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Risk factors for elective and emergency oxygenator exchanges during veno-venous extracorporeal membrane oxygenation

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Abstract

Background: Despite systemic anticoagulation and antithrombotic surface coating, oxygenator dysfunction remains one of most common technical complications of Extracorporeal membrane oxygenation (ECMO). Several parameters have been associated with an oxygenator exchange, but no guidelines for when to perform an exchange are published. An exchange, especially an emergency exchange, has a risk of complications. Therefore, a delicate balance between oxygenator dysfunction and the exchange of the oxygenator exists. This study aimed to identify risk factors and predictors for elective and emergency oxygenator exchanges.

Methods: This observational cohort study included all adult patients supported with veno-venous extracorporeal membrane oxygenation (V-V ECMO). We compared patients' characteristics and laboratory values of patients with and without an oxygenator exchange and between an elective and emergency exchange, defined as an exchange outside office hours. Risk factors for an oxygenator exchange were identified with cox regression analyses, and risk factors for an emergency exchange were identified with logistic regression analyses.

Results: We included forty-five patients in the analyses. There were twenty-nine oxygenator exchanges in nineteen patients (42%). More than a third of the exchanges were emergency exchanges. Higher partial pressure of carbon dioxide (PaCO2), transmembrane pressure difference (ΔP), and hemoglobin (Hb) were associated with an oxygenator exchange. Lower lactate dehydrogenase (LDH) was the only risk factor for an emergency exchange.

Conclusion: Oxygenator exchange is frequent during V-V ECMO support. PaCO2, ΔP and Hb were associated with an oxygenator exchange and lower LDH with the risk of an emergency exchange.

Keywords

extracorporeal membrane oxygenation, exchanges, oxygenator

Introduction

In the past decades, the use of Veno-Venous (V-V) and Veno-Arterial (V-A) Extracorporeal Membrane Oxygenation (ECMO) has increased.[1] While ECMO is lifesaving in selected patients, ECMO mortality remains high. The majority of patient mortality is due to the irreversibility of the disease for which ECMO is initiated, however a significant part is treatment-related mortality due to patient or circuit-related complications.[2] Despite systemic anticoagulation and antithrombotic surface coating, (rapid) functional decline of the oxygenator remains one of ECMO's most common technical complications. The use of modern-day coatings however, still does not prevent exposure to the nonbiologic surface completely and still activates anticoagulant and procoagulant components in the patient, possibly leading to clot formation within the oxygenator and thrombotic deposits on the surface of gas exchange

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fibers.[3] At first, the effects of these clots will hardly be noticeable. However, these may eventually lead to a rapid functional decline of the oxygenator and even an acute stop of the ECMO system. Two oxygenator failure patterns are known: (1) Deteriorating gas exchange by the oxygenator leading to insufficient decarboxylation and oxygenation of the patient; and (2) Oxygenator-induced coagulation disorders characterized by changes in coagulation parameters, leading to an increased risk for hemorrhagic- or thrombotic complications.[4] A failing oxygenator requires replacement. An oxygenator exchange is a high-risk procedure and exposes the patient to the risk of hypoxia, hemodynamic instability, and a pro-inflammatory insult subsequently to blood exposure to a new artificial surface. Several parameters have been associated with oxygenator exchange such as elevated D-dimer levels and increased trans membrane pressure drop (ΔP).[3–16] The risk for complications is potentially higher during an emergency oxygenator exchange. Identifying clinical parameters that predict oxygenator exchanges, to prevent emergency oxygenator exchanges, would be of great value for better ECMO care. The objectives of this study were to identify risk factors and parameters that predict oxygenator exchange in general and emergency exchanges during V-V ECMO support.

Methods

We conducted a retrospective observational cohort study. Institutional approval was given for this study, and the local Medical Ethics review board waived the need for informed consent. This study was performed in a closed format mixed Intensive Care Unit (ICU) in a Dutch tertiary referral hospital. The design and conduct of this study followed the STROBE checklist for observational cohort studies.[17]

We included all consecutive adult patients supported with V-V ECMO for at least 48 hours between October 2018 and March 2022. Oxygenator exchanges were identified by review of the medical record of each patient. Only the first and second exchanges were taken into account and considered as separate events in the analyses to avoid that the characteristics of patients with more than two exchanges would weigh too heavily in the analyses. We extracted patient characteristics, laboratory values, and ECMO characteristics from the electronic charting system EPIC® (Epic Systems Corporation®). Patient characteristics included: sex, age, body mass index (BMI), APACHE IV, SOFA-score, SARS-CoV-2 infection, and ICU survival. Laboratory values extracted included potential clinically relevant variables for oxygenator exchange such as D-dimer, fibrinogen, activated partial thromboplastin time (aPTT), prothrombin time (PT), plasma free haemoglobin (PFHb), Platelets, haemoglobin (Hb), carboxyhaemoglobin (HbCO), Lactate dehydrogenase (LDH), C-reactive protein (CRP), leukocytes and arterial bloodgas analysis (ABGA). The extracted ECMO characteristics included: indication for ECMO, duration of ECMO support, rotations/minute (RPM), blood flow, sweep-flow, ΔP defined as the difference between the pressure at the inlet and outlet of the oxygenator, and pump head efficiency defined as blood-flow in millilitres per revolution. We calculated the percentage ΔP change adjusted for blood flow from 12 and 24 hours before the oxygenator exchange. We used the latest known variables of patients before the oxygenator exchange. We used measurements from the median day of the first oxygenator exchanges for the analysis of patients without an oxygenator exchange under the condition that the patient was still in ECMO; otherwise, the measurements on the last full day of ECMO were used for the analysis. Laboratory values were drawn daily at 6 a.m., therefore, we extracted laboratory- and ECMO values also at 6 a.m. APTT levels were measured 4–6 times daily and were averaged for the relevant day. Emergency exchange was defined as an exchange outside office hours. Although the day shift starts at 8 a.m.; due to logistical reasons, elective oxygenator changes will hardly ever be performed before 10 a.m. Therefore, office hours were defined as between 10 a.m. and 5 p.m.

Institutional guidelines

Our standard V-V ECMO circuit consists of the Cardiohelp® (Maquet-Getinge Group®) device and the corresponding disposable HLS set advanced 7.0 with BIOLINE coating (Maquet-Getinge Group®) and dedicated BIOLINE coated HLS cannulas (Maquet-Getinge Group®). Systematic anticoagulation was achieved with unfractionated heparin (UFH) infusion and aPTT was targeted between 50–70 seconds. The laboratory values were gathered daily except for PFHb, this was measured every 48 hours. Weaning from ECMO was done by lowering the sweep-flow instead of the blood flow to minimize the risk of clot formation. The perfusionist and intensivist checked the oxygenator twice daily for visible clots. The decision to perform an oxygenator exchange was made based on laboratory and ECMO characteristics in a multidisciplinary team of intensivists and perfusionists. The reasons for an oxygenator exchange included oxygenator thrombosis, pump head thrombosis, functional decline of the oxygenator, or acquired coagulation disorders leading to both haemorrhagic and thrombotic complications. There was no strict protocol for when to perform an oxygenator exchange.

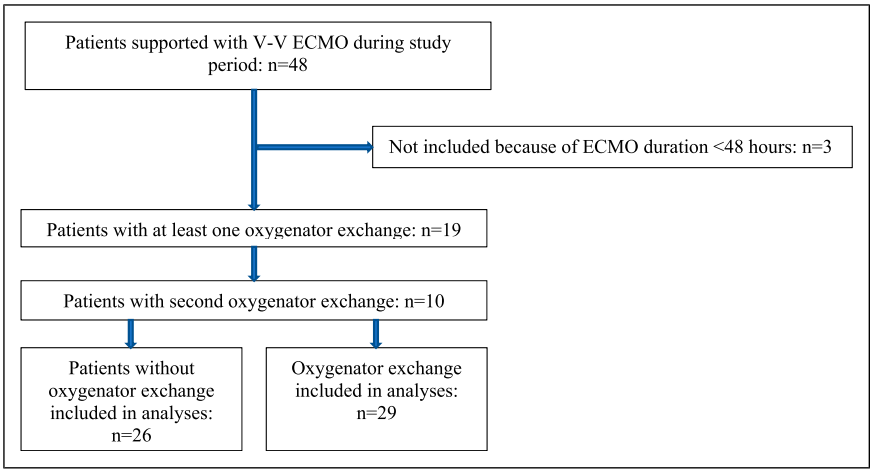

Figure 1. Flow diagram.

Statistical analysis

Statistical analyses were done using IBM SPSS® Statistics software, version 26 (IBM Corporation®). Normally distributed continuous variables were expressed as mean and standard deviation (SD) and non-normally distributed variables as median and interquartile range [IQR]. Categorical variables were expressed as frequencies and percentages (*n*, %). Comparison between patients with and without an oxygenator exchange and between elective and emergency oxygenator exchanges was made with the Fisher's exact test for categorical variables and with either the Mann-Whiney *U* test or *t*-test for continuous variables where appropriate. Univariate Cox regression analyses were used to study if baseline variables were associated with oxygenator exchanges yielding crude hazard ratios (HR) with corresponding 95% confidence intervals (95%CI). To assess risk factors for an oxygenator exchange, we performed a backward stepwise Cox regression analysis using all variables with a *p*-value of <0.10 in univariate analyses, as well as sex and age. Thereafter, a risk score was calculated using the beta's of the remaining variables in the model. Discrimination of the risk score was calculated with the Harrells's concordance (c) statistic and corresponding receiver operating characteristic curve (ROC-curve). Univariate logistic regression analyses were used to study the association between baseline variables and an emergency oxygenator exchange yielding crude odds ratios (OR) with corresponding 95%CI. To assess risk factors for an emergency oxygenator exchange, we performed a backward stepwise logistic regression analysis using all variables with a *p*-value of <0.10 in the univariate logistic regression analyses as well as sex and age. A risk score was calculated using the predicted probabilities of the remaining variables in the model. Discrimination of the risk score was calculated with the ROC-curve and corresponding area under the curve (AUC). Because ΔP depends on the blood flow, we performed a sensitivity analysis using the ΔP/blood-flow ratio of these two variables. A *p*-value <0.05 (two-sided) was considered statistically significant. Listwise deletion was used for missing data.

Results

During the study period, forty-five consecutively patients were supported for at least 48 hours with V-V ECMO and included in the analysis. Figure 1 Shows a flowchart depicting the inclusion of patients and oxygenator exchanges. Twenty-eight (62%) patients were discharged alive. The median duration of ECMO was 16 days. Of these patients, twenty-three (51%) had COVID-19-induced acute respiratory distress syndrome (ARDS) as the reason for ECMO support. Table 1. Shows the baseline characteristics of all patients. Nineteen (42%) patients had at least one oxygenator exchange (on median day twelve), and ten (22%) patients had a second oxygenator exchange (on median day nine), resulting in twenty-nine oxygenator exchanges in the analyses. Patients with an oxygenator exchange were more often male, had a longer duration of ECMO support, higher values of d-dimer, -platelets, -HbCO, -partial arterial pressure of carbon dioxide ($PaCO_2$) (and subsequently a lower pH), -ΔP, lower fibrinogen levels and were more often supported with ECMO because of COVID-19-induced ARDS. The pump head efficiency did not differ between groups.

Table 1. Outcome.

	All n = 55	With oxygenator exchange n = 29 (53%)	No oxygenator exchange n = 26 (47%)	p
Male, n (%)	42 (76%)	27 (93%)	15 (58%)	<0.01
Age, [years], median (IQR)	49 (41–54)	49 (42–53)	49 (39.75–57.25)	0.54
COVID-19, yes, n (%)	32 (58%)	22 (76%)	10 (39%)	<0.01
Alive at discharge, yes, n (%)	36 (66%)	20 (69%)	16 (62%)	0.58
Body mass index, [kg/m^2], median (IQR)	26.51 (23.13–29.07)	26.51 (24.40–28.09)	25.95 (22.45–32.30)	0.70
APACHE IV, median (IQR)	46 (50–86)	57.50 (50.00–84.50)	65 (49.5–86.25)	0.85
Resp-score, mean (SD)	2 (0–3)	1.96 (1.37)	1.62 (2.71)	0.56
SOFA-score, median (IQR)	7 (4–10)	7 (4–9)	8 (5–11.5)	0.09
Indication ECMO, n (%)				0.07
ARDS, viral	39 (71%)	24 (83%)	15 (58%)	
ARDS, bacterial	5 (9%)	1 (3%)	4 (15%)	
ARDS, other	2 (4%)	0	2 (8%)	
Other acute respiratory diagnoses	4 (7%)	3 (10%)	1 (4%)	
Chronic respiratory diagnoses	5 (9%)	1 (3%)	4 (15%)	
Duration of ECMO, [days], median (IQR)	20 (10–30)	30.00 (22.00–38.00)	10.00 (6.75–15.50)	<0.01
Lifespan oxygenator, [hours], median (IQR)	240 (172–371)	232.00 (172.50–353.50)	241.38 (168.5–393.5)	0.63
Second oxygenator exchange, n (%)		10 (35%)		
Revolutions/minute, median (IQR)	3045 (2800–3200)	3100 (2800–3170)	3000 (2420–3275)	0.44
Bloodflow, [l/minute], mean (SD)	4.24 (0.84)	4.43 (0.59)	4.03 (1.00)	0.09
Pump head efficiency, [ml/revolution], mean (SD)	1.43 (0.16)	1.45 (0.13)	1.41 (0.19)	0.35
Sweepflow, [l/minute], median (IQR)	7.00 (4.50–8.00)	7.00 (6.00–8.00)	5.25 (3.38–7.63)	0.03
ECMO FiO_2, [%], median (IQR)	100.00 (72.50–100.00)	100.00 (80.00–100.00)	100 (60–100)	0.37
Delta p, median (IQR)	32.50 (21.00–37.75)	37.00 (34.00–48.00)	21 (17.5–29.5)	0.00
Platelets, [x10^9/l], mean (SD)	173.00 (114.00–235.00)	183.00 (131.50–242.50)	144.50 (87.00–221.50)	0.04
D-dimer, [ug/l], mean (SD)	17663 (55,37–512,00)	35612.50 (162,31.25–658,40.75)	8295 (31,90–176,63)	<0.01
Fibrinogen, [g/l], mean (SD)	4.23 (2.12)	3.47 (1.30)	4.99 (2.50)	0.01
aPTT, [seconds], mean (SD)	56.97 (10.83)	57.29 (11.10)	56.64 (10.74)	0.84
Pt, [seconds], mean (SD)	14.05 (13.05–15.75)	14.10 (13.23–15.53)	14.00 (12.7–16.9)	0.93
Hb, [mmol/l], mean (SD)	4.9 (4.30–5.50)	5.00 (4.40–5.55)	4.80 (4.20–5.38)	0.31
PFHb, [umol/l], median (IQR)	2.00 (1.00–3.00)	1.00 (0.00–3.00)	2.00 (1.00–3.75)	0.39
HbCO, [%], mean (SD)	2.20 (1.70–2.90)	2.60 (2.13–3.80)	1.90 (1.50–2.43)	<0.01
LDH, [U/l], mean (SD)	478.00 (341–624.00)	445.00 (346.50–572.50)	536.50 (327.25–711.50)	0.43
CRP, [mg/l], mean (SD)	93.00 (30.00–207.00)	93.00 (28.00–161.00)	95.00 (39.50–273.00)	0.69
Leukocytes, [x10^9/l], mean (SD)	14.30 (10.60–17.70)	12.80 (10.10–18.15)	14.95 (11.43–18.13)	0.48
PaO_2, [kPa], median (IQR)	8.55 (7.78–9.75)	8.55 (8.00–9.68)	8.65 (7.58–10.2)	0.87
$PaCO_2$, [kPa], mean (SD)	7.11 (1.50)	7.88 (1.24)	6.28 (1.32)	<0.01
Ph, mean (SD)	7.40 (0.07)	7.38 (0.06)	7.42 (0.07)	0.02
Lactate, [mmol/l], median (IQR)	0.90 (0.68–1.33)	0.80 (0.60–1.08)	0.95 (0.70–1.53)	0.07

ECMO: extracorporeal membrane oxygenation; aPTT: activated partial thromboplastin time; Pt: prothrombin time; PFHb: plasma free haemoglobin; Hb: haemoglobin; HbCO: carboxyhaemoglobin; LDH: lactate dehydrogenase; CRP: C-reactive protein; ARDS: Acute respiratory distress syndrome; $PaCO_2$: partial arterial pressure of carbon dioxide; PaO_2: partial arterial pressure of oxygen; FiO_2: fraction of inspired oxygen.

Interestingly, oxygenator exchange had no impact on ICU survival.

Ten (34%) out of twenty-nine exchanges was an emergency exchange. The most prevalent indication for both an emergency and an elective oxygenator exchange was a rising ΔP. Table 2 shows the comparison between emergency and elective exchanges. Prior to an emergency exchange, LDH and CRP were lower compared to an elective exchange. There were no significant differences in other variables.

The association between an oxygenator exchange and all individual variables is reported in Table 3. There was a significant association between higher Hb, PFHb, platelets, ΔP, $PaCO_2$, lower pH, SOFA-score and COVID-19 as indication for ECMO support. With the backward stepwise Cox regression

Table 2. Descriptive statistics comparison elective and emergency oxygenator exchange.

	Elective exchange *n* = 19 (66%)	Emergency exchange *n* = 10 (34%)	*p*
Male, *n* (%)	18 (95%)	9 (90%)	1.00
Age, [years], mean (SD)	47.95 (11.27)	44.50 (10.92)	0.44
COVID-19, yes, *n* (%)	14 (74%)	8 (80%)	1.00
Alive at discharge, yes, *n* (%)	12 (63%)	8 (80%)	0.43
Body mass index, [kg/m^2], median (IQR)	26.19 (25.21–27.63)	28.10 (23.48–30.34)	0.33
APACHE IV, median (IQR)	66.50 (51.00–79.25)	52.50 (50.00–86.00)	0.61
Resp-score, mean (SD)	2.00 (1.10)	1.90 (1.70)	0.86
SOFA-score, mean (SD)	6.60 (2.40)	7.60 (2.90)	0.37
Indication ECMO, *n* (%)			
ARDS, viral	16 (84%)	8 (80%)	
ARDS, bacterial	2 (11%)	0	
ARDS, other	0	0	
Other acute respiratory diagnosis	0	1 (10%)	
Chronic respiratory diagnosis	1 (5%)	1 (10%)	
Duration of ECMO, [days], mean (SD)	28.11 (8.62)	31.50 (13.20)	0.41
Lifespan oxygenator, [hours], mean (SD)	242 (105)	300 (156)	0.25
Revolutions/minute, mean (SD)	3000.88 (208.58)	3131 (223.06)	0.14
Bloodflow, [l/minute], mean (SD)	4.40 (0.54)	4.40 (0.70)	0.98
Pump head efficiency, [ml/revolution], mean (SD)	1.47 (0.11)	1.41 (0.16)	0.22
Sweepflow, [l/minute], median (IQR)	7.00 (5.25–7.50)	8.25 (5.88–9.13)	0.09
ECMO FiO_2, [%, median (IQR)	100 (75–100)	100 [95–100]	0.24
Delta p, median (IQR)	36.00 (32.5–38.5)	40.50 (36.75–54.25)	0.09
Change 12 h delta *p*/blood flow, [%], median (IQR)	4.45 (1.77–24.99)	11.74 (6.23–30.49)	0.24
Change 24 h delta *p*/blood flow, [%], median (IQR)	6.06 (5.15–28.67)	17.30 (7.99–34.58)	0.13
Platelets, [x10^9/l], mean (SD)	202 (110)	186 (53)	0.66
D-dimer, [ug/l], mean (SD)	54710 (54545)	37647 (27180)	0.39
Fibrinogen, [g/l], mean (SD)	3.30 (1.43)	3.60 (1.07)	0.55
aPTT, [seconds], mean (SD)	57.75 (11.50)	56.23 (10.79)	0.74
Pt, [seconds], mean (SD)	14.73 (3.50)	14.3 (1.1)	0.75
Hb, [mmol/l], mean (SD)	4.90 (0.75)	5.10 (0.77)	0.59
PFHb, [umol/l], median (IQR)	1 (0–3)	1.00 (0.25–2.00)	0.64
HbCO, [%], mean (SD)	3.00 (1.30)	2.90 (1.2)	0.74
LDH, [U/l], mean (SD)	568 (264)	389 (73)	0.01
CRP, [mg/l], mean (SD)	138 (111)	65 (36)	0.02
Leukocytes, [x10^9/l], mean (SD)	14.90 (5.90)	14.50 (6.50)	0.86
PaO_2, [kPa], mean (SD)	9.10 (2.45)	8.80 (1.00)	0.66
$PaCO_2$, [kPa], median (IQR)	8.00 (7.35–8.63)	7.55 (6.50–9.05)	0.60
Ph, mean (SD)	7.37 (0.05)	7.38 (0.08)	0.71
Lactate, [mmol/l], median (IQR)	0.87 (0.34)	0.87 (0.40)	0.98

ECMO: extracorporeal membrane oxygenation; aPTT: activated partial thromboplastin time; Pt: prothrombin time; PFHb: plasma free haemoglobin; Hb: Haemoglobin; HbCO: carboxyhaemoglobin; LDH: lactate dehydrogenase; CRP: C-reactive protein ARDS: Acute respiratory distress syndrome; $PaCO_2$: partial arterial pressure of carbon dioxide; PaO_2: partial arterial pressure of oxygen; FiO_2: fraction of inspired oxygen.

Table 3. Cox regression analyses for patients with and without oxygenator exchange.

	Univariate cox regression crude HR (95% confidence interval)	Stepwise backward cox regression[a] HR (95% confidence interval)
Sex, female	3.77 (0.89–15.95)	
Age per 10 years	0.95 (0.67–1.34)	
COVID-19	2.39 (1.02–5.61)	
Alive at discharge	0.81 (0.37–1.79)	
Body mass index, kg/m^2	1.02 (0.95–1.08)	
APACHE IV	1.00 (0.98–1.02)	
Resp-score	1.09 (0.91–1.31)	
SOFA-score	0.88 (0.77–1.00)	
Duration of ECMO, days	1.05 (1.01–1.09)	
ECMO per 100 revolutions/minute	1.08 (0.94–1.42)	
ECMO bloodflow, l/minute	1.48 (0.84–2.61)	
Pump head efficiency, ml/revolution	3.46 (0.31–39.00)	
ECMO sweepflow, l/minute	1.15 (0.96–1.37)	
ECMO FiO_2, %	1.00 (0.98–1.02)	
Delta p	1.03 (1.01–1.05)	1.06 (1.02–1.09)
Platelets per 10×10^9/l	1.05 (1.00–1.10)	
D-dimer per 1000 μg/L	1.01 (1.00–1.01)	
Fibrinogen, g/l	0.90 (0.71–1.14)	
aPTT per 10 seconds	1.04 (0.72–1.50)	
Pt, seconds	0.99 (0.88–1.11)	
Hb, mmol/l	2.29 (1.41–3.71)	3.01 (1.47–6.16)
PFHb, umol/l	1.26 (1.06–1.50)	
HbCO, %	1.18 (0.90–1.55)	
LDH per 10 U/l	1.00 (0.99–1.01)	
CRP per 10 mg/L	1.01 (0.97–1.04)	
Leukocytes, $x10^9$/l	0.99 (0.93–1.06)	
PaO_2, kPa	0.99 (0.81–1.21)	
$PaCO_2$, kPa	1.52 (1.14–2.03)	1.71 (1.11–2.63)
pH per 0.1 units	0.51 (0.27–0.96)	
Lactate, mmol/l	0.77 (0.34–1.74)	

ECMO: extracorporeal membrane oxygenation; aPTT: activated partial thromboplastin time; Pt: prothrombin time; PFHb: plasma free haemoglobin; Hb: Haemoglobin; HbCO: carboxyhaemoglobin; LDH: lactate dehydrogenase; CRP: C-reactive protein; $PaCO_2$: partial arterial pressure of carbon dioxide; PaO_2: partial arterial pressure of oxygen; FiO_2: fraction of inspired oxygen.
[a]Variables entered at sept 1: Sex, age, COVID-19, SOFA-score, platelets, PFHb, Hb, $PaCO_2$, Delta p, duration ECMO.
[b]Harrell's C: 0.77.

analysis, we found that higher $PaCO_2$, ΔP, and Hb were independent risk factors for an oxygenator exchange (Tabel 3). Figure 2 Shows the ROC-curve based on the linear predictor score of the independent indicators. The Harrell's c-statistic for this model was 0.77.

The association between an emergency exchange and all individual variables is reported in Table 4. Only lower LDH was statistically significant associated with the occurrence of an emergency exchange. With the backward stepwise logistic regression analyses, lower LDH remained the only independent risk factor for an emergency exchange, although with only borderline statistical significance (OR = 0.90, 95%CI 0.82–1.00).

Discussion

Despite significant improvement in ECMO equipment, an oxygenator exchange is often necessary. We found that 42% of all patients supported with V-V ECMO in our centre had at least one oxygenator exchange. We identified higher $PaCO_2$, ΔP, and Hb as risk factors for an oxygenator exchange. Over one-third (34%) of all exchanges was an emergency exchange. We identified a

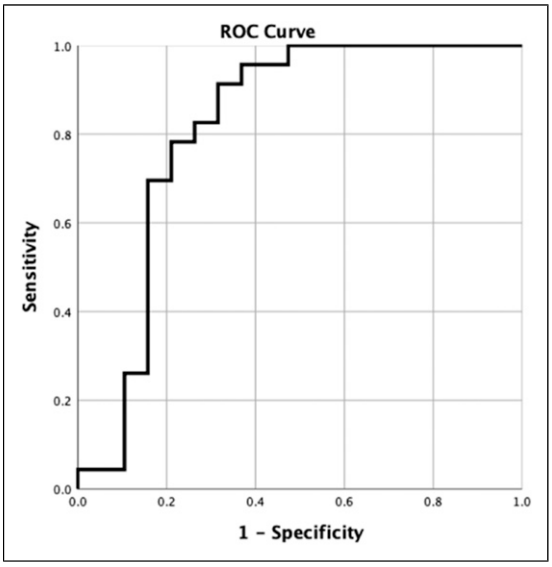

Figure 2. Receiver operating characteristics-curve[1] of the linear predictor score from the cox regression model with Hb, PaCO2 and Delta p. 1. Harrell's C: 0.77.

lower LDH as the only risk factor for an emergency exchange.

The rising $PaCO_2$ in ABGA is most probably due to insufficient carbon dioxide removal due to functional decline of the oxygenator caused by thrombus formation and cellular deposits in the oxygenator.[18] A deteriorating gas exchange is a late marker for functional decline of the oxygenator. An in-vitro setup study showed that alteration of the carbon-dioxide concentration measured at the outlet of the oxygenator was an early indicator for oxygenator deterioration. However, this measurement is not generally performed.[9]

The rise in ΔP is strongly associated with thrombus formation within the oxygenator, but earlier studies showed this to be a late indicator of oxygenator failure. However, a rapidly increasing ΔP signalized oxygenator failure in a previously conducted study.[19] We did not find a correlation between the ΔP change adjusted for blood flow between both 12, 24 hours and the oxygenator exchange. The ΔP depends on the blood flow and resistance, so when analyzing for alteration in ΔP, one should always compare at stable blood flow and RPM. Blood flow differed in time in our patients, however, because we did not alter the blood flow when weaning from V-V ECMO, we believe we could adequately compare ΔP between patients with and without oxygenator exchange. Furthermore, a sensitivity analysis with the ΔP/blood-flow ratio instead of ΔP showed similar results.

In this study, a higher Hb was associated with an oxygenator exchange. A higher Hb level is a known risk factor for arterial and venous thrombotic events. Several mechanisms behind the haemoglobin-associated thrombotic risk have been proposed. However, the exact origin of this complication remains to be elucidated.[20] However, Hb levels were relatively low in both groups of our population (median 4.8 mmol/l in patients without an exchange and 5.0 mmol/l in patients with an oxygenator exchange). As the majority of the patients supported with V-V ECMO received red blood cell (RBC) transfusions with subsequent increase in Hb levels, so it is not distinct if the higher Hb levels or more RBC transfusion is associated with an oxygenator exchange.[21]

In earlier conducted studies, elevated PFHb levels indicated centrifugal pump thrombosis.[22,23] Another study showed elevated PFHb levels in almost two-thirds of all ECMO runs, however, severe hemolysis requiring an oxygenator exchange was uncommon.[14] A possible explanation for this might be that hemolysis is caused by the centrifugal pump instead of the oxygenator. Our results were in line with previous findings. A note of caution is due here since PFHb was measured every 48 hours at our ICU thus the PFHb level at the time of the oxygenator exchange could be different from the actual level.

We found higher D-dimer levels in patients with oxygenator exchange than in patients without one. These results seem consistent with other research, which found the rise in D-dimer levels in the absence of other explaining factors as an early indicator for an oxygenator exchange caused by activation of the coagulation cascade.[5,7,8,13] Although, we did not find an association between increasing D-dimer levels and an oxygenator exchange in the cox-regression analysis, we still believe that monitoring D-dimer levels will give you an advantage as an early marker for functional decline of the oxygenator.

To our knowledge, this is the first study comparing elective oxygenator exchanges with emergency exchanges defined as an exchange outside office hours. In our study 34% of our exchanges were defined as an emergency exchange. One retrospective analysis of 265 V-V ECMO cases compared elective, urgent, and emergency oxygenator exchanges in which the definition was based in the indication of the exchange instead of the exchange time. We found a slightly lower incidence of emergency exchanges than this retrospective analysis, which they described that 45% of their exchanges was considered urgently which is somewhat higher than in our study, but that may also be caused by waiting a bit longer before exchanging an oxygenator. Although, the mean day of the first oxygenator exchange was less than ours (9 days).[13] In addition, this study used another brand of oxygenator than

Table 4. Logistic regression analyses for an emergency oxygenator exchange.

	Univariate logistic regression crude OR (confidence interval 95%)	Stepwise backward logistic regression[a] OR (95% confidence interval)
Sex, female	0.50 (0.03–8.95)	
Age per 10 years	0.75 (0.37–1.52)	
COVID-19	0.70 (0.11–4.48)	
Alive at discharge	0.43 (0.07–2.61)	
Body mass index, kg/m^2	1.08 (0.88–1.33)	
APACHE IV	0.99 (0.95–1.03)	
Resp-score	0.95 (0.53–1.69)	
SOFA-score	1.16 (0.85–1.59)	
Duration of ECMO, days	1.04 (0.96–1.12)	
ECMO per 100 revolutions/minute	1.35 (0.90–2.02)	
ECMO bloodflow, l/minute	0.98 (0.26–3.79)	
Pump head efficiency, ml/revolution	0.02 (0.00–10.46)	
ECMO sweepflow, l/minute	1.59 (0.90–2.79)	
ECMO FiO_2, %	1.04 (0.98–1.10)	
Delta p	1.02 (0.97–1.08)	
Change 12 h delta *p*/blood flow, %	1.01 (0.97–1.10)	
Change 24 h delta *p*/blood flow, %	1.01 (0.97–1.05)	
Platelets per 10×10^9/l	0.98 (0.90–1.07)	
D-dimer per 1000 μg/L	0.99 (0.97–1.01)	
Fibrinogen, g/l	1.24 (0.63–2.42)	
aPTT per 10 seconds	0.88 (0.43–1.82)	
Pt, seconds	0.95 (0.68–1.31)	
Hb, mmol/l	1.34 (0.48–3.76)	
PFHb, umol/l	0.83 (0.52–1.31)	
HbCO, %	0.89 (0.47–1.69)	
LDH per 10 U/l	0.93 (0.86–1.00)	0.90 (0.82–1.00)
CRP per 10 mg/L	0.89 (0.79–1.02)	
Leukocytes, $x10^9$/l	0.99 (0.87–1.13)	
PaO_2, kPa	0.91 (0.59–1.39)	
$PaCO_2$, kPa	0.80 (0.42–1.52)	
pH per 0.1 units	1.28 (0.37–4.29)	
Lactate, mmol/l	1.03 (0.11–9.30)	

ECMO: extracorporeal membrane oxygenation; aPTT: activated partial thromboplastin time; Pt: prothrombin time; PFHb: plasma free haemoglobin; Hb: Haemoglobin, HbCO: carboxyhaemoglobin; LDH: lactate dehydrogenase; CRP: C-reactive protein; $PaCO_2$: partial arterial pressure of carbon dioxide; PaO_2: partial arterial pressure of oxygen; FiO_2: fraction of inspired oxygen.
[a]Variables entered at sept 1: Sex, Age, LDH, CRP, Sweepflow

we do and was performed eight years ago. ECMO equipment has improved significantly since then, so results could be different in current practice.

LDH is a known marker of hemolysis and may therefore be an indicator for pump head thrombosis.[10,24] However, an elevated LDH level is a relatively non-specific finding because it originates not only from RBC but is present in the cytoplasm of almost all cells of the human body and is released after cell damage. LDH is also a known marker of liver damage. In addition, baseline LDH levels are considerably different between patients, so direct comparison is complex.[23] It is somewhat surprising that LDH levels were lower prior to an emergency exchange. Lower LDH levels are associated with RBC-rich and fibrin-poor thrombus formation in the V-A ECMO system. This type of thrombus is most likely caused by low-shear thrombus formation in the ECMO system. The oxygenator is a component of the ECMO circuit with low-shear conditions. So, one might speculate that an RBC-rich

thrombus formation in the oxygenator results in relatively lower LDH levels and could deteriorate the oxygenator function more rapidly than a fibrin-rich thrombus, this may increase the risk for an emergency exchange.[25]

Inflammation and coagulation are tightly linked. In ARDS patients, inflammation is associated with prothrombotic changes and organ injury.[26] LDH is considered an inflammatory marker. Therefore, the higher inflammatory levels prior to the elective exchanges may be explained by the fact that the group was more severely ill, which made physicians more likely to exchange the oxygenator during office hours. Another possible explanation for this is that the increased inflammation parameters caused a more procoagulant effect, making clots in the oxygenator sooner and better noticeable.

This study has several limitations including the well-known limitations of retrospective-observational studies, such as selection bias, incomplete datasets, and lack of strict protocols of ECMO management. Although including all V-V ECMO patients during the study period may have reduced the selection bias, the study population was relatively small. During the study period we exclusively used the Cardiohelp® (Maquet-Getinge Group®) oxygenator, which makes the results possibly not translatable to other oxygenators. Furthermore, the decision to perform an oxygenator exchange is made based on the gathered variables. As a result, different ECMO-intensivists and perfusionists could decide to exchange the oxygenator at different timings based on these variables. Consequently, there may be a risk of a self-fulfilling prophecy, as there were no emergency exchanges due to an acute shutdown of the ECMO system. However, if a strict protocol or algorithm was used to decide whether an exchange was necessary, this study could not have been done. The indication for an oxygenator change was not generally recorded so emergency exchanges during office hours could be missed. However, we believe that the timing of the oxygenator change may better indicate the urgency. Every oxygenator exchange is a high-risk procedure. If an exchange must be performed outside office hours, this risk may increase even more due to a shortage of staff, less experienced staff, and possible delay due to staff arrival time. More than half of the study population was supported by V-V ECMO because of COVID-19-induced ARDS. Patients with COVID-19 often have prothrombotic coagulation abnormalities, so that results may differ in patients with other indications for ECMO.[27,28] However, COVID-19-induced ARDS was not identified as a risk factor for an oxygenator exchange. We included only V-V ECMO patients because we believe oxygenator exchanges in these patients are the most clinically relevant results and differ in other ECMO modalities. Furthermore, oxygenator exchanges in V-A ECMO are less frequent, most probably because these ECMO runs are generally shorter.

Further research is needed on factors that predict oxygenator failure with the aim of defining clear cut-off values for the timing of the exchange. It would be of great value to investigate whether influencing modifiable variables affects the oxygenators' function.

Conclusion

Despite systemic anticoagulation and improvement of the ECMO devices, oxygenator exchange during V-V ECMO support is still frequently necessary; 42% of our patients required at least one oxygenator exchange. Higher $PaCO_2$, ΔP and Hb levels were independent risk factors for an oxygenator exchange and could reliably predict oxygenator exchange. We found that 34% of the exchanges were emergency exchanges and lower LDH levels were associated with an emergency oxygenator exchange.

Author contributions

OVM contributed to the design of the study, performed the collection and analysis of the data, contributed to the interpretation of the data, and prepared the manuscript. WMB, AOL and RFH contributed to the design of the study, interpretation of the data and critical revision of the manuscripts. All authors read and approved the final manuscript.

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Ethical approval

This study was approved by the Medical Ethics Review Committee of the University Medical Center Groningen, Groningen, The Netherlands. The requirement to obtain informed consent from patients enrolled in this study was waived.

Data availability

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

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