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Coagulation complications after conversion from roller to centrifugal pump in neonatal and pediatric extracorporeal membrane oxygenation

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ABSTRACT

Background/purpose: Coagulation complications are frequent, unwanted occurrences in extracorporeal membrane oxygenation (ECMO) treatment, possibly influenced by the pump in the ECMO-circuit. We hypothesized that fewer complications would occur with a smaller, heparin-coated ECMO system with a centrifugal pump (CP) than with one with a roller pump (RP) and that after conversion, complication rates would decrease over time.

Methods: This single-center, retrospective chart study included all first neonatal and pediatric ECMO runs between 2009 and 2015. Differences between groups were assessed with Mann–Whitney U tests and Kruskal–Wallis tests. Determinants of complication rates were evaluated through Poisson regression models. The CP group was divided into three consecutive groups to assess whether complication rates decreased over time.

Results: The RP group comprised 90 ECMO runs and the CP group 82. Hemorrhagic complication rates were significantly higher with the CP than with the RP, without serious therapeutic consequences, while thrombotic complications rates were unaffected. Intracranial hemorrhage rates and coagulation-related mortality rates were similar. Gained experience with the CP did not improve complication rates or survival over time.

Conclusions: Although the CP seems safe, it does not seem beneficial over the RP. Further research is warranted on how pump type affects coagulation, taking into account the severity and implications of coagulation complications.

Level of Evidence: Level III.

1. Introduction

Extracorporeal membrane oxygenation (ECMO) treatment entails the temporary use of an extracorporeal circulation for acute respiratory and/or cardiac failure. The interaction between circulating blood and the non-biological surface of the ECMO circuit activates several inflammatory and coagulation cascades [1]. These cascades and the shear stress induced by ECMO can cause thrombotic complications in both the patient and the ECMO circuit. Dalton et al. showed that thrombotic events occur in 31% of pediatric ECMO runs [2]. To counteract these cascades patients receive continuous anticoagulation therapy, often unfractionated heparin (UFH), increasing the risk of hemorrhagic complications. In addition to anticoagulation therapy, the hemorrhaging risk also increases with extensive use or loss of coagulation factors following the start of ECMO treatment [3]. Dalton et al. also showed that hemorrhagic complications occurred in 38% of pediatric ECMO. Both thrombotic and hemorrhagic events complicate ECMO treatment and are important causes of morbidity and mortality in neonatal and pediatric ECMO [2, 4].

In the last decade, there has been a shift from the use of roller pumps to centrifugal pumps in the ECMO circuit. Centrifugal pumps offer several potential benefits, including smaller circuit size, lower circuit priming volumes, less blood trauma, and a smaller surface area for interaction between blood and

Abbreviations: ACT, activated clotting time; APTT, activated partial thromboplastin time; CNS, central nervous system; CP, centrifugal pump; DIC, disseminated intravascular coagulation; ECMO, extracorporeal membrane oxygenation; ELSO, extracorporeal life support oxygenation; RP, roller pump; UFH, unfractionated heparin; VA ECMO, veno-venous extracorporeal membrane oxygenation; VV ECMO, veno-arterial extracorporeal membrane oxygenation.

Type of Study: Retrospective Comparative Study.

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non-biological surface [5–10]. A smaller surface area may result in less activated inflammatory and coagulation mediators, thus influencing the coagulation process. Despite these expectations, several retrospective analyses of the Extracorporeal Life Support Oxygenation (ELSO) registry data revealed increased odds of hemolysis with centrifugal pumps compared to roller pumps but found no difference in survival to discharge [11–13]. These studies lack information on coagulation management and the potential learning effect after the transition to a centrifugal pump.

In this paper, we have outlined the differences in coagulation complication rates and outcome after conversion from an ECMO system with a roller pump to a new smaller, heparin-coated ECMO system incorporated with a centrifugal pump in neonatal and pediatric ECMO in a high-volume ECMO center. Coagulation complications were defined and categorized following the ELSO registry. We hypothesized that with the new ECMO system with the centrifugal pump fewer thrombotic and hemorrhagic complications would occur and that after implementing the centrifugal pump complication rates would decrease over time with gained experience.

2. Material and methods

2.1. Study design and population

We conducted a single-center, retrospective chart study with a before-after design in a pediatric intensive care unit of a tertiary children's hospital, which serves as the national referral ECMO center. The study was approved by the hospital's medical ethics review committee (MEC-2017-478). The study population consisted of all first ECMO runs in children until the age of 18 years between December 2009 and December 2015. Patients who received extracorporeal cardiopulmonary resuscitation (ECPR) and patients cannulated elsewhere who were not transferred to our hospital within 24 h were excluded from the analysis. ECPR was defined as the rapid deployment of veno-arterial ECMO (VA-ECMO) during cardiopulmonary resuscitation before the return of spontaneous circulation in patients with cardiac arrest or when repetitive cardiac arrests occurred without sustained return of spontaneous circulation. The first 75 patients receiving ECMO treatment with the centrifugal pump described in this study have also been used for another multicenter retrospective study to assess the efficacy and overall complication and survival rates of the Deltastream DP3 pump (Medox Medizintechnik AG, Stolberg,Germany) [14]. While this study demonstrated the efficacy of this pump, there is no information on whether complication and survival rates actually improved by conversion to this type of pump.

2.2. ECMO circuit

Our institute converted from an ECMO system with a roller pump to a new ECMO system with a centrifugal pump over several months at the end of 2011. In the roller pump group (RP group), the ECMO circuit consisted of the Stockert SIII roller pump with either the Medtronic 0800 silicon membrane oxygenator and the Medtronic 1/4″ heat exchanger for neonates or the Medtronic I-2500-2A silicone membrane oxygenator with an integrated heat exchanger for pediatric patients. The circuits had uncoated tubing. Estimated priming volumes of 350 ml were used for neonates and 900 ml for pediatric patients. In the centrifugal pump group (CP group), the ECMO circuit consisted of the Medos DP3 centrifugal pump with either the Medos HILITE® 800 LT with an integrated heat exchanger or the Novalung iLA Activve Membrane Ventilator (iLA activve Minilung petit kit, iLA activve Minilung kit or iLA activve iLa) with an integrated heat exchanger. The circuits had coated tubing. Estimated priming volumes of 225 ml were used for neonates and 360 ml for pediatric patients. For both groups, the uncoated Hospal Multiflow 60 or 100 were used as hemofilters. In the RP group, continuous veno-venous hemofiltration (CVVH) was performed by default in every ECMO patient, as the ECMO circuit was integrated with a hemofiltration system in order to transfuse all blood products in an isovolemic manner. In the CP group, CVVH was only applied when indicated, as it became apparent that less transfusions (especially platelet transfusions) were required during ECMO treatment. The ECMO circuit of the CP group therefor did not include a hemofiltration system. Neonates underwent VA cannulation surgically through the carotid artery and jugular vein with an open technique or centrally in case of ECMO treatment following cardiopulmonary bypass. The pediatric population with a weight below 15 kg underwent VA cannulation surgically through the carotid artery and jugular vein or centrally in case of ECMO treatment following cardiopulmonary bypass. For the pediatric population with a weight above 15 kg, the technique of VA cannulation depended on the underlying disease and vascular width assessed with ultrasound.

2.3. Coagulation management

Intravenous UFH was used as anticoagulation in both groups. Dosages were adjusted based on activated clotting time (ACT) predominantly in the RP group or activated prothrombin time (APTT) predominantly in the CP group. The target range for ACT was between 180 and 200 s. The target range for APTT was between 60 and 85 s if the patient was older than 1 year of age and had no pre-existent coagulation disorders and between 85 and 120 s if the patient was younger than 1 year of age or had present pre-existent coagulation disorders. APTT target ranges were increased in case of thrombus formation, increased D-dimers or hemolysis. APTT target ranges were lowered in case of surgery and hemorrhages. Fibrinogen, D-dimers, and platelets were measured on a daily basis in both groups. Additionally, when dosages were based on APTT levels, antifactor Xa, prothrombin time, factor V, and antithrombin were measured on a daily basis and in case of unexpected changes in APTT values. In both groups, administration of intravenous UFH was stopped in case of life threatening or persistent bleeding. In case of surgical procedures in the roller pump group, ACT target ranges were lowered by 20 s through lowering of the intravenous UHF infusion, platelet levels were lowered to 150 $\times$ 10^9/L, and tranexamic acid was started 24 h before surgery. For the centrifugal pump, intravenous UFH was switched off prior to surgery and restarted within 4 – 6 h after surgery.

2.4. Data collection

All data were routinely collected. Data were extracted from the hospital charts and from the ELSO registry forms. Patient characteristics including age, gender, weight, indication for ECMO, ECMO type (VA-ECMO or veno-venous ECMO (VV-ECMO)), duration of ECMO treatment, and the use of CVVH were collected. Also, all laboratory values of ACT, APTT, fibrinogen, platelet count, and D-dimers were collected. Daily UFH infusion rate (IU/kg/h) and daily infusion rates of red blood cells, platelets and fresh frozen plasma were collected. The primary outcomes were coagulation complications as defined by the ELSO registry including additional complications which are not included in the ELSO registry (marked with (*) in the complications described below). Thrombotic complications included mechanical clots (clots in oxygenator, bladder, hemofilter or undefined mechanical clots), central nervous system (CNS) infarction, and clotting in the pulmonary (*), cardiovascular (*), gastrointestinal, and renal systems (*). Bleeding complications included CNS hemorrhages, cannulation site hemorrhages, catheter insertion site hemorrhages(*), surgical site hemorrhages, hemolysis

(free hemoglobin > 50 mg/dl), disseminated intravascular coagulation (DIC), and hemorrhages in the pulmonary, cardiovascular, gastrointestinal systems, and in the urogenital (*) and ear/nose/throat area (*). Individual complication rates were corrected for duration of the ECMO run to assess median complication rates per 7 days. Survival to discharge and cause of death were assessed. To assess the impact of inexperience after the implementation of a new ECMO system and of the increase of experience over time on the complication rate and outcome, the CP group was equally divided into three consecutive groups (first CP group: $n = 28$; second CP group: $n = 27$; third CP group: $n = 27$) and analyzed.

2.5. Statistical analysis

Continuous data are presented as median (interquartile range) and categorical data as frequency (% of ECMO runs). For the comparison between RP group and CP group and for the comparison of the three consecutive groups that used the CP, the Mann–Whitney U test and the Kruskal–Wallis test for continuous variables and the Pearson chi-square and Fisher's exact test for categorical variables were used. If the null hypothesis of the Kruskal-Wallis test was rejected, post-hoc analysis was performed with the Dunn's test for pairwise comparisons. The Bonferroni correction was then applied to correct for multiple testing. The Spearman rank correlation coefficient was calculated to assess the correlation between the number of coagulation complications per ECMO run and the duration of the ECMO run. To correct the number of coagulation complications for ECMO duration, the number of coagulation complications was divided by the duration of the ECMO run (unit: days) and multiplied by 7 to assess the coagulation complication rate per 7 days ECMO run. Multivariable Poisson regression models were built for the number of coagulation complications, the number of thrombotic complications, and the number of hemorrhagic complications to assess which variables were relevant in the development of complications. The following covariates were considered in the Poisson regression models: ECMO group (RP group or CP group), type of ECMO (VV-ECMO or VA-ECMO), ECMO indication (cardiac or pulmonary indication), surgery on ECMO, use of CVVH, and age category (pediatric patient or neonate). The time at risk in the Poisson regression models was the duration of the ECMO run. To account for possible variation in risk over time, the models for the number of coagulation complications and the number of hemorrhagic complications included the natural logarithm and the square root of the natural logarithm of the duration of ECMO run as covariates. As there was no variation in risk over time for thrombotic complications, the model for the number of thrombotic complications did not include these covariates. The model fit of the final models was evaluated using the Pearson chi-square goodness-of-fit test, and we assessed the possibility of overdispersion by comparing the values of the Akaike information criterion between the Poisson regression model and the corresponding negative binomial regression model. As part of a sensitivity analysis, secondary models were built by adding Year of ECMO treatment and its interaction effect with ECMO group to the final models, to account for possible change in patient care over time. In this sensitivity analysis the combined main effect of *CP group* and the interaction between *Year of Treatment* and *CP group* was tested with a likelihood ratio test. A two-sided p-value of less than 0.05 was considered statistically significant. SPSS version 21.0.0.1 (SPSS Inc, Chicago, IL) was used for statistical analysis.

3. Results

3.1. Demographics

Two hundred and three ECMO runs were performed in the study period. 26 ECPR runs, four second ECMO runs, and a single ECMO run performed mostly elsewhere were excluded from the analysis. One hundred and seventy-two ECMO runs were analyzed, with 90 runs in the RP group (until February 2012) and 82 in the CP group (from September 2011 onwards). Table 1 shows the demographics per pump group. Except for more VA-ECMO runs in the RP group, 60.0% versus 46.3% ($p = 0.046$), and the greater use of CVVH in the RP group, 96.7% versus 29.3% ($p<0.001$), there were no significant differences between the two groups. Both groups had comparable numbers of patients with congenital diaphragmatic hernia, 20% in the RP group vs. 21% in the CP group ($p = 0.527$). The RP group had 1 (1.1%) oncological patient while the CP group had 5 (6.1%) oncological patients ($p = 0.075$). The surgeries that patients underwent during ECMO runs are listed in Supplementary Table 1. A large part was made up of patients who underwent surgical repair for congenital diaphragmatic hernia.

3.2. Coagulation management

In Table 2, laboratory values and UFH and transfusion rates per pump group are listed. The CP group showed significantly lower APTT values and higher fibrinogen and maximum D-dimers levels while receiving less platelets than the RP group. Lower UFH infusion rates were applied in the pediatric patients of the CP group than of the RP group.

3.3. Coagulation complications

As summarized in Table 3, the CP group showed significantly more coagulation complications and more ECMO runs with coagulation complications than the RP group. The number of coagulation complications per ECMO run was weakly correlated with the duration of ECMO treatment (ρ=0.460; $p<0.001$). After correcting for duration, the CP group also showed significantly higher coagulation complication rates than the RP group. The pediatric patients in the RP group showed a median coagulation complication rate per 7 days ECMO of 0.47 (0–1.68) versus a median rate of 1.13 (0–2.65) in the CP group ($p = 0.020$). The difference was owing to a higher incidence of hemorrhagic complications in the CP group, as the pediatric patients showed a higher incidence of cannulation site bleedings, hemolysis, DIC and hemorrhages from the ENT-area. Notably, the increased incidence of hemolysis was not accompanied by a significantly increased number of ECMO runs with circuit changes as shown in table 1. The two groups showed comparable numbers of ECMO runs with thrombotic complications and thrombotic complications rates per 7 days ECMO. Also, intracranial hemorrhage rates in both groups were similar (5.6% vs 7.3%, $p = 0.637$).

Table 4 summarizes the adjusted rate ratios from the multivariable Poisson regression analysis. The CP group showed an increased coagulation complication rate by a rate ratio of 1.788 compared to the RP group (95% CI: 1.295–2.468). Undergoing surgery while on ECMO treatment increased the coagulation complication rate by 1.954 times (95% CI: 1.382–2.763). Type of ECMO, ECMO indication, use of CVVH, and age category had no significant effect on coagulation complication rates. Separating thrombotic and hemorrhagic complications revealed that hemorrhagic complication rates were 2.605 times greater in the CP group than in the RP group (95% CI: 1.671–4.059). Hemorrhagic complication rates were also 2.022 times higher if a patient underwent surgery while on ECMO treatment (95% CI: 1.274–3.210). Thrombotic complication rates were 1.778 times higher if patients were treated with VA ECMO than with VV ECMO (95% CI: 1.064–2.972) and 1.621 times higher if a patient underwent surgery while on ECMO treatment (95% CI: 1.046–2.514). Supplementary Table 2 summarizes the sensitivity analyses for the Poisson regression analyses. After adjustment for *Year of treatment*, the combined main effect of *CP group* and the interaction between *Year of Treatment* and *CP group* did not

Table 1
Patient characteristics per pump group.

	RP group	CP group	*P*-value
ECMO runs	90	82	
Age (years)	0.067 (0.001–2.25)	0.323 (0.003–4.176)	0.557
Neonate	48 (53.3%)	36 (43.9%)	0.217
Gestational age of the neonatal population (weeks)	38.6 (37.5–39.9)	38.7 (38.0–40.4)	0.356
Weight (kg)	3.8 (3.0–12.0)	5.2 (3.3–16.6)	0.072
Male	50 (55.6%)	40 (48.8%)	0.374
ECMO type			0.047*
VV-ECMO	35 (38.9%)	42 (51.2%)	
VA-ECMO	54 (60.0%)	37 (45.1%)	
VV-ECMO converted to VA-ECMO	0	1 (1.2%)	
VA-ECMO converted to VV-ECMO	1 (1.1%)	0	
VV-ECMO converted to VA-ECMO converted to VV-ECMO	0	2 (2.4%)	
Duration of ECMO run (hours)	176.4 (95.9–270.4)	124.0 (76.0–263.9)	0.205
ECMO runs with circuit changes	13 (14.4%)	21 (25.6%)	0.066
CVVH during ECMO run	87 (96.7%)	24 (29.3%)	<0.001*
Surgery during ECMO run	31 (34.4%)	18 (22.0%)	0.070

Table 2
Laboratory values and heparin infusion and transfusion rates per pump group.

	RP group		CP group		
	N	Median (IQR)	*N*	Median (IQR)	*P*-value
ACT (s)	86	175 (170 - 177)	54	179 (168 - 201)	0.170
APTT (s)	84	149 (101 - 180)	82	81 (71 - 109)	<0.001*
Fibrinogen (g/L)	90	2.1 (1.6 – 2.9)	81	2.6 (1.8 – 3.8)	0.047*
Maximum value D-dimers (mg/L)	82	2.1 (0.9 – 8.0)	81	29.8 (9.3 – 59.7)	<0.001*
Platelet count (10^9/L)	90	134.2 (111.8 – 134.3)	82	112.8 (94.8 – 147.1)	0.135
UFH infusion rate (IU/kg/h)°	89	40.1 (30.3 – 46.1)	82	34.5 (34.5 – 41.6)	0.010*
UFH infusion rate in neonates (IU/kg/h) °	*48*	*40.1 (32.9 – 45.1)*	*36*	*37.9 (30.2 – 46.1)*	*0.678*
UFH infusion rate in pediatric patients (IU/kg/h) °	*41*	*40.1 (28.0 – 48.6)*	*46*	*29.1 (21.5 – 37.3)*	*0.008**
Infusion of packed red blood cells (ml/kg/d)	90	0.47 (0.22 – 0.94)	82	0.50 (0.28 – 0.80)	0.646
Infusion of fresh frozen plasma (ml/kg/d)	90	0.10 (<0.01 – 0.43)	82	0.18 (<0.01 – 0.77)	0.145
Infusion of platelets (ml/kg/d)	90	1.11 (0.42 – 1.78)	82	0.53 (0.10 – 1.00)	<0.001*

Table 3
Coagulation complications during ECMO run and outcome per pump group.

	RP group	CP group	*P*-value
ECMO runs	90	82	
ECMO runs with coagulation complications	46 (51.1%)	56 (68.3%)	0.014*
Coagulation complications	99	140	
Coagulation complication rate per 7 days ECMO	0.34 (<0.01 – 1.68)	1.15 (<0.01 – 2.08)	0.010*
ECMO runs with hemorrhagic complication(s)	30 (33.3%)	42 (51.2%)	0.018*
Hemorrhagic complications	43	88	
Cannulation site bleeding	5	17	
Surgical site bleeding	11	12	
Gastrointestinal hemorrhage	6	7	
Hemolysis	3	21	
DIC	1	5	
Central nervous system hemorrhage	5	6	
Pulmonary hemorrhage	5	5	
Cardiovascular hemorrhage	4	3	
Urogenital hemorrhages	2	5	
Hemorrhages ear/nose/throat area	1	5	
Hemorrhages peripheral/arterial catheter	0	2	
Hemorrhagic complication rate per 7 days ECMO	<0.01 (<0.01 – 0.63)	0.38 (<0.01 – 1.39)	0.012*
ECMO runs with thrombotic complication(s)	35 (38.9%)	35 (42.7%)	0.505
Thrombotic complications	56	52	
Pulmonary clotting	2	4	
Cardiovascular clotting	5	4	
Central nervous system infarction	4	4	
Circuit-related thrombotic complications	45	40	
Thrombotic complication rate per 7 days ECMO	<0.01 (<0.01 – 0.72)	<0.01 (<0.01 – 0.83)	0.464
ECMO runs with thrombotic and hemorrhagic complications	19 (21.1%)	20 (24.4%)	0.608
Died on ECMO treatment	17 (19.9%)	23 (28.0%)	0.058
Mortality owing to coagulation complications	5 (5.6%)	7 (8.5%)	0.477
Survival to discharge	47 (52.2%)	51 (62.2%)	0.187

Table 4
Poisson regression models for number of coagulation complications.

Model	Dependent variable	Covariate	Adjusted rate ratios	95% CI	*P*-value
I	Number of coagulation complications*	CP group (reference = RP group)	1.788	1.295–2.468	<0.001**
		VA ECMO (reference = VV ECMO)	1.234	0.885–1.720	0.214
		Surgery on ECMO	1.954	1.382–2.763	<0.001**
		Pulmonary ECMO indication (reference = cardiac ECMO indication)	0.905	0.605–1.354	0.627
		CVVH	1.132	0.785–1.633	0.506
		Neonate	0.788	0.575–1.078	0.136
II	Number of thrombotic complications	CP group (reference = RP group)	1.165	0.716–1.896	0.539
		VA ECMO (reference = VV ECMO)	1.778	1.064–2.972	0.028**
		Surgery on ECMO	1.621	1.046–2.514	0.031**
		Pulmonary ECMO indication (reference = cardiac ECMO indication)	0.962	0.544–1.702	0.895
		CVVH	0.904	0.509–1.606	0.730
III	Number of hemorrhagic complications*	CP group (reference = RP group)	0.805	0.519–1.248	0.331
		VA ECMO (reference = VV ECMO)	2.605	1.671–4.059	<0.001**
		Surgery on ECMO	0.934	0.600–1.453	0.761
		Pulmonary ECMO indication (reference = cardiac ECMO indication)	2.022	1.274–3.201	0.003**
		CVVH	0.785	0.454–1.358	0.386

significantly affect hemorrhagic complication rates or thrombotic complication rates. These results imply that there was no significant change in the level or the trend of these complication rates after the introduction of the centrifugal pump.

3.4. Outcome

As shown in Table 3, outcome did not significantly differ between the RP group and the CP group. In the RP group, 80.0% were weaned from ecmo treatment versus 70.7% in the CP group ($p = 0.058$). In the RP group, 52.2% survived to discharge versus 62.2% of the CP group ($p = 0.187$). In addition, survival to discharge did not significantly differ between the RP group and the CP group when neonatal and pediatric groups were analyzed separately (neonatal: 50.0% versus 61.1%, $p = 0.311$; pediatric: 54.8% versus 63%, $p = 0.430$). Five patients in the RP group (5.6%) and 7 patients in the CP group (8.5%) died owing to coagulation complications. In the RP group, 2 patients died owing to bleeding complications including 1 intracranial hemorrhage, 1 owing to an cerebral infarction, and 2 owing to a combination of intracardiac thrombi and intraabdominal hemorrhages. In the CP group, 5 patients died owing to bleeding complications including 4 intracranial hemorrhages, while 2 patients died owing to pulmonary thrombotic complications.

3.5. Coagulation complications after conversion to centrifugal pump

Table 5 displays the effects of experience on coagulation complications after conversion to a new ECMO system with the centrifugal pump. Baseline demographics did not significantly differ between the three consecutive groups except for the number of surgeries during ECMO runs, which increased over time. The number of ECMO runs with hemorrhagic complications did not significantly differ between the groups but the total number of hemorrhagic complications was threefold in the third group compared to the first group. The second group had the highest incidence of ECMO runs with thrombotic complications owing to an increase of mechanical clotting. This was also apparent by the increase of the number of ECMO runs with system changes and the higher maximum D-dimer values. The thrombotic complication rate was lower in the third group than the second group, although it remained higher than in the first group. Correcting for ECMO duration resulted in median coagulation complication rates which were not significantly different for both hemorrhagic and thrombotic complications between the three groups. The number of CNS hemorrhages and infarctions were comparable between the three groups. Survival rates did not differ between the three groups ($p = 0.837$). Mortality owing to coagulation complications was lower in the last group, but this difference was not significant ($p = 0.632$).

4. Discussion

Our study has demonstrated that conversion from an ECMO system with the roller pump to a new smaller and heparin-coated ECMO system with the centrifugal pump increased hemorrhagic complications rates. However, conversion did not significantly affect the number of thrombotic complications, the number of circuit changes, the occurrence of neurological complications (i.e. infarction or hemorrhage), survival, and, most importantly, mortality owing to coagulation complications. Inexperience with a new ECMO system also did not seem to affect complication rates or outcome, as complication rates were comparable over the three consecutive groups of patients treated with the centrifugal pump.

The possible explanation for the increase of hemorrhagic complications in the CP group is multifold. Hemorrhagic complications in the CP group included hemolysis, cannulation site bleedings, DIC, and hemorrhages in the ear/nose/throat area. As shown by former ELSO studies and ours, the use of centrifugal pump increases hemolysis, possibly owing to shear stress. Neonatal and pediatric ELSO data showed increased odds of hemolysis for patients undergoing support with centrifugal pumps [11, 12]. Several retrospective studies have showed hemolysis to be a common complication of centrifugal pumps and also associated with worse outcomes [13, 15, 16]. In contrast, Dalton et al. performed a prospective cohort study in 8 hospitals and did not find pump type to be associated with bleeding, thrombosis, hemolysis or mortality [17]. Although the centrifugal pump seems to increase the risk for hemolysis, the CP group did not show more circuit changes or more thrombotic complications compared to the RP group. Also, as free hemoglobin was not always measured in the past, the increase of hemolysis rates might be (partly) explained by more routine testing of free hemoglobin in the CP group [13]. One should also point out that

Table 5
Effect of experience after conversion to the centrifugal pump on coagulation complication rates and outcome.

	First CP group	Second CP group	Third CP group	*p*-value
ECMO-runs	28	27	27	
UFH infusion rate (IU/kg/h)	28.4 (21.9–40.8)	35.2 (27.7–40.8)	36.0 (26.0–46.7)	0.310
Neonates	11 (39.3%)	12 (44.4%)	14 (51.9%)	0.593
Duration ECMO run (hours)	90.7 (63.7–246.2)	137.5 (87.3–320.0)	153.3 (82.5–275.4)	0.345
Surgery on ECMO	2	8	10	0.002*
ECMO runs with system changes	3	12	6	0.015*
APTT (s)	77 (70 – 77)	81 (73 – 102)	92 (71 – 109)	0.453
Maximum D-dimers (mg/L)	21.1 (2.9–35.2)	67.4 (20.9–100.0)	15.0 (8.4–55.3)	0.002*
ECMO type				0.708
VV ECMO	16 (57.1%)	13 (48.1%)	15 (55.6%)	
VA ECMO	12 (42.9%)	14 (51.9%)	12 (44.4%)	
ECMO runs with coagulation complications	16 (57.1%)	20 (74.1%)	20 (74.1%)	0.460
Coagulation complications	24	56	60	
Median coagulation complication rate per 7 days ECMO	0.604 (<0.001–1.809)	1.330 (0.738–2.100)	1.621 (<0.001–2.047)	0.142
ECMO runs with hemorrhagic complication(s)	10 (35.7%)	17 (63.0%)	15 (55.6%)	0.111
Hemorrhagic complications	14	31	43	
Cannulation site bleeding	6	6	5	
Surgical site bleeding	1	4	7	
Gastrointestinal hemorrhage	0	2	5	
Hemolysis	3	8	10	
DIC	0	4	1	
Central nervous system hemorrhage	3	2	1	
Pulmonary hemorrhage	0	2	3	
Cardiovascular hemorrhage	0	2	1	
Urogenital hemorrhages	1	0	4	
Hemorrhages ear/nose/throat area	0	1	4	
Hemorrhages peripheral/arterial catheter	0	0	2	
Median hemorrhagic complication rate per 7 days ECMO	<0.001 (<0.001–0.809)	0.622 (<0.001–1.575)	0.603 (<0.001–2.036)	0.112
ECMO runs with thrombotic complication(s)	7 (25.0%)	17 (63.0%)	11 (40.7%)	0.034*
Thrombotic complications	10	25	17	
Pulmonary clotting	0	3	1	
Cardiovascular clotting	2	1	1	
Central nervous system infarction	1	2	1	
Circuit-related thrombotic complications	7	19	14	
Median thrombotic complication rate per 7 days ECMO	<0.001 (<0.001–0.325)	0.386 (<0.001–1.222)	<0.001 (<0.001–0.649)	0.086
ECMO runs with thrombotic and hemorrhagic complications	1 (3.6%)	14 (51.9%)	6 (22.2%)	0.001*
Died on ECMO treatment	7 (25.0%)	8 (28.6%)	8 (28.6%)	0.929
Mortality owing to coagulation complications	3 (10.7%)	3 (11.1%)	1 (3.7%)	0.632
Survival to discharge	17 (60.7%)	16 (59.3%)	18 (66.7%)	0.837

while the ELSO categorizes hemolysis as a hemorrhagic complication, it is not a true hemorrhagic complication. Hemolysis is a sign of abnormal breakdown of red blood cells. In addition, over time our ECMO patients were sedated less and mobilized much earlier. The risk of hemorrhaging through manipulation and movement could therefore have been higher in the CP group, a possible explanation for the increase of cannulation site bleedings. Of the 5 patients who developed DIC, 3 suffered from (severe) sepsis. It is more likely that the development of DIC was caused by sepsis than the ECMO circuit. Thus, although the CP group showed more hemorrhagic complications than the RP group, the consequences of these complications were limited. However, follow-up studies are necessary to further delineate long term sequelae.

Multivariate analysis showed that both hemorrhagic and thrombotic complication rates were affected by whether patients underwent surgery during ECMO treatment. As UFH infusion was ceased before surgery to prevent intraoperative hemorrhaging, this could have increased the risk of thrombotic complications. As UFH infusion was restarted after surgery while patients had surgical wounds, this could have increased the risk of hemorrhagic complications.

During the study period, APTT instead of ACT was increasingly used as leading coagulation parameter and separate UFH regimes were used for neonatal and pediatric patients. Additional adjustments to the coagulation protocol were made for special circumstances such as surgery. Despite the change in the leading coagulation parameter, median ACT values were comparable between the RP group and the CP group. While maximum values of D-dimers were higher in the CP group than in the RP group, thrombotic complication rates were comparable between the two groups. As one could not adjust for UFH infusion rates in the regression models, it is unclear whether and how the different UFH regimes affected the development of coagulation complications. Although lower UFH infusion rates were administered in pediatric patients of the CP group, they showed higher hemorrhagic complication rates than the RP group. Similarly, in adult patients, Halaweish et al. found a higher incidence of non-surgical bleeding complications in the CP group compared to the RP group despite higher UFH use in the latter [18]. A possible explanation would be that owing to the smaller ECMO circuit with the centrifugal pump and the less frequent use of CVVH ECMO patients would require less UFH to prevent thrombotic complications. However, our multivariable analysis showed that the new ECMO system with the centrifugal pump or the use of CVVH did not significantly affect thrombotic complication rates. Also, the increased hemolysis rates, responsible for the largest part of the increase in complication rates, were not related to UFH administration.

To our knowledge, no pediatric studies have reported the impact of conversion to a new ECMO system over time. The first group of patients after conversion had the lowest number of coagulation complications. This could be explained by selection of eligible patients during the introduction of the new pump. After full conversion to the centrifugal pump the number of coagulation complications increased. However, the number of coagulation complications was associated with ECMO duration, as is apparent by the comparable coagulation rates. The increase of the total

number of coagulation complications over time could then possibly be explained by the longer ECMO runs in the second and third groups. In our study, the inexperience that accompanies the conversion to a new ECMO system with a different pump did not significantly affect survival rates over time.

Our study has several limitations. This was a retrospective single center chart study with a limited number of patients. ELSO studies included more patients, but comprised a more heterogeneous group of patients as these were treated by different centers with different experience levels and different coagulation protocols [12, 13]. In contrast to these studies, we were able to study ECMO circuit changes, administered UFH and different coagulation parameters owing to the presence of one single treatment protocol. Owing to the before-after study design, there is a possible bias, as we could not account for changes, if any, in treatment (aside from changes in the ECMO circuit) over time. However, the number of patients in our study was limited as we wanted to include patients who were treated in a short time period before and after the moment of conversion to a new pump. This would limit the possible, if any, other changes in treatment. In addition, the sensitivity analyses of the regression model showed that Year of treatment did not affect complication rates, i.e. possible change in treatment over the years showed no significant effect on complication rates. Still, larger prospective studies are necessary to confirm our findings. Owing to the retrospective character of the study, we were not able to take into the account when the coagulation complications occurred during the ECMO run. However, statistical adjustments were made to the multivariate models to account for the possible variation in risk over time. We observed less VA ECMO runs in the CP group than in the RP group. As similar indications for type of ECMO treatment (VV of VA ECMO) were uphold during the study period in both groups, we consider this finding to be coincidental. Because of the limited number of patients, it was not possible to perform a coagulation analysis for VV ECMO and VA ECMO separately (as indications for ECMO treatment differed) and for neonatal and pediatric patients separately (as indications for ECMO treatment and management differed). Although these variables were included in the multivariate models in order to account for possible differences between these groups, it could be disputed whether this was sufficient. Because limited information on coagulation complications and individual management on ECMO treatment was documented in the time period before 2009, it was not possible to collect data before 2009. For this reason, no a priori power analysis was performed and a convenient sample size of the last 100 patients in the RP group and the first 100 patients of the CP group were used for this study. Furthermore, during the study period APTT replaced ACT as the main leading coagulation parameter to adjust UFH dosages. The impact of a new leading coagulation parameter could not be assessed, but it may partly explain the lower UFH infusion rates used in the CP group. Both groups, however, showed similar median ACT levels despite different main leading coagulation parameters. Regardless of lower UFH infusion rates compared to the RP group, the CP group did not show more thrombotic complications. Finally, while our study findings can be generalized as ELSO definitions for coagulation complications were used, there is a lack of clear uniform definitions [2]. The ELSO only offers a registry list for complications. There is no insight into the severity and the clinical implications of these complications. In addition, as discussed before, hemolysis is perhaps unfairly categorized as a hemorrhagic complication. New consensus-based definitions and categorization of coagulation complications are necessary for accurate interpretation of coagulation issues during ECMO treatment. Prospective studies into ECMO treatment with standardized care protocols would then be the next step in the more accurate assessment of these coagulation complications. In an effort to achieve this, our institution is, as of 2019, conducting a prospective study, the CHEKid-study (NL6977), in collaboration with other ECMO centers, on coagulation monitoring and hemostatic complications in children receiving ECMO treatment.

5. Conclusions

Conversion from an ECMO system with a roller pump to a different ECMO system incorporated with a centrifugal pump in neonatal and pediatric ECMO treatment resulted in more hemorrhagic complications without severe therapeutic consequences. Serious neurological coagulation complications including intracranial hemorrhages, the number of circuit changes and outcome did not significantly differ between the groups. Conversion from an ECMO system with the roller pump to a different ECMO system incorporated with a centrifugal pump appeared to be safe but did not improve coagulation complication rates or outcome over time. Future research on ECMO-related coagulation complications requires more uniform definitions, taking in consideration the severity and clinical implications of these complications.

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Supplementary materials

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