORs) and corresponding 95% CIs. A p value of less than 0.05 was deemed significant. R, Version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria) was used for all data analysis (18) and figures were generated using PRISM GraphPad, Version 10.0.2 (GraphPad Software, Boston, MA).

RESULTS

A total of 346 patients from the Minnesota Venovenous ECMO Consortium Registry were included in this analysis and their characteristics are provided in **Table 1**. A total of 156 patients had IA during their ECMO run and 190 had CA. Of the 156 who had IA, 25 (16%) patients began their ECMO run without anticoagulation, of which 9 (5.7%) resumed anticoagulation to then have it interrupted again (**Supplemental Table 1**, http://links.lww.com/CCX/B403). The average length of time on ECMO was 6.8 days (interquartile range [IQR], 3.9–11.7 d) in the CA group compared with 22.3 days (IQR, 11.9–42 d) in the IA group ($p < 0.001$).

Unfractionated heparin was administered to176 patients (92.6%) in the CA group and 147 (94.2%) in the IA group. The IA group had 32 individuals (20.5%) who also received a bivalirudin drip during their run, compared with the 11 individuals in the CA group (5.3%; $p < 0.001$). There were statistically significant differences between IA and CA groups in the baseline RESP score, COVID-19 infection status, individual age, tobacco use and alcohol use disorders, length of time on ECLS, and cannula size (Table 1). No other baseline prothrombotic variables were noted to have a statistically significant difference between groups.

Multivariable logistic regression was performed to adjust for baseline differences between individuals who had CA and those who had IA (**Fig. 1**). Individuals in the IA group were not statistically significantly more likely to experience an overall thrombotic complication (OR, 0.69; 95% CI, 0.27–1.70). The IA group also demonstrated no statistically significant difference in HIT (OR, 1.55; 95% CI, 0.25–12.99), CNS infarction (OR, 2.70; 95% CI, 0.17–9.88), myocardial infarction (OR, 0.02; 95% CI, $2.92e^{-11}$–7.8), pulmonary embolism (OR, 1.18; 95% CI, 0.13–11.1), or DVT (OR, 0.39; 95% CI, 0.13–1.07).

Raw group analysis between CA and IA groups showed a statistically significant difference in ECMO circuit changes ($p < 0.001$). In the CA group, a total of 28 individuals (14.7%) required circuit change, compared with a total of 80 individuals (51.3%) in the IA group. The most common indication for circuit change in the IA group was oxygenator failure (34.6%), followed by clots in the circuit (22.4%) and hemolysis (9%). The trend remains the same for the CA group; oxygenator failure (10%), clots in circuit (3.2%), and hemolysis (1.6%). After adjustment, logistic regression showed the IA group had no statistically significantly increased risk of receiving a circuit change (OR, 1.36; 95% CI, 0.52–3.49).

Subgroup analysis of the 156 patients who had IA during ECMO run was performed. Thrombotic and equipment complications were stratified by number of times anticoagulation was interrupted and length of time anticoagulation was interrupted in days (**Tables 2** and **3**). Table 2 shows a statistically significant difference in overall aggregate thrombotic complication occurrence, specifically DVT occurrence, and number of circuit changes expressed in patient percentages stratified by times anticoagulation was interrupted ($p = 0.001$). Correspondingly, Table 3 demonstrates a statistically significant difference in overall thrombotic complications, CNS infarction, and DVT stratified by days anticoagulation was interrupted ($p = 0.031$, 0.032, and 0.005 correspondingly).

TABLE 1.
Baseline Characteristics of Individuals Undergoing Venovenous Extracorporeal Membrane Oxygenation

Demographics	Baseline Characteristics		p
	Continuous Anticoagulation, *n* = 188	Interrupted Anticoagulation, *n* = 156	
Age, median (IQR)	44.35 (33.88–55.12)	48.59 (38.56–57.99)	0.003[a]
Sex (%)			
Male	126 (66.3)	104 (66.7)	1.000
Race (%)			
Asian	13 (6.8)	10 (6.4)	1.000
Black/African American	37 (19.5)	24 (15.4)	0.395
Hispanic	8 (4.2)	14 (9.0)	0.113
White (non-Hispanic)	117 (61.6)	96 (61.5)	1.000
Native American/Native Alaskan	8 (4.2)	6 (3.8)	1.000
Native Pacific Islander	1 (0.5)	0 (0)	1.000
Other/declined to answer	7 (3.7)	6 (3.8)	1.000
Body mass index, median (IQR)	31.38 (26.48–36.97)	31.34 (27.45–36.75)	0.909
Sequential Organ Failure Assessment, median (IQR)	8 (5–10)	7 (5–9)	0.391
Respiratory ECMO Survival Prediction, median (IQR)	5 (3–6)	4 (2–5)	0.013[a]
COVID-19 positive (%)	41 (21.6)	79 (50.6)	< 0.001[a]
Time on extracorporeal life support, hr, median (IQR)	163.22 (95.38–281.60)	535.60 (285.10–1008.76)	< 0.001[a]
ECMO indication (%)			0.025[a]
Pneumonia	148 (77.9)	132 (84.6)	
Trauma/burn	10 (5.3)	5 (3.2)	
Acute respiratory distress syndrome secondary to septic shock	2 (1.1)	5 (3.2)	
Idiopathic pulmonary fibrosis	10 (5.3)	4 (2.6)	
Cystic fibrosis	0 (0)	3 (1.9)	
Asthma	11 (5.8)	1 (0.6)	
Pulmonary edema	1 (0.5)	0 (0)	
Trasfusion-associated circulatory overload or transfusion related acute lung injury	0 (0)	1 (0.6)	
Medication-induced lung injury	1 (0.5)	3 (1.9)	
Pulmonary hemorrhage	3 (1.6)	1 (0.6)	
Other	4 (2.1)	1 (0.6)	

ECMO = extracorporeal membrane oxygenation, IQR = interquartile range.
[a]$p < 0.05$.

DISCUSSION

Overall, venovenous ECMO patients who had IA at least once during their ECMO run or who began their ECMO run without anticoagulation were not significantly more likely to require ECMO circuit changes or experience thrombotic complications after adjustment for potential confounding factors. However, we found that an increased duration of time that anticoagulation was interrupted, and an increased number of IAs, were significantly associated with an increased risk of thrombotic complications and ECMO circuit changes, suggesting a dose-dependent

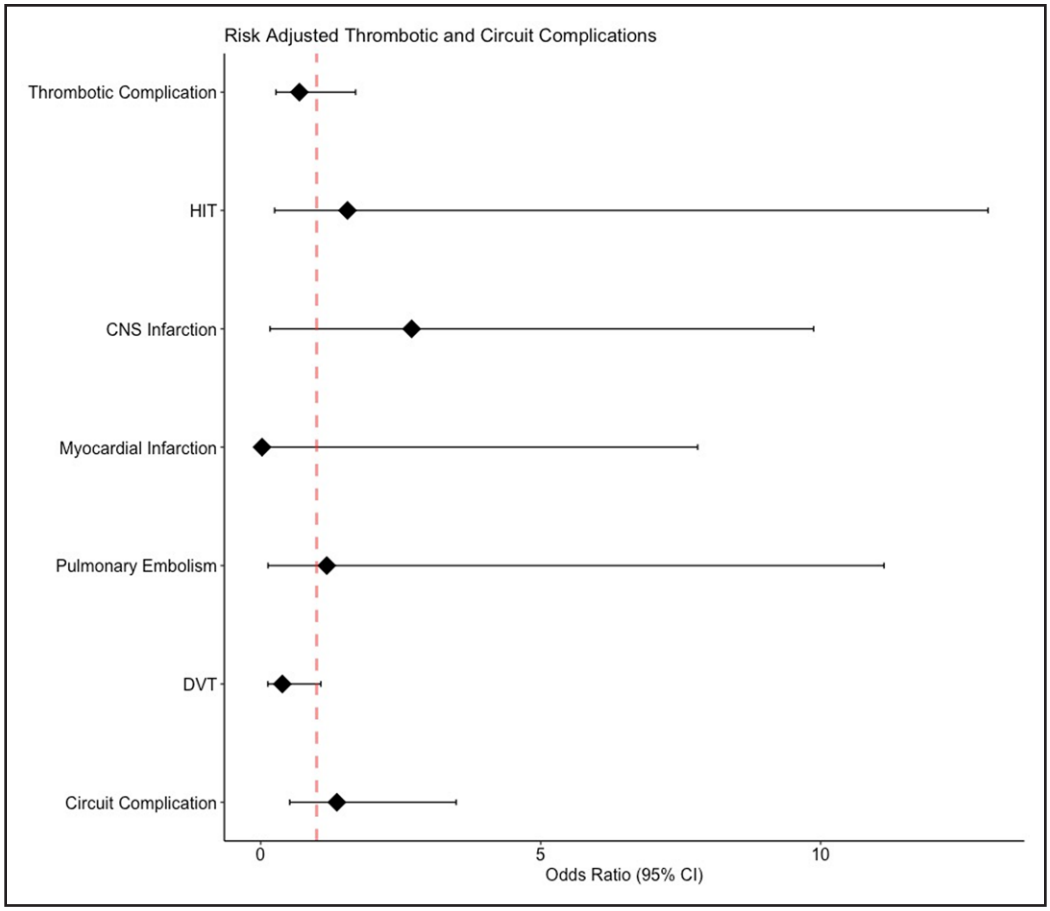

Figure 1. Risk adjusted logistic regression of thrombotic and circuit complications of individuals undergoing venovenous extracorporeal membrane oxygenation. DVT = deep vein thrombosis, HIT = heparin-induced thrombocytopenia.

relationship between interrupting anticoagulation and an increasing rate of thrombotic complications.

Our findings recapitulate findings from past studies. A systematic review that investigated venovenous ECMO complications published in 2021 reported no pooled difference in the rates of thrombotic complications between ECMO patients with CA and patients who had IA for at least 24 hours (2). Krueger et al (16) found no difference during venovenous ECMO between CA and daily venous thromboembolism (VTE) prophylaxis with low molecular weight heparin. Finally, another study found no difference in thrombotic events in individuals undergoing venovenous ECMO for acute respiratory distress syndrome between low level CA and standard VTE prophylaxis (15). Our data suggests that CA during a venovenous ECMO course does not account for a lessened risk of thromboembolic events.

Interestingly, we found that individuals in the IA group underwent statistically significantly more ECMO circuit changes. However, when controlling for baseline differences including total time on ECLS, there was no statistically different odds of ECMO circuit change when anticoagulation was interrupted. The most common reason for circuit change in the IA group was for oxygenator failure followed closely by clots in the circuit. Typically, an oxygenator failure during ECMO is attributed to clot burden and subsequent reduced pump efficiency. The reason for thrombosis of the ECMO circuit, like hemorrhagic events, is likely multifactorial in nature, relating to the underlying acuity of patients, stasis of blood flow, and contact with nonbiologic materials present in the circuit (19). The cause of increased ECMO circuit changes remains unclear but is likely multifactorial based on differential prevalence of underlying patient risk factors. Type of anticoagulation used and length of ECLS are two variables statistically significantly different between comparator groups particular to ECMO run. Bivalirudin was used more frequently in the CA group and is routinely done so when there is concern for HIT in an individual. These underlying risk factors likely attributed to anticoagulation being interrupted at any given point during ECMO run.

Our data also demonstrates a direct response relationship between both the number of times anticoagulation was interrupted and the length of time that anticoagulation was interrupted, and overall thrombotic complications. To our understanding, this is the first time this has been reported from a multicenter study. Agreeably, across this subgroup analysis a difference in ECMO circuit changes was also noted. These

TABLE 2.

Thrombotic and Equipment Complications of Individuals Who Had Anticoagulation Interrupted During Venovenous Extracorporeal Membrane Oxygenation Run Stratified by Number of Times the Anticoagulation Was Interrupted

Interruptions (*n*)	1	2	3	4	5	≥ 6	*p*
Patients (*n*)	77	37	17	12	6	7	
All thrombotic	4 (7%)	10 (27%)	2 (12%)	6 (50%)	3 (50%)	3 (43%)	0.001[a]
Heparin-induced thrombocytopenia	2 (3%)	3 (8%)	0 (0%)	1 (8%)	1 (17%)	1 (14%)	0.34
CNS infarction	1 (2%)	0 (0%)	2 (12%)	0 (0%)	0 (0%)	0 (0%)	0.072
Pulmonary embolism	0 (0%)	2 (5%)	0 (0%)	1 (8%)	0 (0%)	1 (14%)	0.099
Deep vein thrombosis	1 (1%)	5 (14%)	0 (0%)	4 (33%)	2 (33%)	1 (14%)	0.001[a]
Circuit change	12 (20%)	19 (51%)	11 (64%)	6 (50%)	3 (50%)	6 (86%)	< 0.001[a]

[a]$p < 0.05$.

Data are reported as frequency (%) unless otherwise specified.

TABLE 3.

Thrombotic and Equipment Complications of Individuals Who Had Anticoagulation Interrupted During Venovenous Extracorporeal Membrane Oxygenation Run Stratified by Number of Days Anticoagulation Was Interrupted

Days Interrupted	1	2	3	4	5	≥ 6	*p*
Patients (*n*)	60	23	19	5	4	44	
All thrombotic	6 (12%)	2 (11%)	2 (11%)	1 (20%)	2 (50%)	15 (35%)	0.031[a]
Heparin-induced thrombocytopenia	3 (5%)	1 (4%)	1 (5%)	0 (0%)	0 (0%)	3 (7%)	0.98
CNS infarction	1 (2%)	0 (0%)	0 (0%)	0 (0%)	1 (25%)	1 (2%)	0.032[a]
Pulmonary embolism	1 (2%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)	2 (5%)	0.862
Deep vein thrombosis	1 (2%)	0 (0%)	1 (5%)	1 (20%)	1 (25%)	9 (21%)	0.005[a]
Circuit change	13 (26%)	9 (50%)	7 (37%)	3 (60%)	1 (25%)	24 (56%)	0.053

[a]$p < 0.05$.

Data are reported as frequency (%) unless otherwise specified.

data suggest that the longer and more frequently anticoagulation is interrupted, the patient accrues a higher risk. Our data represents a more detailed analysis describing the additive nature of repeated or continual IAs. Furthermore, our analysis is of a significantly larger patient population than previously published literature. Based on these data, of individuals undergoing venovenous ECMO who have their IA, the interruption should be limited in length and frequency.

Our analysis is limited first and foremost by its retrospective design. Data from this analysis should be considered as hypothesis generating and not as practice recommendations. It is possible that our study is underpowered for the primary outcome of thromboembolic events. Further prospective studies are recommended to explore these and related findings. Second, ECMO standard operating procedures and protocols regarding anticoagulation or complication management varies based on performing center. Not uncommonly, individuals have a planned ECMO run to be completed entirely without the use of anticoagulation. Indications for interrupting anticoagulation, including length and frequency, are largely dependent on institution and individual provider. Furthermore, thrombotic complications are not systematically screened for at our centers, complications captured were discovered by clinicians and described in the medical record. Finally, our data, although multicenter, is from a specific region and may

not be generalizable to other national or international populations.

CONCLUSIONS

Our multicenter analysis found a similar frequency of thrombotic events in patients on ECMO when anticoagulation was interrupted vs. administered continuously. Further investigation into the impact of the frequency and duration of these interruptions is warranted.

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