

Original Articles

Predictors of Oxygenator Exchange in Patients Receiving Extracorporeal Membrane Oxygenation

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Abstract: Thrombosis within the membrane oxygenator (MO) during extracorporeal membrane oxygenation (ECMO) can lead to sudden oxygenator dysfunction with deleterious effects to the patient. The purpose of this study was to identify predictors of circuit exchange during ECMO. This is a single-center, retrospective study of all patients who received ECMO at our institution from January 2010 to December 2015. Changes in potential markers were compared on Day 3 vs. Day 0 before MO exchange. Of the 150 patients who received ECMO, there were 58 MO exchanges in 35 patients. Mean ECMO duration was 21.1 (± 12.7) days. D-dimer (DD) ($\mu\text{g/mL}$) (mean difference -2.6 ;

95% confidence interval [CI]: -4.2 to -1.1 ; $p = .001$) increased significantly in the 3 days leading up to MO exchange, whereas fibrinogen (mg/dL) (mean difference 90.7; 95% CI: 41.8–139.6; $p = .001$), platelet (PLT) count (1,000/ μL) (mean difference 23.3; 95% CI: 10.2–36.4; $p = .001$), and heparin dose (units/h) (mean difference 261.7; 95% CI: 46.3–477.1; $p = .02$) decreased. Increasing DD or decreasing fibrinogen, PLT count, or heparin dose may indicate an impending need for MO exchange in patients receiving ECMO. Early identification of these changes may help prevent sudden MO dysfunction. **Keywords:** ECMO, oxygenator exchange. *J Extra Corpor Technol. 2019;51:61–6*

Extracorporeal membrane oxygenation (ECMO) has been used in patients with pulmonary and/or cardiac failure since the 1970s (1). Allowing the failing pulmonary and cardiac systems to recover or bridge to other interventions has proven to be life-saving (2). Although ECMO has demonstrated clinical utility, it is not without risk of complications. The leading causes of morbidity and mortality associated with ECMO are bleeding and thrombosis (1). Thrombosis, either systemic or within the ECMO circuit, can be a life-threatening event, and patients are typically anticoagulated systemically to prevent either.

Clots formed within the circuit can embolize to end organs and those that do not embolize can decrease the functionality of the membrane oxygenator (MO), putting the patient at risk of hypoxic end-organ damage. A malfunctioning MO requires replacement, which further exposes the patient to risk of hypoxia, hemodynamic instability, and an additional pro-inflammatory insult secondary to re-exposure of blood to a new artificial surface. These consequences are more likely to occur during an emergent exchange (3). Thus, the ability to use clinical monitoring to predict an MO exchange may be beneficial. Previous studies have elucidated laboratory predictors of MO exchange (D-dimer [DD], anti-Xa); however, these studies are limited in the range of patients evaluated, either by age or by type of ECMO performed (3,4). The primary aim of our study is to identify parameters that may predict circuit exchange in both adult and pediatric ECMO patients on venoarterial (VA) or venovenous (VV) support.

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MATERIALS AND METHODS

Study Design

This is a retrospective observational chart review performed on patients at a 487-bed, acute-care academic medical center who received ECMO support from January 2010 to December 2015. Patients who required an MO exchange were eligible for inclusion. MO exchanges were identified by review of the medical record of each patient. Each circuit change was treated as a separate event. The day of circuit change was defined as Day 0. Circuit changes were excluded from analysis if they happened within 48 hours of ECMO initiation or if any data point was missing for Day 3 or Day 0 before circuit exchange (Figure 1).

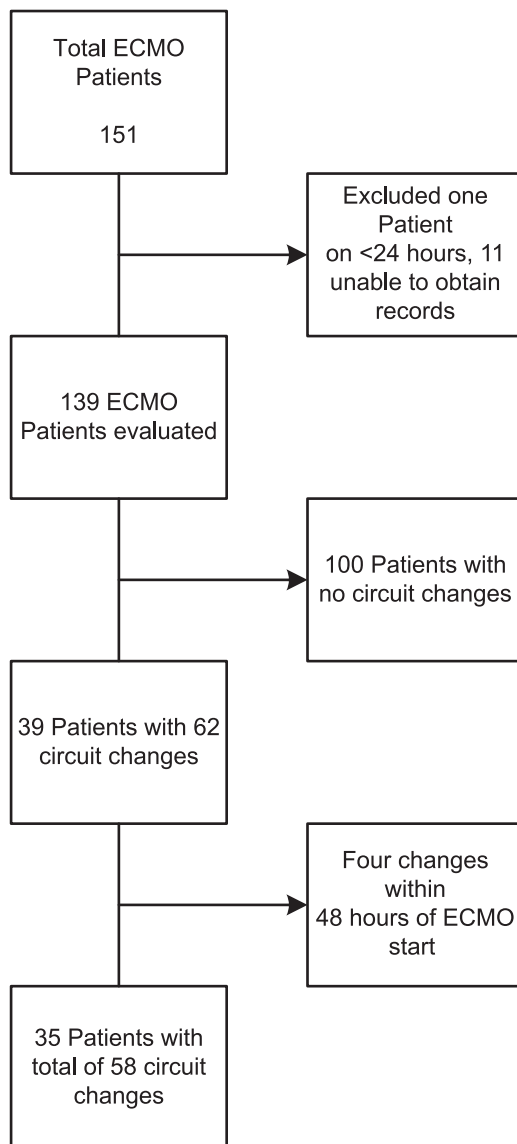


Figure 1. Stratification of patients based on inclusion criteria. Each circuit change is treated as a separate event.

Laboratory values extracted include platelet count, partial thromboplastin time (PTT), fibrinogen, DD, prothrombin time (PT), international normalized ratio (INR), activated clotting time (ACT), antithrombin III level, native thromboelastogram (n-TEG), and n-TEG with heparinase parameters (R, K, maximum amplitude [MA], angle, and coagulation index). Our standard practice is to monitor ACT hourly, PTT every 4–6 hours, PT/INR and fibrinogen every 12 hours, platelet count at least twice daily unless transfusion is required, and antithrombin III level and TEGs daily. All laboratory values during the ECMO support were recorded and averaged per day. ECMO circuit flow rate, sweep, and MO arterial-venous pressure gradients were recorded at the highest and lowest point per 24-hour time period. Morning arterial blood gases (pH, pCO₂, and pO₂) were recorded. Anticoagulant dosing was collected by hour and averaged for the day. Daily transfusions of packed red blood cells (pRBCs), platelets, fresh frozen plasma (FFP), and cryoprecipitate (cryo) were recorded in milliliters (mL). The average daily values of each laboratory were recorded for the 3 days before MO exchange and the day of the event. The change in laboratory parameters from Day 3 to Day 0 was evaluated as potential predictors of the need for MO exchange. This study was approved by the university's investigational review board.

ECMO Hemostasis, Technique, and Usual Circuit Change Criteria

Patients were treated with VV or VA ECMO using a heparin-coated circuit (Bioline; Maquet Cardiopulmonary AG, Hirrlingen, Germany) consisting of a Quadrox oxygenator and a Rotaflow centrifugal blood pump (both Maquet Cardiopulmonary). Systemic anticoagulation was administered starting with a goal target ACT of 160–220 seconds, depending on baseline bleeding and assessed risk of bleeding. In general, our VA ECMO anticoagulation was initiated with the target of an ACT of 180–220 seconds and our VV patients with an ACT of 160–180 seconds. We tolerate a lower target ACT range in VV ECMO because of the lower risk of arterial embolic complications. Anticoagulation targets were tailored to the individual throughout the ECMO course using ACT, PTT, and n-TEG. Antithrombin III was administered at provider discretion, but goal antithrombin level of at least 85% was the usual target. Decision to change the MO was left to the physician's discretion. Most commonly, MO changes occurred when gas exchange via the MO was impaired, resulting in significant increase in sweep and/or FiO₂ requirements, visible clot within the arterial side of the MO, or significant increase in MO pressure gradient. Protocolized transfusion of cryoprecipitate, platelets, and pRBC was standard of care and products were given to maintain fibrinogen levels >150 mg/dL, PLT >80–100 1,000/ μ L, and hematocrit (HCT) of 25%, respectively.

Statistical Analysis

Demographic and clinical variables were evaluated descriptively using proportions with percentages or means with SDs as appropriate. Each laboratory parameter was evaluated descriptively by calculating the change in value from Day 3 to Day 0. A paired Student’s *t*-test was used to compare the values at Day 3 to Day 0. Because some patients had more than one MO exchange, the values were adjusted for clustering by patient. A two-sided alpha of .05 was considered to be statistically significant. All analyses were conducted in STATA 13 (StataCorp, College Station, TX).

RESULTS

During the study period, a total of 151 patients received ECMO therapy (Figure 1). Of these, 35 patients required a total of 58 MO exchanges (no. of MO exchanges per patient/no. of patients: 1/21, 2/10, 3/1, 4/2, and 6/1). Mean ECMO duration was 21.1 ± 12.7 days. Median duration until circuit exchange was 8.5 days [interquartile range (IQR) 5–12]. Demographic data are provided in Table 1.

D-dimer (µg/mL) (mean difference -2.6; 95% confidence interval [CI]: -4.2 to -1.1); *p* = .001) and circuit sweep (mean difference -.6; 95% CI: -.94 to -.23) increased in the 3 days leading up to MO exchange, whereas fibrinogen (mg/dL) (mean difference 90.7; 95% CI: 41.8–139.6; *p* = .001), PLT count (1,000/µL) (mean difference 23.3; 95% CI: 10.2–36.4; *p* = .001), and heparin dose (units/h) (mean difference 261.7; 95% CI: 46.3–477.1; *p* = .02) decreased in the 3 days preceding MO exchange. There was a decrease in two thromboelastograph (TEG) parameters including MA (mm) (mean difference 4.1; 95% CI: -.1 to 8.4; *p* = .055) and coagulation index (mean difference .5; 95% CI: -.09 to 1.1; *p* = .095) in the 3 days leading up to MO exchange, but this difference was not statistically significant. Parameters, including ACT, anti-thrombin level, flow rate, MO pressure gradient (delta p), arterial pH, pCO₂, pO₂, PTT, INR, TEG R, TEG K, and TEG angle, did not show a statistically significant difference in the 3 days leading up to MO exchange (Table 2).

Values for laboratory and circuit parameters on Day 3 of exchange and Day 0 of exchange are reported in Table 3. Blood product replacement in the 3 days leading up to and including the day of the exchange are reported in Table 4.

DISCUSSION

These data demonstrate that an increase in DD or decrease in fibrinogen, PLT count, heparin dose, TEG MA, or TEG coagulation index may indicate an impending need

Table 1. Patient characteristics including reason for ECMO, type of ECMO, and other co-morbidities.

	Mean (SD)
Age	31.6 ± 20.2
BMI	29.9 ± 9.7
Male gender	n (%)
Age <18 years	17 (48.6)
Race	7 (20)
Caucasian	18 (51.4)
Hispanic	10 (28.6)
Other/unknown	7 (20)
Reason for ECMO	
ARDS	20 (57.2)
Acute hypoxic respiratory failure	5 (14.3)
Cardiac arrest	3 (8.6)
Cardiogenic shock	4 (11.4)
Post-partum pulmonary hypertension	1 (2.9)
Transplant rejection	1 (2.9)
Pulmonary hypertension	1 (2.9)
Survival	
Died on ECMO	15 (42.9)
Survived decannulation, died in hospital	7 (20)
Survived decannulation and discharged	13 (37.1)
Type of ECMO	
VA	12 (34.3)
VV	21 (60)
VV + VA	2 (5.7)
Surgery before ECMO	
Lung transplant	2 (5.7)
Emergent C-section	1 (2.9)
Emergent ORIF	1 (2.9)
Heart + kidney transplant	1 (2.9)
Valve replacement/repair	2 (5.7)
Fixation of tibia	1 (2.9)
Pneumonectomy	1 (2.9)
Rastelli	1 (2.9)
Tetralogy of Fallot (ToF) repair	1 (2.9)
VATS	1 (2.9)
Co-morbidities	
Cath lab before ECMO	0 (0)
Intra-aortic balloon pump	1 (2.9)
Cerebrovascular disease	0 (0)
COPD	2 (5.7)
Hypertension	7 (20)
Previous cardiac surgery	4 (11.4)
Atrial fibrillation	4 (11.4)
Myocardial infarction	4 (11.4)
Peripheral vascular disease	2 (5.7)
Obesity (BMI >30)	13 (37.1)
Diabetes mellitus	3 (8.6)
Heart failure with reduced ejection fraction	5 (14.3)
Dialysis	1 (2.9)
Infection	6 (17.1)
CRRT during ECMO	16 (45.7)

for MO exchange in patients receiving ECMO. It is likely that during ECMO, a consumptive coagulopathy process occurs with advanced age of the MO, accounting for the increased DD values and decreased fibrinogen and PLT count. Decreasing TEG MA value and decreasing TEG coagulation index values support this as well, as the MA value speaks to the overall strength of clot formation, and the coagulation index represents a summary parameter of the overall hyper- or hypocoagulability of the patient. It is

Table 2. Summary of markers evaluated to predict MO exchange.

	No. of Observations	Mean Difference (95% CI)	<i>p</i> -Value
ACT	55	4.6 (−4.6, 13.9)	.317
n-TEG parameters with heparinase			
R	47	2.3 (−.6, 5.1)	.117
K	47	−1 (−1.1, .9)	.842
ANG	47	−8.8 (−30.6, 13)	.416
MA	47	4.1 (−.1, 8.4)	.055
CI	47	.5 (−.9, 1.1)	.095
AT level	47	−1.8 (−9.4, 5.7)	.625
Anticoagulant dose			
mcg/kg/min (argatroban)*	2	−.5 (−7.9, 6.9)	.552
Units/h (heparin)	40	261.7 (46.3, 477.1)	.02
Units/kg/h (heparin)	53	3.7 (−.1, 7.4)	.056
DD	54	−2.6 (−4.2, −1.1)	.001
PT	58	−.7 (−1.4, .4)	.064
Fibrinogen	58	90.7 (41.8, 139.6)	.001
PTT	57	2.3 (−9.4, 13.9)	.696
INR	58	−.7 (−.1, .01)	.08
PLT count	58	23.3 (10.3, 36.4)	.001
pH	55	.02 (−.007, .04)	.16
pCO ₂	56	−.3 (−.4, 3.4)	.876
pO ₂	56	7.5 (−3.5, 18.4)	.176
Flow rate	56	.13 (−.06, .3)	.182
Sweep	55	−.6 (−.9, −.2)	.002
MO pressure gradient (delta p)	16	.63 (−3.8, 3.9)	.972

*Anticoagulant of choice based on institution formulary in patients with suspected heparin-induced thrombocytopenia (HIT) or abrupt decrease in PLT count of at least 50% with or without thrombosis.

Table 3. Comparison of laboratory and circuit parameter values on Day 3 of MO exchange and Day 0 of MO exchange.

	Day 3 of Circuit Change, Median [IQR]	Day 0 of Circuit Change, Median [IQR]
AT level (%)	93.5 [76.6, 110]	96.5 [83.3, 106]
PTT (sec)	51.2 [38.1, 65.5]	52 [40, 66.4]
Fibrinogen (mg/dL)	405 [298.3, 573.7]	306 [245.8, 406.8]
DD (μg/mL)	7.6 [3.9, 15.8]	15 [6.2, 20]
INR	1.1 [1, 1.2]	1.2 [1.1, 1.5]
PLT count (1,000/μL)	125 [98, 167]	104.3 [83.1, 148.4]
Patient ABG pH	7.39 [7.35, 7.43]	7.38 [7.34, 7.41]
Patient ABG pCO ₂	47 [35.7, 54]	44.2 [39, 55]
Patient ABG pO ₂	69.3 [59.3, 102]	64.2 [56.3, 86.3]
n-TEG w/heparinase CI	−.1 [−1.7, 1]	−.5 [−1.8, .6]
n-TEG w/heparinase MA	53.4 [49, 61]	52 [43, 58]
Flow rate (L/min)	4.1 [3.2, 4.9]	4 [3, 4.8]
MO pressure gradient (delta p)	26 [19.3, 30.1]	25.3 [20, 29]
Sweep (L/min)	4.2 [3.2, 6]	5.3 [3.1, 7.1]

likely that the aforementioned also explains why heparin doses decreased in the 3 days before MO exchange as decreasing n-TEG coagulation index value would have been a trigger to decrease anticoagulant dosing per our ECMO anticoagulation protocol.

The goal of anticoagulation during ECMO is to prevent thrombotic events and maintain the patency of the ECMO circuit while minimizing the patient's risk of bleeding. Historically, the most commonly used anticoagulation monitoring parameter has been ACT (1,2,4). However, there has been apprehension about the accuracy of using ACT to provide adequate anticoagulation

during ECMO support as ACT can be affected by several factors, including coagulopathy, platelet dysfunction, antithrombin level, hypothermia, and hemodilution. The result can also be affected by technical factors when performing the test (1). Studies have shown that using ACT as the lone measurement to guide anticoagulation leads to suboptimal anticoagulation (4) and is inferior to activated PTT in guiding anticoagulation and correlating to anti-factor Xa levels (5,6). Our study showed no association between ACT values and need for MO exchange, highlighting the need to monitor multiple anticoagulation parameters.

Table 4. Blood product usage from Day 3 to Day 0 of MO exchange.

	Day 3 to Day 0
AT III dose (units)	
Median [IQR]	282 [0, 2,748]
Mean (SD)	1,355.3 (1,812)
Cryo volume (mL)	
Median [IQR]	0 [0, 261]
Mean (SD)	158 (271.3)
FFP volume (mL)	
Median [IQR]	0 [0, 294.3]
Mean (SD)	265 (609)
PLT volume (mL)	
Median [IQR]	0 [0, 797]
Mean (SD)	582.4 (1,125)
pRBC volume (mL)	
Median [IQR]	815 [353, 1,757]
Mean (SD)	1,442 (1,693)

Researchers have shown utility in clinical markers such as DD in predicting MO exchange. Lubnow et al. (3) demonstrated that a sudden increase in DD level accompanied by a reduction of platelet count within 3 days before an MO exchange was a sensitive indicator of the device activating the coagulation cascade and postulated that these laboratory values could be used to predict an upcoming MO exchange. This finding was consistent in our study. TEG monitoring has not been studied extensively to identify the possible clinical utility in assisting anticoagulation management. Another major gap in the present literature is the lack of representation of the adult ECMO-supported population. Most of the present literature focuses on pediatric patients, who differ vastly from adult patients with respect to their coagulation system. Our study provided a large percentage of adult patients. Whereas the present literature offers pieces to this complex puzzle, our study has the potential to offer practitioners additional information when monitoring these patients to help better determine an impending circuit change.

One laboratory parameter that was not addressed in our study but has shown to be useful in prior studies is anti-factor Xa levels. Irby et al. (4) showed anti-factor Xa monitoring to be also useful for predicting MO exchange. Their study concluded that higher anti-factor Xa concentrations were associated with freedom from circuit/MO change and that a .01 IU/mL decrease in anti-factor Xa increased the odds for circuit/MO change by 5% (4). Our institution was unable to perform the unfractionated heparin anti-Xa test at the time of this retrospective review; however, since then, this test has been made available.

The many different ECMO anticoagulation strategies throughout the literature captured at different ECMO centers across the world highlight the complexity in monitoring and managing the anticoagulation in this

patient population. This also shows that no single marker can consistently be used to fully dictate the anticoagulation strategy in these patients. By collecting the combination of coagulation, inflammatory, ECMO circuit, and physiologic markers over the course of our study, we were able to provide a whole picture view of what is taking place within the non-biologic circuit. Our study supports the present literature by emphasizing the value of using multiple markers to predict MO exchange. As ECMO continues to be used more commonly in clinical practice, we believe our study, combined with the aforementioned literature, will assist in the guidance of monitoring these patients in an effort to reduce sudden MO exchange and encourage more robust prospective trials to move toward a standardized approach in monitoring patients on ECMO support.

Our study has several limitations. Given the observational nature of our design, it is difficult to draw definitive conclusions. Although including all patients on ECMO over this time period may reduce the selection bias associated with retrospective analyses, this retrospective review did present challenges through the collection process. In 2013, our institution changed to an electronic medical record system. Before this date, most of the data were collected by hand on ECMO flow sheets. When collecting the data, the difference in the completeness of data before and after this change in computer systems was evident. Although we do not feel this significantly affected the accuracy of our findings, it is worth mentioning. Also, because of the retrospective nature of this study, we had to rely on the documentation provided over several years in regard to reporting of events (MO exchange). In addition, several patients required more than one MO exchange, and each of these exchanges was evaluated as a separate event. On review, it does not appear that this would have skewed our results, as all of the patients with multiple MO exchanges received ECMO support for longer durations of time ranging from 720 to 1,427 hours. It is, therefore, unlikely that these patients simply had a hypercoagulable predisposition that led to their multiple MO exchange events.

Other factors that may lead to MO exchange could also have contributed to variability in our results. These factors include various thresholds for transfusion, underlying coagulopathy, and surgeon, ECMO intensivist, and pharmacist variability in discretion regarding MO exchange and patient management over the course of the study period. Last, our study does not include a control group of patients who did not require MO exchange. As such, our data should be viewed as descriptive only and not predictive. However, these data highlight the need for prospective studies with real-time multivariate assessment of coagulation parameters in predicting MO failure and need for exchange.

In conclusion, MO exchange was preceded by increasing DD and decreasing fibrinogen levels, platelet counts, MA,

and coagulation index on thromboelastogram and heparin doses. Multivariable assessment of a patient's coagulation using these laboratory values may be useful in monitoring the need for an MO exchange.

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