Comparison of Anticoagulation Strategies in Patients Requiring Venovenous Extracorporeal Membrane Oxygenation: Heparin Versus Bivalirudin*

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OBJECTIVES: Extracorporeal membrane oxygenation is a life-sustaining therapy for severe respiratory failure. Extracorporeal membrane oxygenation circuits require systemic anticoagulation that creates a delicate balance between circuit-related thrombosis and bleeding-related complications. Although unfractionated heparin is most widely used anticoagulant, alternative agents such as bivalirudin have been used. We sought to compare extracorporeal membrane oxygenation circuit thrombosis and bleeding-related outcomes in respiratory failure patients receiving either unfractionated heparin or bivalirudin for anticoagulation on venovenous extracorporeal membrane oxygenation support.

DESIGN: Retrospective cohort study.

SETTING: Single-center, cardiothoracic ICU.

PATIENTS: Consecutive patients requiring venovenous extracorporeal membrane oxygenation who were maintained on anticoagulation between 2013 and 2020.

INTERNVENTIONS: IV bivalirudin or IV unfractionated heparin.

MEASUREMENTS AND MAIN RESULTS: Primary outcomes were the presence of extracorporeal membrane oxygenation in-circuit–related thrombotic complications and volume of blood products administered during extracorporeal membrane oxygenation duration. One hundred sixty-two patients receiving unfractionated heparin were compared with 133 patients receiving bivalirudin for anticoagulation on venovenous extracorporeal membrane oxygenation. In patients receiving bivalirudin, there was an overall decrease in the number of extracorporeal membrane oxygenation circuit thrombotic complications ($p < 0.005$) and a significant increase in time to circuit thrombosis ($p = 0.007$). Multivariable Cox regression found that heparin was associated with a significant increase in risk of clots (Exp[B] = 2.31, $p = 0.001$). Patients who received bivalirudin received significantly less volume of packed RBCs, fresh frozen plasma, and platelet transfusion ($p < 0.001$ for each). There was a significant decrease in the number major bleeding events in patients receiving bivalirudin, 40.7% versus 11.7%, $p < 0.001$.

CONCLUSIONS: Patients receiving bivalirudin for systemic anticoagulation on venovenous extracorporeal membrane oxygenation experienced a decrease in the number of extracorporeal membrane oxygenation circuit-related thrombotic events as well as a significant decrease in volume of blood products administered.

KEY WORDS: anticoagulation; bivalirudin; extracorporeal membrane oxygenation; respiratory failure; unfractionated heparin

***See also p. 1208.**

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Patients who are suffering from respiratory failure but are otherwise hemodynamically stable with adequate cardiac function can be maintained on venovenous extracorporeal membrane oxygenation (VV-ECMO) to provide temporary life support while providing lung protective ventilation preventing against additional barotrauma while allowing for lung recovery or transplantation (1). Contact between blood and the nonbiologic surfaces of the ECMO tubing is highly thrombogenic and necessitates the use of anticoagulation for the prevention of clot formation (2). Although the Extracorporeal Life Support Organization (ELSO) guidelines recommend the use of anticoagulation in ECMO, they do not make a recommendation for selection of a specific anticoagulant (3).

Unfractionated heparin (UFH) has been the primary agent used for this purpose due to its wide availability, low cost, and rapid reversal with protamine (3, 4). Despite the widespread use of UFH in ECMO, its use is associated with many known complications such as heparin-induced thrombocytopenia (HIT), heparin resistance, and variable response from heparin due to its bonding to various plasma proteins (5, 6). The development of thrombocytopenia is common and multifactorial in ECMO patients, thus making the diagnosis of HIT challenging in patients who are receiving UFH (7–9). Even though the estimated occurrence rate of HIT in patients receiving ECMO is approximately 1%, the hypercoagulable state created by HIT can result in significant morbidity and mortality in the ECMO patient (10).

Due to the known shortcomings of UFH in ECMO patients, direct thrombin inhibitors such as bivalirudin have been used in patients who were suspected of developing HIT due to its lack of immunogenic properties and more favorable pharmacokinetics such as significantly shorter half-life than UFH (7, 11–16). However, these studies have been limited by small samples size, heterogeneous patient populations, and inadequate power to detect differences in rates of bleeding and thrombotic complication (11–13). To the best of our knowledge, none of the studies that have compared the use of UFH and bivalirudin so far have focused exclusively on respiratory failure patients on VV-ECMO.

Based on the available evidence suggesting that bivalirudin is at least as safe and efficacious as UFH with the added benefit of no potential for causing HIT, the ECMO program at University of Pittsburgh Medical Center (UPMC) Presbyterian Hospital transitioned to bivalirudin as a standard of therapy for device prophylaxis in all ECMO patients in 2017. The goal of our study is to compare the efficacy and safety of heparin and bivalirudin for anticoagulation in respiratory failure patients requiring VV-ECMO.

METHODS

This retrospective observational study was approved by the University of Pittsburgh Institutional Review Board (PRO12110220) and was performed in accordance with the principles set out in the Declaration of Helsinki. The study was completed at The UPMC Presbyterian Hospital. UPMC Presbyterian Hospital is an academic tertiary-care hospital that acts as the primary ECMO center for the UPMC Health System with approximately 80–100 ECMO cannulations occurring annually.

Patient Population

Patients were identified through review of an internal ECMO database maintained by perfusion services at UPMC Presbyterian Hospital between 2013 and May 2020. Patients requiring venoarterial ECMO (VA-ECMO) and those requiring VV-ECMO but managed without anticoagulation were excluded from our study. Patients that transitioned between the anticoagulants were also removed from the analysis. Anticoagulation protocols, cannulation strategies, and ECMO-related equipment are available in the **Appendix** (http://links.lww.com/CCM/G215).

Study Variables

All relevant demographic and ECMO-related variables were either retrieved from the said database or obtained through manual review of the electronic medical record. Indications were classified into the following categories: acute respiratory failure, prelung transplantation, postlung transplantation, postthoracic surgery, and all other indications. Patients that were placed onto VV-ECMO pretransplantation and remained on VV-ECMO support posttransplantation remained classified as pretransplant. Admission types were considered either medical or surgical. Prelung transplantation was considered to be a medical

admission. ECMO in-circuit thrombosis was defined as a visible thrombosis on any portion of the ECMO circuit that was determined to require a change in either ECMO cannula tubing, pump, and/or oxygenator. To account for the duration of ECMO support, the number of in-circuit thrombosis and blood products administered was normalized to events and milliliter per ECMO day, respectively.

Clinical End Points

There were two primary outcomes of the study, development of ECMO in-circuit thrombosis, and total volume of blood products transfused. The development of ECMO thrombosis was evaluated in multiple ways: development of in-circuit thrombosis, time to initial in-circuit thrombosis, and in-circuit thrombosis per ECMO day. Additionally, noncircuit-related thrombotic complications were evaluated through a review of clinical progress notes, relevant imaging, or diagnostic tests documented in the medical record. Patient information was reviewed from the day of cannulation until death or seven days postdecannulation. The volume (in mL) of packed RBCs (PRBCs), fresh frozen plasma (FFP), and platelets (PLTs) were also compared between the two groups. Patients were also evaluated for major and minor bleeding events as defined by the ELSO criteria (3). Both primary end points were only evaluated after the initiation of either UFH or bivalirudin.

Secondary outcomes were hospital length of stay, survival to ECMO decannulation, and survival to 1-year post-ECMO decannulation. Patients cannulated for ECMO after May 1, 2019, were evaluated for survival as of May 1, 2020. Subgroup analyses were completed for the primary outcomes based on the following variables: initiation of anticoagulation with the first 24 hours of ECMO cannulation, medical versus surgical admission type, and presence/absence of lung transplantation.

Statistical Analysis

Categorical variables were analyzed with chi-square tests, whereas continuous variables were analyzed with Mann-Whitney *U* tests due to nonnormality in the data. Time to event was analyzed with Kaplan-Meier log rank test as well as multivariable Cox regression, with time on ECMO (d) and oxygenator system change as the time and event. Due to the nonnormality of the data related to transfusion requirements, linear regression analysis was not completed. Instead, subgroup analysis was completed with Mann-Whitney *U* tests for each specified subgroup. Analyses were performed in SPSS (version 25; IBM Corp., Armonk, NY) and R (version 3.6.2; R Core Team, Vienna, Austria) A p value of less than 0.05 was considered to be statistically significant.

RESULTS

A total of 295 patients were enrolled in our study, with 162 receiving UFH and 133 receiving bivalirudin. Baseline demographics and indication for VV-ECMO are illustrated in **Table 1**. There were significantly more patients placed on VV-ECMO for acute respiratory failure in the bivalirudin group ($p < 0.001$). A significantly higher proportion of patients receiving UFH experienced at least a single in-circuit thrombosis event (32.7% vs 17.3%, $p = 0.003$). The results remained constant when normalizing to in-circuit thrombosis per ECMO day ($p = 0.003$) (**Table 2**). There was no difference in noncircuit-related thrombotic events between the two groups ($p = 0.42$) (Table 2). Kaplan-Meier analysis found that patients receiving bivalirudin had significantly longer time to clot relative to those receiving heparin (χ^2 [1] = 7.2, $p = 0.007$). Of patients experiencing an in-circuit thrombus, there was no difference in time to the first event between the bivalirudin group (9 d, interquartile range [IQR], 5.5–18.4 d) and the heparin group (8.7 d, IQR, 4.8–15.3 d) ($p = 0.55$). In a multivariable Cox regression using sex, admission type, presence of lung transplant, age, and whether or not the patient received anticoagulation in the first 24 hours as covariates, administration of heparin was associated with more than double the risk of in-circuit thrombosis, relative to bivalirudin (Exp[B] = 2.31, $p = 0.001$) (**Fig. 1** and **Table 3**).

Patients who received bivalirudin received significantly less PRBC, FFP, and PLT relative to those who received UFH throughout the entirety of VV-ECMO (Table 2). The results remained significant when normalizing for mL of PRBC, FFP, and PLT administered per VV-ECMO day. As depicted in Table 2, there was a significant difference in patients experiencing a major bleeding event, favoring the use of bivalirudin (40.7% vs 11.7%, $p < 0.001$). Transfusion requirement

TABLE 1.
Patient and Clinical Characteristics

Variable	Unfractionated Heparin ($n = 162$)	Bivalirudin ($n = 133$)	p
Age, yr, median (IQR)	49 (36–61)	49 (36–61)	0.81
Gender, *n* (%)			
Female	67 (41.4)	52 (39.1)	0.69
Male	95 (58.6)	81 (60.9)	
Cannulation year, *n* (%)			
2013	20 (12.3)	0 (0)	Not available
2014	41 (16)	1 (0.8)	
2015	26 (16)	0 (0)	
2016	49 (30.2)	3 (2.3)	
2017	18 (11.1)	18 (13.5)	
2018	7 (4.3)	42 (31.6)	
2019/2020	1 (0.6)	69 (51.9)	
Primary diagnosis, *n* (%)			
Acute respiratory failure	58 (35.8)	87 (65.4)	< 0.001[a]
Postlung transplantation	34 (21)	23 (17.3)	0.42[a]
Prelung transplantation	38 (23.5)	13 (9.8)	0.002[a]
Postthoracic surgery	15 (9.3)	5 (3.8)	0.06[a]
Other	17 (10.5)	5 (3.8)	0.03[a]
Admission type, *n* (%)			
Medical	108 (66.7)	101 (75.9)	0.08
Surgical	54 (33.3)	32 (24.1)	

[a]Post hoc analysis of adjusted standardized residuals.

of greater than 10 mL/kg in a 24-hour period was the most common major bleeding criteria with 48% and 70% of all major bleeding events in the UFH and bivalirudin group, respectively. In the specified subgroup analyses, the use of bivalirudin remained associated with a strongly significant decrease in PRBC, FFP, and PLT in each subgroup: admission type, presence/absence of transplantation, and initiation of anticoagulation with 24 hours of VV-ECMO cannulation.

There was a trend toward shorter ECMO duration and shorter length of stay for patients who received bivalirudin (**Table 4**). Patients receiving bivalirudin survived to decannulation from VV-ECMO more frequently than those receiving UFH (72.9% vs 62.3%, $p = 0.054$) and were significantly more likely to be alive at 1 year after VV-ECMO cannulation (66.9% vs 54.3%, $p = 0.029$). Sensitivity analysis using only survival data of patients that completed postdecannulation 1-year follow-up showed a similar numerical difference (67.5% vs 54.5%, $p = 0.07$).

DISCUSSION

Our study demonstrates that the use of bivalirudin for device prophylaxis for VV-ECMO not only reduced

TABLE 2.
Extracorporeal Membrane Oxygenation In-Circuit Thrombosis and Blood Product Administration

Outcome	Unfractionated Heparin ($n = 162$)	Bivalirudin ($n = 133$)	p
In-circuit thrombosis, *n* (%)	53 (32.7)	23 (17.3)	0.003
In-circuit thrombosis per extracorporeal membrane oxygenation day, mean[a] (SD)	0.02 (0.07)	0.007 (0.03)	0.003
Packed RBC,[b] mL, mean[a] (SD)	2,617.6 (3,422.0)	992.1 (2,039.9)	< 0.001
Fresh frozen plasma,[b] mL, mean[a] (SD)	477.6 (1,296.4)	22.6 (557.6)	< 0.001
Platelet,[b] mL, mean[a] (SD)	548.0 (1,158.7)	94.1 (630.9)	< 0.001

[a]Data reported as 5% trimmed mean (SD).
[b]Postanticoagulation initiation transfusion requirements.

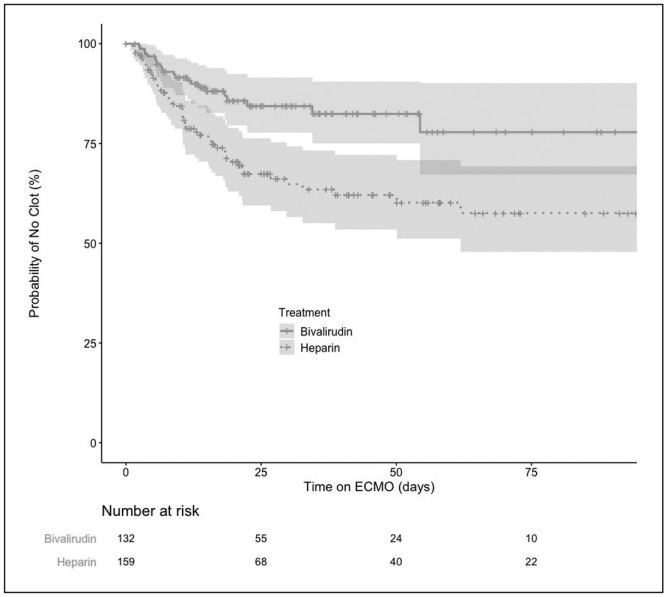

Figure 1. Freedom from in-circuit thrombosis based on anticoagulation strategy used on venovenous extracorporeal membrane oxygenation (ECMO). Multivariate Cox regression analysis using sex, admission type, presence of lung transplant, age, and whether or not the patient received anticoagulation in the first 24 hr as covariates shows a decrease in the probability of thrombotic event with the use of bivalirudin compared with unfractionated heparin ($p = 0.001$ for anticoagulation strategy used).

the rate of in-circuit thrombotic events but decreased blood product administration. With anticoagulation being essential for patients on ECMO, finding the anticoagulant that can achieve the best balance between thrombosis and hemorrhage is essential. Anticoagulation with bivalirudin for VV-ECMO provided a better balance than UFH in our cohort.

One of the advantages of using bivalirudin for VV-ECMO anticoagulation over UFH is clarifying the diagnostic differential of thrombocytopenia. A retrospective review by Glick et al (10) revealed that of a group of 119 patients who received UFH for anticoagulation on ECMO, 19% had clinical signs of HIT, yet only one patient received laboratory diagnosis of HIT, illustrating the high number of ECMO patients that require an evaluation of HIT. Despite the first reported successful use of bivalirudin for anticoagulation in a patient who had developed acute HIT secondary to heparin use on ECMO occurred in 2007 (13), its use has been limited by increased drug acquisition cost, lack of a reversal agent, and partial dependence on renal excretion (10, 14).

One of the perceived weaknesses of bivalirudin-based anticoagulation for ECMO patients is a higher drug acquisition cost relative to UFH. With an average wholesale price of a 250-mg vial of bivalirudin at $174 compared with a continuous infusion of UFH at $10, there is an appreciable difference in medication expense. In an effort to offset these cost considerations, we performed a medication use evaluation that demonstrated compounding two, 125-mg infusions of bivalirudin from a single vial led to a substantial degree of cost savings of nearly 75% (unpublished data). However, the cost of care for a VV-ECMO patient extends beyond the chosen anticoagulant and includes ECMO console, disposable equipment such as oxygenators, and blood product administration to control bleeding. Previous studies have completed cost evaluations of UFH compared with bivalirudin for ECMO

TABLE 3.
Multivariable Cox Regression: Odds of Developing In-Circuit Thrombosis

Variable	b	SE	Exp(B)	95% CI	*p*
Heparin	0.84	0.26	2.31	1.38–3.84	0.0013
Sex–Male	0.14	0.24	1.16	0.72–1.86	0.56
Admit type–surgical	–0.82	0.35	0.44	0.22–0.87	0.018
Transplant	–0.31	0.27	0.73	0.43–1.24	0.25
Age	–0.01	0.01	0.99	0.97–1.00	0.13
Anticoagulation first 24 hr	0.36	0.31	1.43	0.78–2.63	0.25

TABLE 4.
Extracorporeal Membrane Oxygenation-Related Secondary Outcomes

Outcome	Unfractionated Heparin (*n* = 162)	Bivalirudin (*n* = 133)	*p*
Length of stay, d, mean[a] (SD)	44.4 (47.3)	35.3 (31.1)	0.07
ECMO duration, hr, mean[a] (SD)	238.8 (333.0)	229.2 (284.7)	0.07
Survival to ECMO decannulation, *n* (%)	101 (62.3)	97 (72.9)	0.054
Survival to 1-yr postdecannulation, *n* (%)	88 (54.3)	87 (66.9)	0.029

ECMO = extracorporeal membrane oxygenation.
[a]Data presented are 5% trimmed means.

patients with mixed results. Ranucci et al (11) found a 58% difference in favor of bivalirudin and while Berei et al (17) noted no appreciable difference. A complete cost analysis was beyond the scope of our current study; however, our findings support those previously noted that bivalirudin is a viable strategy for ECMO device prophylaxis.

Although the previously published literature has been able to demonstrate that bivalirudin results in more consistent level of therapeutic anticoagulation, their small samples sizes and heterogeneous patient populations have been unable to demonstrate superiority in clinical outcomes such as thrombosis and bleeding. A potential explanation for bivalirudin having more predictable anticoagulation effects is due to its lack of binding to plasma proteins such as antithrombin III (5, 14, 15). A pilot study conducted at our institution that included all ECMO patients demonstrated a decrease in time to consecutive therapeutic anticoagulation levels (UFH: 48 hr, bivalirudin: 30 hr, $p = 0.03$) and an increase in percentages of anticoagulation levels within goal range (37% vs 56%, $p = 0.01$) (18). Berei et al (17) studied a primarily VA-ECMO cohort and, unlike previous studies, did not notice a difference in time to therapeutic anticoagulation or time in therapeutic range of anticoagulation between UFH and bivalirudin. In their high-intensity group (activated partial thromboplastin time goal of 65–90 for UFH and 60–80 for bivalirudin), bivalirudin patients did spend a significantly increased time in therapeutic level of anticoagulation, but it did not translate into improved bleeding or thrombotic outcomes; however, only a total of 44 patients were able to be evaluated. The high-intensity group in their study more closely resembles the targeted levels of anticoagulation at our institution. It is also possible that the VA-ECMO patient may not receive the degree of benefit that we demonstrated in our VV-ECMO cohort.

In addition to the significant decrease in in-circuit thrombotic events seen in patients receiving bivalirudin, patients on bivalirudin were significantly less likely to require transfusions of PRBC, FFP, and PLT. A large cohort

study by Smith et al (19) found that higher volumes of RBC transfusions are associated with an increase in all-cause hospital mortality rates in noncardiac patients maintained on ECMO. In addition to the increased morbidity and mortality, higher volume of blood product transfusions is associated with significant increases in healthcare costs and more exposure to patients under isolation precautions by nursing staff (1, 20, 21).

With decreases in in-circuit thrombotic complications and transfusion requirements, bivalirudin appears to strike a better balance than UFH for anticoagulation in respiratory failure patients on VV-ECMO. Despite the positive findings of our study, it is not without limitations. The retrospective nature of our study design is unable to establish the superiority of bivalirudin over UFH that could potentially be demonstrated in a randomized control trial for VV-ECMO. To evaluate a larger sample size, we included patients over a 7-year period, and despite no overt changes in our clinical blood product transfusion practice guidelines, we are unable to rule out variations in practice over time. However, our results were consistent while controlling for cofactors or through multiple subgroup analyses. We did not evaluate the levels of anticoagulation at the time of thrombosis or blood product administration; however, previous studies including our internal pilot study have demonstrated an increase in time at goal levels of anticoagulation while on ECMO. As such, we were unable to conclude if the differences seen between the two groups were due to differences in time in therapeutic range of anticoagulation. In addition, all the patients in our study were maintained on VV-ECMO and the results may not be necessarily applicable to VA-ECMO patients. Our study cohort consisted of a relatively high proportion of patients either pre- or postlung transplantation that may not be indicative of VV-ECMO populations at other ECMO centers.

CONCLUSIONS

Compared with UFH, the use of bivalirudin for VV-ECMO anticoagulation was more efficacious by decreasing the number ECMO in-circuit thrombosis and safer by decreasing the need for blood product transfusions after the initiation of anticoagulation. Further study into the comparison of bivalirudin and UFH in VV-ECMO is warranted in multicenter, randomized clinical trials.

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