The Hematological Effects of Extracorporeal Membrane Oxygenator Exchange

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Membrane oxygenator failure during venovenous (V-V) extracorporeal membrane oxygenation (ECMO) can lead to life-threatening hypoxia, high replacement costs, and may be associated with a hyperfibrinolytic state and bleeding. The current understanding of the underlying mechanisms that drive this is limited. The primary aim of this study therefore is to investigate the hematological changes that occur before and after membrane oxygenator and circuit exchanges (ECMO circuit exchange) in patients with severe respiratory failure managed on V-V ECMO. We analyzed 100 consecutive V-V ECMO patients using linear mixed-effects modeling to evaluate hematological markers in the 72 hours before and 72 hours after ECMO circuit exchange. A total of 44 ECMO circuit exchanges occurred in 31 of 100 patients. The greatest change from baseline to peak were seen in plasma-free hemoglobin (42-fold increase $p < 0.01$) and the D-dimer:fibrinogen ratio (1.6-fold increase $p = 0.03$). Bilirubin, carboxyhemoglobin, D-dimer, fibrinogen, and platelets also showed statistically significant changes ($p < 0.01$), whereas lactate dehydrogenase did not ($p = 0.93$). Progressively deranged hematological markers normalize more than 72 hours after ECMO circuit exchange, with an associated reduction in membrane oxygenator resistance. This supports the biologic plausibility that ECMO circuit exchange may prevent further complications such as hyperfibrinolysis, membrane failure, and clinical bleeding. *ASAIO Journal* 2023; 69;e308–e314

Key Words: extracorporeal membrane oxygenation, hemolysis, membrane oxygenator dysfunction

Thrombosis and bleeding are the leading causes of morbidity and mortality in patients supported with extracorporeal membrane oxygenation (ECMO).[1–3] Although the underlying disease may contribute to both of these complications, the ECMO oxygenator and circuit results in an interaction between blood and nonendothelial surfaces that can trigger an intense inflammatory response. This can activate the coagulation system leading to thrombosis and oxygenator failure, as well as fibrinolysis with associated hemolysis and in severe cases bleeding.[2,4–6] The resultant release of free hemoglobin can contribute to organ dysfunction through direct cytotoxicity, vasoconstriction, acute kidney injury through tubular necrosis, and further activation of the coagulation cascade.[1] Once this occurs, replacing the membrane oxygenator and ECMO circuit (ECMO circuit exchange) may be the only way to reverse this process.[2,7]

Extracorporeal membrane oxygenation circuit exchanges require the patient to come off ECMO support, sacrifice blood volume, risk air embolism, are expensive and may cause hemodynamic instability, particularly if the ECMO circuit exchange is performed in an emergency.[8] Therefore, ECMO circuit exchanges should only be performed when the risks of hematological complications attributable to the ECMO circuit are greater than the risk of performing an ECMO circuit exchange. Venovenous (V-V) ECMO is associated with higher rates of hemolysis[9] and the requirement for ECMO circuit exchange for hematologic complications.[10]

There has been limited literature published on the hematological effects of changing an ECMO circuit.[1,7,8,11,12] Most studies examine hematological markers at a single time point, and few have examined the dynamic nature of the hematological changes, including before and after an ECMO circuit exchange. There is also a lack of literature exploring the factors associated with ECMO circuit exchange or whether they can be predicted earlier.

The primary aim of our study was to investigate the dynamic hematological changes that occur in the 72 hours before and after ECMO circuit exchange in V-V ECMO. Secondary aims were to look at the frequency of ECMO circuit exchanges and examine the clinical factors associated with an ECMO circuit exchange.

Materials and Methods

Study Design

This was a single-center, retrospective study. The Alfred Hospital Ethics Committee reviewed and approved the study design and waived the requirement for consent (Project 332/19).

Setting

The setting was a 60-bed, quaternary referral intensive care unit (ICU) that has more than 3,000 admissions per year in Melbourne, Australia. It provides state services for burns and

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hyperbaric medicine, heart and lung transplant, ventricular assist devices (VAD), and has had an ECMO-program since 1990, delivering more than 100 ECMO treatments annually.

Participants

The population included 100 consecutive adult V-V ECMO patients identified from the Alfred ECMO database from September 1, 2013, to June 30, 2018. In patients with multiple ECMO runs, only the first was included in the analysis.

Extracorporeal Membrane Oxygenation Management

The standard ECMO equipment used in the ICU are Maquet Rotaflow consoles with PLS 2050 circuits and Maquet Cardiohelp consoles with HLS Advanced 7.0 circuits, which are both heparin-coated and use Quadrox oxygenators with a 1.8 m^2 surface area. Cannulation is preferentially bifemoral with a multistage access and single stage return cannula. Anticoagulation is protocolized with a heparin infusion with activated partial thromboplastin time (APTT—laboratory therapeutic range 52–94) measured every 6 hours for the duration of the heparin infusion and modifications to the target range at the discretion of the treating intensivist. Bilirubin, lactate dehydrogenase (LDH), D-dimer, fibrinogen, and platelets are measured daily while on ECMO. Plasma-free hemoglobin (PFHb) is routinely measured six hourly and repeated if results are unexpectedly elevated (>0.05 g/L). Oxygenator transmembrane pressure (TMP) is recorded hourly by nursing staff and reported if the trend is rising. Extracorporeal membrane oxygenation circuit exchange is not strictly protocolized within the institution but follows a standardized approach,[13] including replacing the membrane oxygenator and circuit tubing en bloc on both HLS and PLS circuits. In addition to management by the treating intensivist, all patients on ECMO are reviewed daily by a senior ECMO intensivist and managed by specialist ECMO nurses.

Data Collection

The digital medical record for each patient was reviewed to identify ECMO circuit exchange events. The reason for ECMO circuit exchange was categorized as (1) bleeding attributed to ECMO associated coagulopathy, (2) thrombosis within the circuit, (3) intravascular hemolysis, or (4) equipment failure. The ECMO revolutions per minute (RPM), blood flow, and oxygenator TMP were recorded before and after the ECMO circuit exchange. Flow indexed TMP was defined as the TMP per liter of ECMO circuit blood flow and was used as a marker of oxygenator resistance. If a patient had multiple ECMO circuit exchange events this was recorded, and each exchange was considered as a separate event. Laboratory data (bilirubin, carboxyhemoglobin, D-dimer, fibrinogen, LDH, platelets, PFHb) were analyzed for the 72 hours before and after the ECMO circuit exchange event, with time of exchange defined as time zero. This observation period was selected to acquire baseline values, evaluate the time course for derangement of laboratory values and investigate the time taken for resolution to prior values after ECMO circuit exchange. D-dimer to fibrinogen ratio was the ratio between the D-dimer and time matched fibrinogen and is reported as a ratio of microg/mL:g/L. Plasma-free hemoglobin was analyzed using spectrophotometric methods on an Abbot Alinity analyzer. Carboxyhemoglobin values were measured *via* co-oximetry on a Siemens RAPIDPoint500 blood gas analyzer with one point calibration every half an hour, two-point calibration performed every 2 hours and full calibration performed every 6 hours. Demographic data, comorbid medical conditions, length of stay, and mortality data were extracted from the Australian and New Zealand Intensive Care Society (ANZICS) Adult Patient Database.

Outcomes

The primary outcome of the study was a time analysis examining the hematological markers of hemolysis or hyperfibrinolysis in the 72 hours before and after ECMO circuit exchange. Secondary outcomes were to investigate the frequency of ECMO circuit exchanges and clinical factors associated with ECMO circuit exchange. In addition, circuit RPM, blood flow, and TMP were collected to assess circuit resistance before and after ECMO circuit exchange.

Statistical Analysis

Statistical analysis was performed using SAS software version 9.4 (SAS Institute, Cary, NC). Continuous variables were summarized using means and standard deviations (SD) or medians and interquartile ranges (IQRs) according to data type and distribution. Categorical variables were reported as counts and percentages. Changes in hematological markers in the 72 hours before and after ECMO circuit change were assessed using linear mixed-effects modeling with results presented as means and 95% CIs. The association between ECMO circuit exchange and hospital mortality was assessed using logistic regression with results reported as odds ratios (ORs) and 95% CIs. To account for severity of illness, the analysis was further adjusted by the Australia and New Zealand Risk of Death (ANZROD) score[14] as a covariate in the regression model. All calculated p values were two-tailed and a p value <0.05 was chosen to indicate statistical significance.

Results

From September 1, 2013, to June 30, 2018, 100 patients underwent V-V ECMO and were included in the study. The median age was 42.8 years (±15.3), 55% were male, median Acute Physiology Age Chronic Health Evaluation (APACHE) III[15] score was 70 (IQR 56–92.5) and the most frequent indications for V-V ECMO were bacterial pneumonia 32 of 100 (32%) and viral pneumonia 22 of 100 (22%). The median duration of ECMO support was 8 days and the overall mortality was 39 of 100 (39%) (Table 1).

A total of 44 ECMO circuit exchanges occurred in 31 of 100 patients. The reasons for ECMO circuit exchange were circuit thrombus 25 (57%), intravascular hemolysis 12 (27%), bleeding attributed to ECMO associated coagulopathy 3 (7%), equipment failure 2 (4.5%), and unknown 2 (4.5%). In patients who underwent ECMO circuit exchange (n = 31), the mean number of exchanges was 1.4 and the median circuit age when exchanged was 6 days (IQR 2.25–10.25) (Figure 1). The mortality was numerically higher in the ECMO circuit exchange cohort 15 of 31 (48.4%) *versus* 24 of 69 (34.8%), $p = 0.20$. Of

Table 1. Baseline Demographics, Outcomes, and Diagnosis Requiring ECMO Support in Patients who Had an ECMO Circuit Exchange *Versus* No Circuit Exchange

	Circuit Exchange, n = 31	No Circuit Exchange, n = 69
Age (mean and SD)	42.5 (15.5)	44.9 (15.4)
Male (n and %)	18/31 (58%)	37/69 (54%)
APACHE III (median and IQR)	69 (56–99.5)	70 (57–91)
ANZROD (median and IQR)	0.17 (0.05–0.32)	0.12 (0.06–0.32)
Number of circuit exchanges per patient (mean and SD)	1.4 (0.9)	
Circuit age in days when exchanged (mean and IQR)	6 (2.25–10.25)	
APACHE chronic medical conditions (n and %)		
Immune suppressive disease	0/31 (0)	1/69 (1.5)
Immunosuppressive therapy	4/31 (13)	17/69 (25)
Acquired immunodeficiency syndrome	0/31 (0)	0/69 (0)
Leukemia/myeloma	0/31 (0)	0/69 (0)
Metastatic cancer	0/31 (0)	1/69 (1.5)
Lymphoma	0/31 (0)	0/69 (0)
Hepatic failure	0/31 (0)	0/69 (0)
Cirrhosis	0/31 (0)	1/69 (1.5)
Respiratory disease	5/31 (16)	20/69 (29)
Cardiovascular disease	1/31 (3)	3/69 (4.5)
Renal disease	0/31 (0)	2/69 (3)
Outcomes		
ECMO duration (median days and IQR)	14 (8.5–20)	7 (4–10)
Mechanical ventilation (median days and IQR)	17.7 (10.9–27.9)	10.4 (6.2–20.2)
ICU length of stay (median days and IQR)	19.3 (13.8–36.6)	15.7 (7.8–27.2)
Hospital length of stay (median days)	26.5 (14.3–55.5)	25.2 (12.5–50.1)
ICU Mortality (n and %)	15/31 (48.4)	24/69 (34.8)
Hospital Mortality (n and %)	15/31 (48.4)	24/69 (34.8)
Diagnosis resulting in ECMO requirement (n and %)		
Bacterial pneumonia	12/31 (38.7)	20/69 (28.9)
Viral pneumonia	8/31 (25.8)	14/69 (20.3)
Lung transplant primary graft dysfunction	2/31 (6.5)	10/69 (14.5
Aspiration pneumonia	0/31 (0)	8/69 (11.6)
Chemical pneumonitis (inhalational injury)	3/31 (9.7)	0/69 (0)
ARDS diagnosis unknown	0/31 (0)	3/69 (4.3)
Fungal pneumonia	0/31 (0)	2/69 (2.9)
Airway compression from mass lesions	0/31 (0)	2/69 (2.9)
Other	6/31 (19.4)	10/69 (14.5)

ANZROD, The Australian and New Zealand Risk Of Death model; APACHE III, Acute Physiology and Chronic Health Evaluation III score; ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IQR, interquartile range.

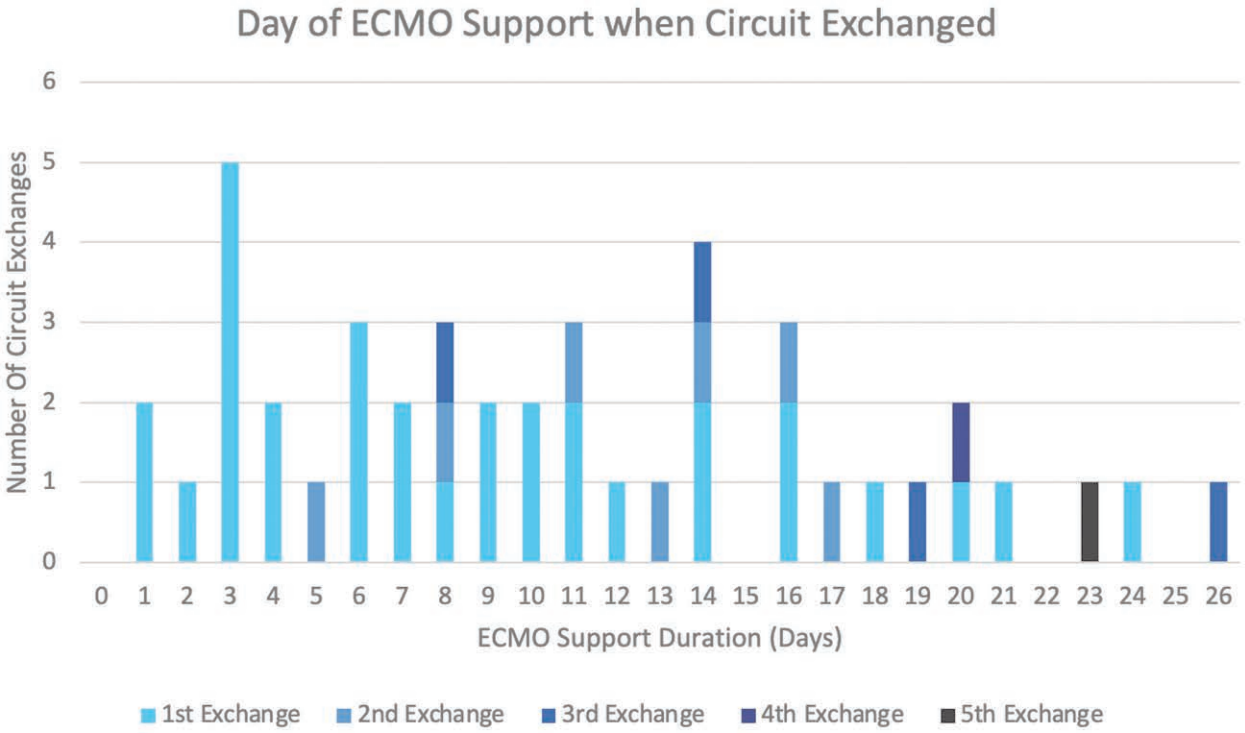

Figure 1. Day of ECMO support when ECMO circuit exchanged, including those with multiple exchanges (1st to 5th). ECMO, extracorporeal membrane oxygenation.

the cohort who required two or more ECMO circuit exchanges (n = 7), all patients survived except one very unstable patient with overwhelming sepsis and diffuse intravascular coagulation, who had a cardiac arrest and died despite a prolonged attempt at resuscitation during their second ECMO circuit exchange. Other demographic differences between the groups are presented in Table 1.

The median duration of ECMO support was significantly higher in the ECMO circuit exchange group 7 (4–10) *versus* 15 (8.5–20) days, $p = 0.0002$. Extracorporeal membrane oxygenation circuit exchange was not associated with hospital mortality (OR 2.16, 95% CI 0.78–5.99, $p = 0.14$) even after adjusting for the severity of illness using the Australian and New Zealand Risk of Death model.[14]

The mean RPM and flow indexed TMP (mmHg/L of blood flow) immediately before and immediately after ECMO circuit exchange are presented in Figure 2. The blood flow was similar before (3.96 L/min) and after (3.98 L/min) ECMO circuit exchange but was maintained with a lower RPM level.

Anticoagulation at the time of ECMO circuit exchange was most commonly heparin (32/44 ECMO circuit exchanges) with a mean APTT of 53.6 (±13.9) (therapeutic anticoagulation reference range 52–94). Three patients were on bivalirudin for suspected heparin-induced thrombotic thrombocytopenic syndrome (HITTS), although only one patient had their HITTS diagnosis confirmed on serotonin release assay. They required three ECMO circuit exchanges. Nine patients were not anticoagulated at the time of ECMO circuit exchange, five due to active bleeding, three due to coagulopathy and one patient was randomized to the low dose arm of an ECMO anticoagulation pilot study.[16] Visible fibrin stranding in the membrane oxygenator was documented in 66% of ECMO circuit exchange events.

Results from the time analysis are presented in Figure 3. Plasma-free hemoglobin showed the largest percentage change over the observation period. Carboxyhemoglobin also showed a significant rise and fall, although with a lower percentage change. In contrast to other markers, bilirubin continued to rise after ECMO circuit exchange. Platelets and fibrinogen decreased, while D-dimer increased up to the time of ECMO circuit exchange, with these parameters returning to baseline after ECMO circuit exchange. The D-dimer:fibrinogen ratio showed a larger percentage change than other markers of thrombosis or hyperfibrinolysis. Changes in LDH were not statistically significant.

The median number of units of packed red blood cells transfused before ECMO circuit exchange was 2 and the median number of units of platelets transfused was 0. Fresh–frozen plasma or cryoprecipitate was transfused in 16% of patients with an ECMO circuit exchange during the observation period. Two patients were taken to the operating theater for active hemorrhage in the 24 hours before ECMO circuit exchange, and one patient was taken to the operating theater in the 24 hours after ECMO circuit exchange for active hemorrhage.

Discussion

In this observational study of 100 V-V ECMO patients, we present a comprehensive analysis of hematological markers of circuit dysfunction before and after ECMO circuit exchange. We found that almost one-third of V-V ECMO patients required an ECMO circuit exchange and a subgroup of patients required multiple ECMO circuit exchanges during their time on ECMO support. Time analysis demonstrated a near-complete resolution of the elevated markers of hemolysis and hyperfibrinolysis in the 72 hours after ECMO circuit exchange. We also observed a reduction in the transmembrane pressure after ECMO circuit

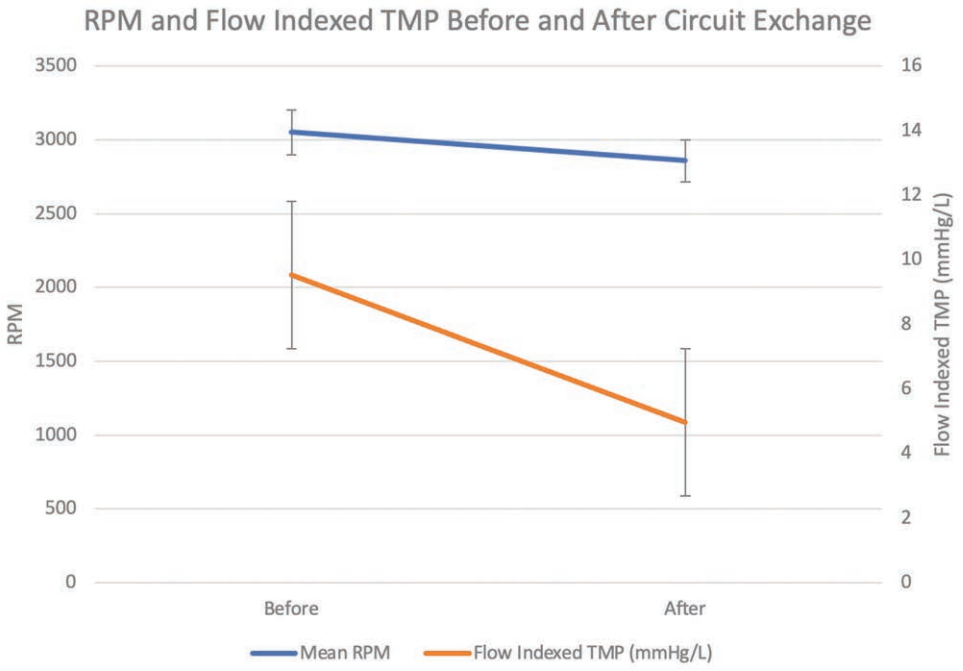

Figure 2. Graph comparing RPM and flow indexed TMP per liter of circuit blood flow before and after ECMO circuit exchange with 95% confidence intervals. ECMO, extracorporeal membrane oxygenation; RPM, revolutions per minute; TMP, transmembrane pressure.

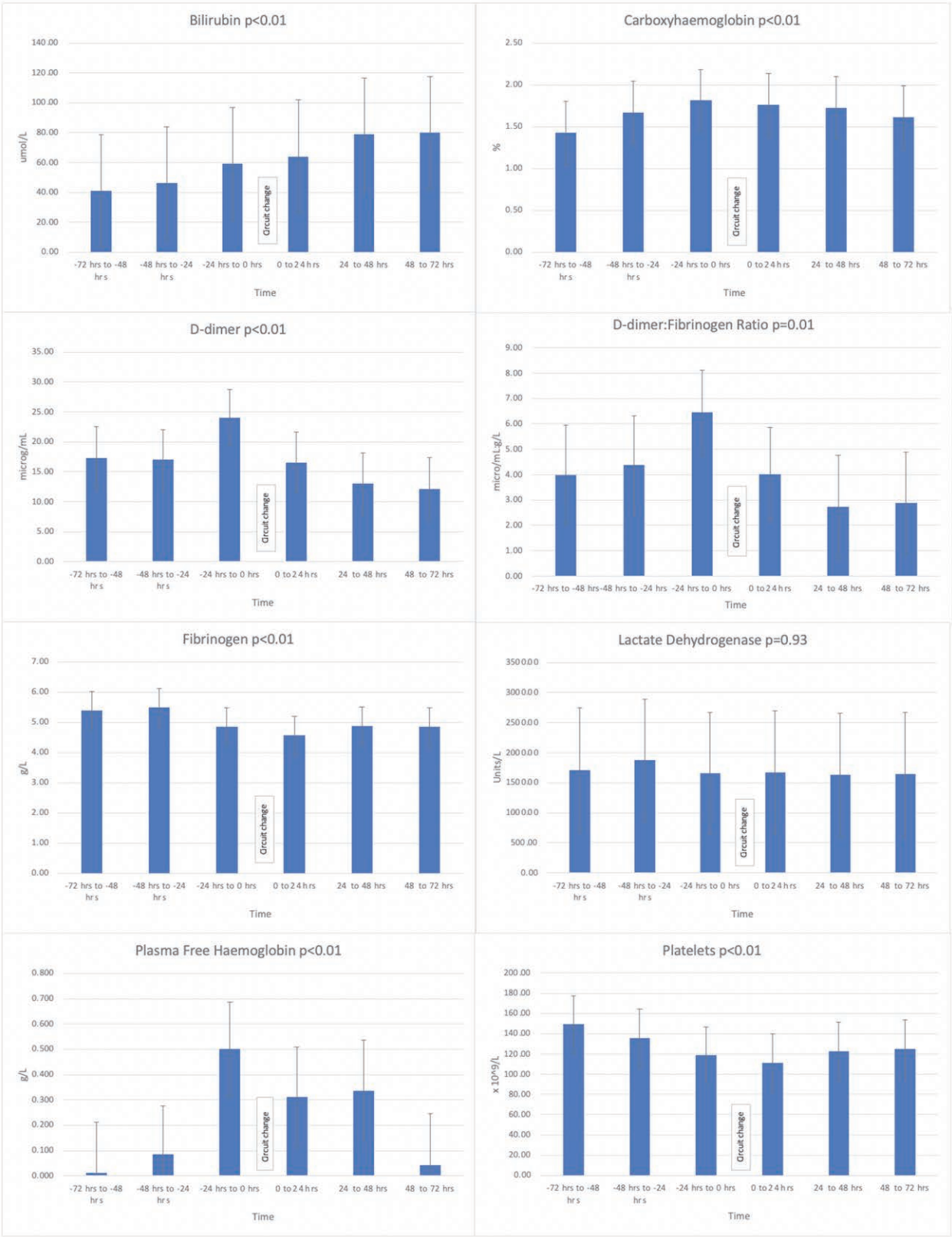

Figure 3. Graphs showing mean ± 95% CI values of hematological markers divided into 24 hour intervals for the 72 hours before and after ECMO circuit exchange (time zero). ECMO, extracorporeal membrane oxygenation.

exchange, demonstrating a reduction in resistance to circuit blood flow.

These data support the biologic plausibility that an ECMO circuit exchange can reverse hematological abnormalities

attributed to the ECMO circuit. Pump head thrombosis is a late complication of ECMO circuit dysfunction and is a medical emergency with acute intravascular hemolysis and an audible noise or vibration from the pump head. Appelt *et al.* reported an incidence of pump head thrombosis of 9% in V-V ECMO.[9] In our cohort there was no incidence of documented pump head thrombosis, suggesting that the earlier time to ECMO circuit change (6 *vs.* 9 days) may prevent progression to pump head thrombosis. Despite the earlier timing of ECMO circuit exchanges in our cohort, the frequency of exchanges (1.4 per patient) was consistent with previously published studies.[8,9,11]

Plasma-free hemoglobin is considered the gold standard for measurement of intravascular hemolysis on ECMO and its measurement is recommended by the Extracorporeal Life Support Organization (ELSO).[17] In our time analysis, PFHb showed the largest increase in the 24 hours before ECMO circuit exchange and it rapidly returned to baseline by 72 hours. These data support PFHb as the optimal marker of circuit dysfunction. However, the assay is not available in most laboratories,[11] and it can be falsely elevated with traumatic sampling. The method our laboratory uses to perform this analysis is spectrophotometric, validated against the cyanide colourmetric method. Spectrophotometric methods may be susceptible to interference from lipemia or bilirubin,[11] although our data demonstrate a clear rise and fall in PFHb despite progressive elevation of bilirubin, suggesting this effect is of limited clinical relevance.

The D-dimer:fibrinogen ratio is a novel measure of circuit dysfunction used at our institution. It showed a much higher percentage change than the D-dimer or fibrinogen used in isolation. A previous study has shown that a proportion of ECMO patients have persistently high D-dimer even after an ECMO circuit exchange, which limits its use as a marker in this setting.[8] However, a rising D-dimer in the setting of a falling fibrinogen is suggestive of hyperfibrinolysis and the D-dimer:fibrinogen ratio may be complimentary to PFHb or may be used when PFHb is unavailable. This warrants further prospective evaluation.

We found that bilirubin continued to rise after ECMO circuit exchange despite a return to baseline in the other markers of hemolysis, and this is probably more consistent with impaired hepatic and biliary clearance of conjugated bilirubin due to critical illness. This may result in covalent binding of bilirubin to albumin, a fraction called the delta bilirubin, which prolongs bilirubin's normal half-life from 2 to 4 hours to 12 to 14 days.[18]

The finding that the mean level of anticoagulation was at the low end of the protocolized therapeutic range is consistent with the literature regarding bleeding in this population.[2] We did not record ECMO cannula site bleeding as this is difficult to quantify. Instead, we recorded transfusion requirements or the need for operative intervention as markers of significant hemorrhage. As nearly one-third of the cohort were not anticoagulated at the time of ECMO circuit exchange, it is possible that clinical bleeding complications which were not recorded in our dataset resulted in interruptions to anticoagulation and may have contributed to the decision to exchange the ECMO circuit.

Implications

This is the first study to comprehensively assess multiple hematological parameters in the period both before and after an ECMO circuit exchange. The findings confirm the ELSO recommendation[17] that PFHb remains the most sensitive marker of circuit dysfunction. It also suggests that the D-dimer:fibrinogen ratio may be a useful alternative when PFHb is unavailable. ECMO circuit exchange was found to reverse hematological derangement of most but not all biomarkers within 72 hours, reduce circuit resistance and may also prevent progression to circuit-related complications such as pump head thrombosis. Taken together, ECMO circuit exchange can play an important clinical role when such changes become apparent.

Strengths

This study provides a comprehensive analysis of the hematological markers of ECMO circuit dysfunction in the period before and after ECMO circuit exchange, which has not previously been described in the literature. Data collection and clinical management were standardized to reduce variation and bias.

Weaknesses

There are several limitations with this study in addition to the single-center design. First, the reason for ECMO circuit exchange was not always clearly stated in the medical record and circuit thrombosis and hemolysis may have occurred concurrently. In this case, the documentation from the most senior medical staff was selected. Second, the clinicians were not blinded to the test results throughout the study, and ECMO circuit exchanges were based on these results. Third, the analysis of laboratory data was limited to patients who had an ECMO circuit exchange only, without comparison with those where ECMO circuit exchange was not required. Fourth, the finding that ECMO circuit exchange was not a statistically significant contributor to mortality, even after adjustment for the ANZROD severity of illness,[14] may reflect the population size used in this study. Finally, there may be survivor bias as the cohort who had an ECMO circuit exchange had a longer duration of ECMO support and longer ICU length of stay.

This dataset was collected before the coronavirus disease 2019 (COVID-19) pandemic and as such, our findings are not applicable to this population. The hematological effects of ECMO circuit exchanges in patients with COVID-19 on V-V ECMO warrants further investigation.

Further Research

Future research should focus on identifying earlier hematological markers of circuit dysfunction, which would potentially allow interventions that protect the circuit to be initiated, such as adjusting anticoagulation regimes. This may allow comparative prospective studies of standardized hematological and circuit management regimes that may impact on patient survival.

Conclusions

We found that ECMO circuit exchange is common in patients on V-V ECMO. Progressively deranged hematological markers normalize after ECMO circuit exchange, with an associated reduction in membrane oxygenator resistance. This supports the biologic plausibility that ECMO circuit exchange may prevent further progression to a hyperfibrinolytic state,

membrane oxygenator failure and clinical bleeding. The D-dimer:fibrinogen ratio shows promise as a marker of circuit thrombosis and hyperfibrinolysis and warrants further prospective evaluation.

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