

Plasma-Free Hemoglobin Levels in Advanced vs. Conventional Infant and Pediatric Extracorporeal Life Support Circuits

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Abstract: Extracorporeal life support (ECLS) is a reliable method to support pediatric patients with reversible cardiorespiratory failure associated with congenital heart disease, respiratory insufficiency, or after cardiac surgery. In 2010, our institution adopted an infant/pediatric extracorporeal membrane oxygenation (ECMO) circuit that contains a magnetically levitated centrifugal pump, polymethylpentene oxygenator, and shorter tubing length (ECMO II circuit). Our prior circuit contained a nonocclusive roller pump, polypropylene oxygenator, venous compliance chamber, and hemoconcentrator (ECMO I circuit). A retrospective chart review comparing ECMO I and ECMO II daily plasma-free hemoglobin (PFH) values was conducted. We hypothesized that the PFH is similar between the two ECMO circuit groups. We reviewed medical records of children 3 years of age or younger weighing less than 13 kg who required ECLS between January 2008 and February 2012. PFH levels from 18 ECMO II patients were compared with levels in a retrospective group of an equal

number of well-matched ECMO I circuit patients. There was no significant difference between ECMO I and ECMO II circuit groups regarding mean time on ECMO, age in days, and weight. There was also no significant difference in the group mean levels of PFH between ECMO I and ECMO II circuits. There was a significant increase in PFH with hours on ECMO ($p < .01$) within and between both circuit groups ($p < .01$) and a significantly greater increase in PFH with ECMO hours ($p = .0091$) in the ECMO I circuit group. Although there was no significant difference in average PFH with the change in ECMO II circuit technology, advancements such as the magnetically levitated blood pump and polymethylpentene gas exchange device has been associated with significantly fewer mechanical component change-outs ($p = .0156$) and less clots and fibrin build-up in the circuits ($p = .0548$). **Keywords:** plasma free hemoglobin, extracorporeal life support, extracorporeal membrane oxygenation, centrifugal, roller. *JECT. 2013;45:21–25*

In January 2010, our extracorporeal membrane oxygenation (ECMO) team adopted an infant/pediatric extracorporeal life support (ECLS) circuit change that replaced the roller pump with a magnetically levitated centrifugal pump and the polypropylene membrane oxygenator with a polymethylpentene oxygenator. Fewer connectors and shorter tubing lengths were used and circuit manifold shunts were used only on the smallest patients. The circuit evolution has been termed “ECMO II” (Dr. Robert Bartlett, personal communication, AmSECT International Conference, Reno, NV, March 2010).

Plasma-free hemoglobin (PFH) levels greater than 15–50 mg/dL are most commonly caused by the shear stress and pressure drop regularly experienced during ECLS (1–6). As a result, the PFH may increase 10- to 25-fold during ECLS. ECLS circuit technology is evolving and compared with the pre-existing circuit components, the new blood propulsion and oxygenation devices are described as possibly less traumatic to cellular elements and less hemolytic (7).

ECMO II oxygenators are now constructed of polymethylpentene, a hollow fiber surface that allows gas transfer, but unlike the traditional polypropylene fiber, it restricts the passage of plasma proteins reducing the need and frequencies of change-outs (8). In addition, the perpendicular construction of fibers to the blood pathway has given way to lower resistance and decreased pressure drop. The decreased pressure drop also allows the ability for use with centrifugal pumps. Centrifugal pumps, unlike roller pumps, are preload- and afterload-dependent innately

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producing less negative pressure and cavitation, which should result in less hemolysis. The third-generation magnetically levitated centrifugal pumps are reported to allow less heat transfer and less thrombosis as a result of the lack of bearings and seals and less blood stagnation (7). Together these components permit a smaller extracorporeal circuit size with reduced prime volume and surface area. The smaller circuit is easier and safer to transport.

With our change to the ECMO II circuit technology, we hypothesized that ECMO patient daily PFH levels would be reduced. We tested the hypothesis that there was no difference between daily PFH levels for ECMO I and ECMO II circuit patients and there was no difference in PFH level change with hours on ECMO between the two circuit patient groups.

METHOD

After our quality improvement project qualified for Mayo Clinic Institutional Review Board exemption, the medical records of children younger than 3 years of age weighing less than 13 kg who required ECLS between January 2008 and February 2012 were reviewed. Eighteen ECMO II patient daily PFH levels were compared with levels in a retrospective group of an equal number of well-matched ECMO I circuit patients. The patients were matched as best as possible according to age, body weight, indication for ECMO, ECMO cannulation mode, and total time on ECMO. A retrospective review was also performed using the Extracorporeal Life Support Organization (ELSO) database results to benchmark our results to other institutions.

ECMO I Circuit

The ECMO I circuit consisted of a 15% underoccluded Sorin S5 roller pump (Sorin Group USA, Inc., Arvada, CO), the Minimax oxygenator (Medtronic, Inc., Minneapolis, MN), and the ¼-inch ID Better Bladder compliance chamber (Circulatory Technology Inc. Oyster Bay, NY). Safety devices included Sorin air sensors and ancillary flow probes (Transonic Systems Inc., Ithaca, NY). The roller pump occlusion was set to 15% nonocclusion by direct ultrasonic flow measurement. Thirty-two four-way stopcocks, 12 feet of Medtronic Carmeda treated tubing, 3 feet of Super Tygon (Saint-Gobain Performance Plastics, Akron, OH) roller pump raceway tubing, and 13 straight connectors were used. The circuit and occlusion setting technique are described in an earlier publication (9). The priming volume was approximately 1000 mL.

ECMO II Circuit

The ECMO II circuit consisted of a CentriMag or PediMag pump, console, and flow probe (Thoratec, Pleasanton, CA) and Quadrox iD pediatric oxygenator (Maquet Cardiopulmonary AG, Hirrlingen, Germany). Noninvasive O₂

saturation, hematocrit/hemoglobin, and emboli detection measurements were monitored with the Spectrum M3 (Spectrum Medical, Fort Mill, SC). Two four-way stopcocks and 12 feet of ¼-inch ID Carmeda tubing were used and only cannulae connectors are inserted in the inlet and outlet blood lines. The priming volume was approximately 480 mL.

Both circuits used a 1/8-inch ID manifold, surface-modified cannulae and tubing (DLP and Carmeda Bio-Active surface; Medtronic Inc., Minneapolis, MN), and CDI 500 (Terumo Cardiovascular Systems, Ann Arbor, MI). Blood temperature was regulated by the Cincinnati Sub-Zero ECMO-Heater (Cincinnati, OH). The Hemocor HPH Mini was placed (Minntech Inc., Minneapolis, MN) in all ECMO I circuits but only used for patients who required hemoconcentration for the ECMO II circuit cases.

Cannulation sites in the majority of patients who required both respiratory and cardiac support postcardiotomy were located in the right atrium and ascending aorta. Respiratory-supported patients (one patient in the ECMO I group and two patients in the ECMO II group) were cannulated in the internal jugular vein using the OriGen double-lumen cannula (OriGen Biomedical, Austin, TX). Blood flow rates varied between 80 mL/kg/min and 150 mL/kg/min.

The hemoglobin was maintained above 10 g/dL by transfusion and all patients were administered sodium heparin (2–15 U/kg/h) or argatroban (1–10 µg/kg/min) as an anticoagulant. Unless the patient was bleeding, in both groups, the activated partial thrombin time was generally maintained above 55 seconds. In both groups, thromboelastography (TEG-5000; Haemonetics Corporation, Braintree, MA) kaolin-activated R-time target was maintained above 12–15 minutes (approximately three times greater than the heparinase and kaolin-activated R-time) and the kaolin-activated alpha angle was maintained less than 30° with anticoagulation therapy. The kaolin-activated clotting time (i-STAT; Abbott Point of Care, Princeton, NJ) was maintained approximately 1.25–1.5 times baseline. Antithrombin was monitored and supplemented to treat levels below 50% on all patients regardless of anticoagulation therapy. If the patient was bleeding more than 2 mL/kg/h, anticoagulation therapy was usually suspended for patients in both groups.

Measurement of Plasma-free Hemoglobin

Blood samples for PFH analysis were drawn every 12–24 hours from the patient's arterial line as part of routine daily ECMO care. PFH was calculated using spectrophotometry at specific wavelengths on a Perkin-Elmer Lambda 35 spectrophotometer (Waltham, MA).

Statistical Analysis

PFH values were compared between ECMO circuit groups by analysis of variance using Tukey comparisons. Nonparametric data were compared using χ^2 analysis. JMP 10.0 statistical analysis software (SAS Institute, Cary, NC) was used. Contingency tables were constructed to compare

our data with the ELSO database reports. Differences in the rate of change in PFH with ECMO hours between the two circuit groups were analyzed with a least squares linear fit model. Survival curves were compared with the log-rank χ^2 test. A *p* value < .05 was considered statistically significant.

RESULTS

The two circuit patient groups are well-matched (Table 1). Thirty-six patient records were reviewed between January 2008 and February 2012. The patients had all agreed to allow their medical records to be reviewed for quality projects in the state of Minnesota. Two hundred sixty-six PFH levels were collected between 1 and 323 elapsed hours of ECMO; 139 PFH observations were collected for ECMO I and 127 observations for ECMO II circuit patients.

Thirty-three of the 36 patients were postoperative cardiac surgical patients supported with venoarterial ECMO. Three patients were not postcardiotomy and were supported with venovenous ECMO. The surgical procedures performed included Blalock-Taussig shunts, tricuspid valve repair, myectomy for hypertrophic obstructive cardiomyopathy, patent ductus arteriosus closure, reconstruction of the aorta and pulmonary arteries, repair of transposition of the great arteries and atrial and ventricular septal defects, anomalous coronary artery repair, and arterial switch operations. One patient was rescued during a catheterization laboratory electrical ablation procedure. One patient experienced anaphylactic shock after a bone marrow transplant and required venovenous support.

The percent of patient procedures and days in which the PFH was greater than 50 mg/dL is reported in Table 1. No significant differences were observed comparing the mean or median daily PFH values for the two ECMO circuit patient groups (Table 2). Mean PFH values, the days with PFH values lower than 50 mg/dL, tended to be lower in

Table 1. Patient demographic information by circuit group.

Measurement	ECMO I	ECMO II	<i>p</i> Value
Patient age (days)	226 ± 326	363 ± 490	.3316
Percent male	56	61	.7352
Body weight (kg)	5.5 ± 2.9	6.1 ± 3.7	.6001
ECMO run hours	139 ± 76	153 ± 87	.5393
Percent procedures	72	56	.3047
with PFH > 50 mg/dL			
Percent days in run	25 ± 5	20 ± 20	.5699
with PFH > 50 mg/dL			

Eighteen patients were included in each group. Values are mean ± 1 standard deviation. ECMO I, roller pump and polypropylene membrane oxygenator; ECMO II, centrifugal pump and polymethylpentene oxygenator; PFH, plasma-free hemoglobin.

Table 2. Distribution of observed daily PFH values by circuit group.

Circuit Group	10%	25%	Mean	Standard Deviation	Median	75%	90%
ECMO I	10	17	58	102	27.5	48	108
ECMO II	13	18	36	32	27.6	40	70
<i>p</i> value			.3647		.7418*		

Eighteen patients were included in each group. Values are mean ± 1 standard deviation. Percent distributions are percentile ranks.

*Wilcoxon/Kruskal-Wallis test between medians.

PFH, plasma-free hemoglobin; ECMO I, roller pump and polypropylene membrane oxygenator; ECMO II, centrifugal pump and polymethylpentene oxygenator.

Table 3. Least squares linear fit model: PFH by circuit type by ECMO hours.

Parameter	Estimate	Standard Error	t Ratio	Probability > t
Intercept	31.0	7.4	4.17	<.0001
Circuit group	12.2	4.6	2.63	.0091
ECMO hours	.2	.1	2.91	.0039
Circuit group* ECMO hours	.2	.1	3.18	.0016

Analysis of variance probability >F = .0002. With 266 daily observations from two groups of 18 patients, the observed statistical power was .7442. PFH, plasma-free hemoglobin; ECMO, extracorporeal membrane oxygenation.

the ECMO II circuit group but were not significantly different. The PFH values increased significantly with time on ECMO (Table 3). PFH increased more with increasing ECMO hours for the ECMO I group compared with the ECMO II slope (Figure 1).

Oxygenator survival without replacement was significantly greater in the ECMO II circuits than the ECMO I circuits (Figure 2). The appearance of threatening thrombus in the ECMO II circuits was substantially reduced in the ECMO II circuits after the first 100 hours of ECMO (Figure 3).

ELSO database subscribers report the mechanical complication of PFH greater than 50 mg/dL. The ELSO database search for the same time period and same types of pumps as our chart review for the same age and weight patients resulted in 90 hemolysis complication event reports from 1079 ECMO runs (Table 4). Our patient incidence of PFH > 50 mg/dL was significantly greater than the reports in the ELSO database (Table 4).

DISCUSSION

In our ECMO service, the use of the ECMO II circuit has allowed a reduction in prime volume and circuit surface area in addition to compact, easy, quick-to-prime ability and portability. ECMO II circuit component

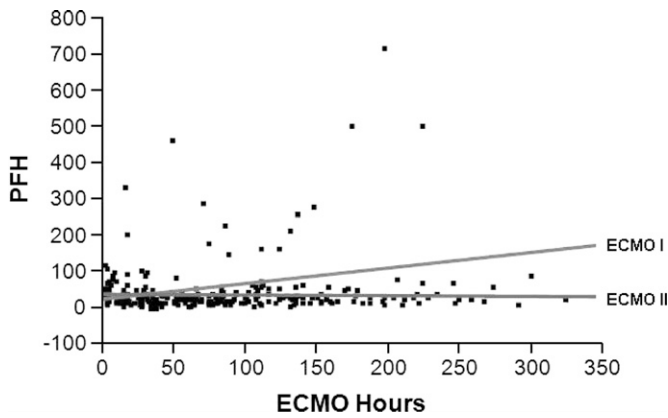


Figure 1. Regression plot: plasma-free hemoglobin vs. ECMO hours by ECMO circuit type. PFH, plasma-free hemoglobin (mg/dL); ECMO I, roller pump and polypropylene membrane oxygenator; ECMO II, centrifugal pump and polymethylpentene oxygenator. The slopes are significantly different ($p = .0039$).

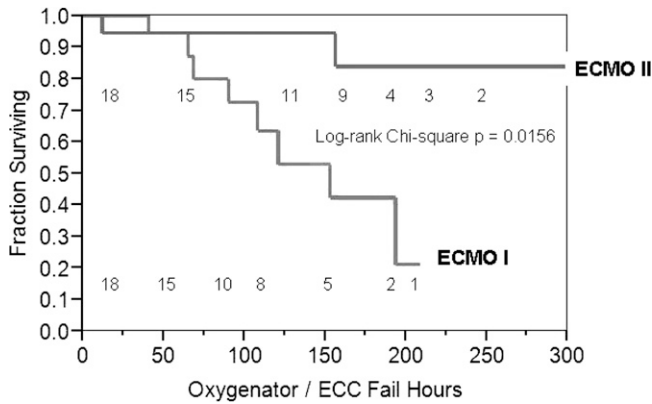


Figure 2. Circuits without oxygenator replacement ECMO I vs. ECMO II. ECMO II, centrifugal pump and polymethylpentene oxygenator; ECMO I, roller pump and polypropylene oxygenator. Oxygenator wet-out or excessive clot were the main failure events. The ECMO II oxygenator survival was significantly longer ($p = .041$). Numbers are oxygenators and circuits surviving failure and at risk.

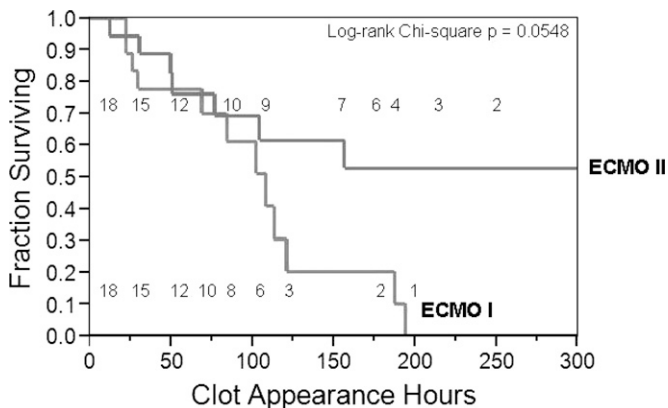


Figure 3. Circuits without serious thrombus formation ECMO II vs. ECMO I. After 100 hours, the appearance of threatening thrombus formation in ECMO II circuits tended to be lower ($p = .0548$). ECMO II, centrifugal pump and polymethylpentene oxygenator; ECMO I, roller pump and polypropylene oxygenator. Numbers are circuits surviving thrombus and at risk.

Table 4. Contingency table of reported PFH >50 mg/dL.

Pump	Database	Years	Patients	Patients' PFH	PFH %	<i>p</i> Value
Sorin S3	ELSO	2008–2010	920	80	.087	<.0001
Sorin S5	MCR	2008–2010	18	13	.722	
CentriMag	ELSO	2010–2012	159	10	.063	<.0001
CentriMag	MCR	2010–2012	18	10	.556	

CentriMag includes 1/4-inch and 3/8-inch connectors. Sorin S3 and S5 roller pump designs are equivalent. PFH % is expressed as a fraction. PFH, plasma-free hemoglobin >50 mg/dL; ELSO, Extracorporeal Life Support Organization; MCR, Mayo Clinic Rochester.

improvements in tubing and cannula surface coating, levitated centrifugal blood pump, and polymethylpentene gas exchange devices have focused on decreasing systemic inflammatory reactions, prime volumes, pressure drops, shear stress, and turbulence to increase biocompatibility and safer duration on ECLS.

One method to evaluate circuit compatibility is the daily monitoring of PFH levels, which are the result of hemolysis when red blood cells are fragmented by transfusion reactions and/or mechanical means. Our observations generally support that the ECMO II circuit patients experience less than or equal daily PFH levels compared with the ECMO I patients, especially when the time on ECMO is considered as a variable (Table 3). The ECMO team at the University of Arkansas published the results of hemolysis observations in seven centrifugal pump pediatric patients vs. 14 roller pump pediatric ECMO patients (7). In January 2011, the Arkansas team reported significantly lower daily hemolysis levels and demonstrated longer circuit component life for the centrifugal pump patients. Unlike the University of Arkansas report, we did not find a significant daily average difference between the roller pump and centrifugal pump patient groups. In the first 6 days of ECMO, our daily mean PFH values ranged from 25 to 70 mg/dL. Perhaps the use of a very nonocclusive roller pump in the ECMO I circuit reduced the PFH levels in this report. To maintain a hemoglobin level ≥ 10 mg/dL, especially in postcardiotomy patients, packed red blood cells (PRBCs) were administered frequently in the initial hours of an ECMO as a result of bleeding and hemodynamic instability. The PRBCs given are often older containing a higher amount of PFH, which could have led to the increased levels. If levels of PFH reach a threshold, continual renal replacement therapy (CRRT) is attached inline to the ECMO circuit. CRRT aids in reduction of PFH but also produces a degree of PFH (1).

The ELSO database was used to benchmark our data. The focus was on the mechanical complication of a PFH > 50 mg/dL. The analysis of ELSO's infant database containing the same parameters as our study yielded a significantly lower occurrence of PFH on ECMO in both

groups. We believe that there is such a discrepancy between ELSO's and our results because PFH may not be available or is not a routinely monitored value by reporting institutions.

Oxygenator change-out is accompanied by the opportunity for technical errors and additional risk to the patient during ECLS (10). With the conversion to ECMO II, our institution has witnessed a significant reduction in oxygenator change-outs resulting from plasma wet-out, device clot, and fibrin build-up in most ECMO procedures (Figure 2).

The reduction in foreign surface area has allowed for less prime volume, faster set-up and priming abilities as well as creating a small footprint expanding ECMO transportation to unspecialized aircraft and road vehicles. Conversion to, from, or in addition to another ECLS circuit such as a centrifugal left ventricular assist device, right ventricular assist device, biventricular assist device, and/or insertion of CRRT connections to the ECMO circuit has been without difficulty. The use of CRRT is associated with increases in PFH during pediatric ECMO (3). The increased survival of the ECMO II circuits without perfusionist intervention is in part the result of the improved surfaces in the oxygenator and the improved hemodynamics of the smaller levitated centrifugal pump.

The ECMO II circuit supports the use of lower RPMs without the addition of shunts and ECMO bridges. The small footprint and connectorless system provides a degree of safety for fewer accidental disconnections, less blood turbulence, and maintenance of normothermia without a heater-cooler. Troubleshooting suspecting concerns has become straightforward and quicker as a result of the circuit's simplicity allowing for faster complication identification and appropriate notice of personnel response. When the patient's acuity scores are low, the staffing model has evolved from one ECMO specialist and an intensive care unit bedside registered nurse for all pediatric ECMO patients to the occasional use of one intensive care unit bedside registered nurse who is also a certified ECMO specialist.

The main limitation to our study was its retrospective design and the limited number of variables that we analyzed. The observed statistical power in our report was .7442; however, future prospective studies should examine additional factors to the age of PRBC, use of CRRT, and other variables influencing PFH during ECMO.

CONCLUSION

There was no difference in daily or group PFH levels between the ECMO I roller pump and microporous membrane oxygenator circuits and ECMO II centrifugal pump, continuous membrane oxygenator circuit patient experiences. The rate of rise in PFH with elapsed ECLS hours was greater in the ECMO I patient group. ECMO II circuit components survive significantly longer during use than ECMO I circuit components leading to fewer complications and fewer high-risk required circuit interventions.

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