

## RESEARCH ARTICLE

### A Pediatric Lung Assist System

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## Abstract

Respiratory disease remains a pervasive medical condition amongst the pediatric health population. Mechanical ventilation and extracorporeal membrane oxygenation (ECMO) are used to bridge patients to transplant or recovery when conventional therapy fails. Patients undergoing these treatments may be sedated for extended periods of time, resulting in deconditioning of the patient's musculature. Patients who remain awake on ECMO, however, can participate in physical therapy and combat muscle wasting. Typical ECMO circuits are complex and present a major consumer of hospital resources for these patients undergoing rehabilitation and ambulation. Our research group has pursued the integration of mechanical circulatory and respiratory assistance into a compact platform device, the ModelAS, to address this clinical need. The aim of this review is to summarize published work on the pediatric application of the ModelAS. A breadth of topics will be reviewed, including the design requirements, device evolution, in-vitro results, and in-vivo results of the device.

## 1. Introduction

Pediatric acute and chronic respiratory disease continue to remain a global health concern. In the United States alone, the cost of hospitalization due to respiratory indications accounts for 9% of all pediatric hospital expenditures.<sup>1</sup> Invasive mechanical ventilation (IMV) and extracorporeal membrane oxygenation (ECMO) are used for temporary support in acute respiratory failure and as a bridge to lung transplantation for chronic cases. The application of these therapies continues to grow; In a multicenter clinical trial it was found that 30% of US pediatric intensive care unit admissions required IMV<sup>2</sup> and the cumulative runs of pediatric ECMO for pulmonary indications has increased by 103% in the last decade.<sup>3,4</sup>

In pediatric lung transplantation mechanical ventilation (MV) and ECMO have been associated with 2-3 times the mortality rate of patients who do not require invasive pulmonary support.<sup>5</sup> The incidence of ECMO as a bridge to transplant in

pediatric patients, however, has increased over time (3.6% in 2009 to 16.7% in 2019) while the associated mortality rate has decreased (75% in 2010 to 33.3% in 2018).<sup>5</sup> The improvement of patient selection, ECMO circuit components, and the push to ambulate patients while on ECMO may be responsible for this trend. IMV and ECMO have historically required immobilization or pharmaceutical sedation of patients, resulting in muscular atrophy and poor post-transplant outcomes.<sup>6</sup> Awake ECMO, which permits pre-transplant rehabilitation, has shown to combat this progressive deconditioning in the adult population, resulting in improved post-transplant outcomes.<sup>7-11</sup> Studies comparing ambulatory and non-ambulatory ECMO in the pediatric population have not been published at the time of this article's writing. It has been shown, however, that ambulation in the pediatric population while on ECMO can be performed without adverse events.<sup>8,12-15</sup> Ambulation and rehabilitation while on ECMO, due to circuit size and complexity, require careful monitoring by up to 7 specialists.<sup>7,9</sup> To improve patient outcomes,

patient safety, and to reduce the resource load of ambulatory ECMO, researchers have turned to investigating more efficient and compact respiratory support systems.

Over the last decade our group has developed the Modular Extracorporeal Lung Assist System or ModELAS. The ModELAS integrates a centrifugal pump and hollow fiber membrane (HFM) bundle into a single unit. Different HFM bundles are paired with the centrifugal pump to provide venovenous adult oxygenation, venovenous pediatric oxygenation, or low flow extracorporeal CO<sub>2</sub> removal (ECCO<sub>2</sub>R). For the pediatric and adult oxygenation applications, the device is intended to provide long term ambulatory venovenous ECMO (1-3 months of support). The device is intended to support a patient for 7 days or less in the extracorporeal CO<sub>2</sub> configuration. This review will summarize the design requirements, device evolution, in-vitro results, and in-vivo results of the pediatric application of the ModELAS.

## **2. Device Description and Evolution**

### ***2.1 Device Requirements and Key Specifications***

The performance specifications for the pediatric device were to provide 90% of the respiratory support for patients between 5-25 kg at a blood flow rate of 1-2.5 L/min. This translates to an oxygenation rate of 35-106 mL/min, according to the Mosteller formula,<sup>16</sup> for patients spanning the targeted weight spectrum. The geometry of a stacked type HFM bundle capable of achieving the required rates of oxygenation was determined<sup>16</sup> to have a diameter of 1.75 inches and a gas exchanging surface area of 0.3 m<sup>2</sup>. Details on bundle<sup>17</sup> and device<sup>16</sup> fabrication have been previously published.

The anticipated device implantation strategy was venous drainage via a right atrium cannulation with an 18 Fr DLP® malleable venous cannula (#68118, Medtronic, Minneapolis, MN) and arterial return via a pulmonary artery 14Fr DLP® straight tip arterial cannula (#75014, Medtronic, Minneapolis, MN). The required pressure head of the centrifugal pump was therefore the sum of the pressure drops across the venous and arterial cannulas added to the pressure differential between a pediatric right atrium and pulmonary artery. The pressures in the heart were assumed to be those of a patient with severe pulmonary hypertension.<sup>16</sup>

### ***2.2 Device Evolution***

Our laboratory's first paired pump lung device intended for venovenous pediatric ambulatory ECMO was known as the Pittsburgh Pediatric Ambulatory Lung (P-PAL). The device configuration was altered to a more marketable device, the ModELAS, after initial benchtop testing and a subset of acute in-vivo studies were performed with the P-PAL. The HFM bundle and centrifugal pump used in the pediatric application of the ModELAS are identical to those used in the P-PAL. There are, however, two primary differences between the devices, the first difference being the configuration of the bundle. In the P-PAL device the HFM was oriented vertically with the axis parallel to the axis of the centrifugal pump. In the ModELAS, the HFM is oriented horizontally with the axis perpendicular to the axis of the centrifugal pump (Figure 2.1). This change shortened the blood flow channel between the pump and bundle compartments, allowed for easier device priming, and reduced the overall device size (device weight reduced from 1157 to 721 g).

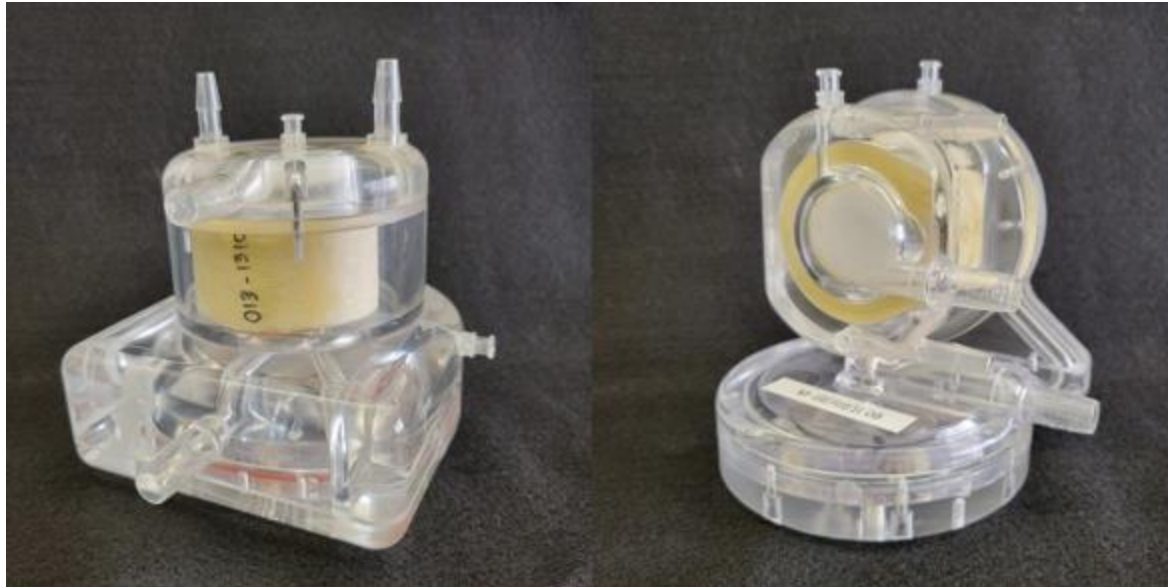


Figure 2.1: A: Pittsburgh Pediatric Ambulatory Lung (P-PAL). B: The pediatric modality of the Modular Extracorporeal Lung Assist System (ModELAS).

The second difference between the two versions of the device is that the bundle compartment of the ModELAS is removable, while that of the P-PAL is not. The removable bundle compartment allows HFM bundles of different sizes to be paired with the centrifugal pump platform. This interchangeable bundle design (Figure 2.2) allows for the same centrifugal pump to be utilized for adult ECMO (HFM bundle of  $0.65 \text{ m}^2$ ),<sup>18-20</sup> low flow ECCO<sub>2</sub>R (HFM bundle of  $0.65 \text{ m}^2$ ),<sup>21,21</sup> or pediatric ECMO (HFM bundle of  $0.3 \text{ m}^2$ ).<sup>16,22</sup>

The incorporation of three device modalities into a single platform ultimately simplifies the medical device commercialization process. There is some reluctance in the field to pursue medical devices intended for pediatrics as the size of the patient population, and therefore market, is of a small-scale compared to that of the adult population. The modular platform of

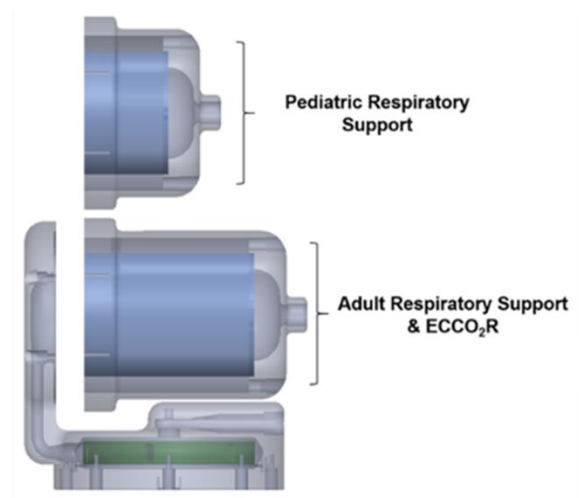


Figure 2.2: Diagram of the ModELAS pump platform and modular bundle housing design.

the ModELAS reaches both therapeutic markets, making the system more attractive for entities intending to commercialize a respiratory assist system.

### 3. In-Vitro Studies

In-vitro studies of hydrodynamic performance, in-vitro oxygenation, and hemolysis were performed for both the P-PAL and ModELAS. In-vitro data for the ModELAS is reviewed in detail in the following section. In-vitro data for the P-PAL has been previously published.<sup>16</sup> P-PAL and ModELAS data have shown to be statistically equivalent.

#### 3.1 Hydrodynamic Performance

The hydrodynamic performance of the centrifugal pump was evaluated using a carboxymethylcellulose (CMC, Sigma Aldrich, St. Louis, MO) solution as a blood analogue. The solution was prepared to have a viscosity of 3.5 cP at 37°C confirmed with a capillary viscometer (Cannon Instrument Company, State College, PA). The ModELAS was connected to a compliant reservoir submerged in a heated water bath. Over the course of the experiment the water bath maintained the temperature of the blood analogue fluid to within  $37 \pm 2^\circ\text{C}$ . Transducers (Honeywell International Inc., Morris Plains, NJ) measured the inlet and

outlet pressure of the device at impeller rotation rates of 1000, 1200, 1400, 1600, and 1800 RPM. Flow rate was modulated between 0-3 L/min using a Hoffman clamp at the outlet of the device and was measured using an ultrasonic flow probe (Transonic Systems Inc., Ithaca, NY). The pressure drop across the cannulas was measured using the same methods as was used for the device. A Biomedicus BP80-X pump (Medtronic, Minneapolis, MN) drove blood flow through the cannulas.

The pressure head generated by the centrifugal pump as a function of flow rate at impeller rotation rates of 1000, 1200, 1400, 1600, and 1800 RPM is shown in Figure 3.1. The required pressure is the sum of the pressure drops across the venous and arterial cannulas added to the pressure differential between a pediatric right atrium and pulmonary artery with severe pulmonary hypertension.<sup>16</sup>

The centrifugal pump of the ModELAS achieved the required pressure head predicted for in-vivo use, up to 2.5 L/min, in

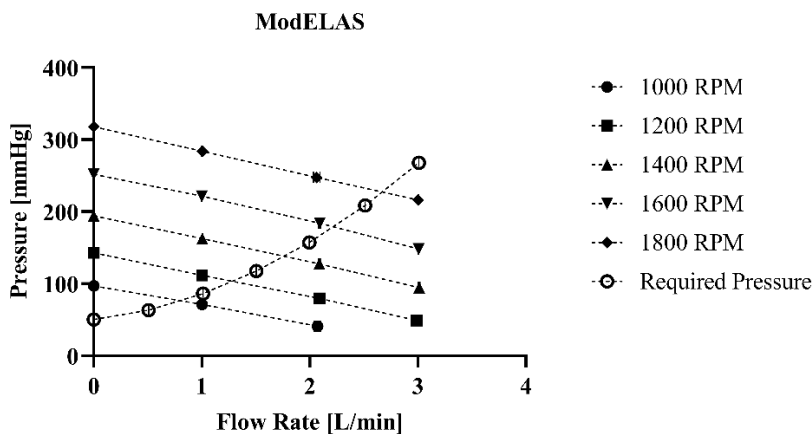


Figure 3.1: Generated pressure heads as a function of flow rate at impeller rotation rates of 1000, 1200, 1400, 1600, and 1800 RPM for the ModELAS

the most critically ill pediatric patient population.

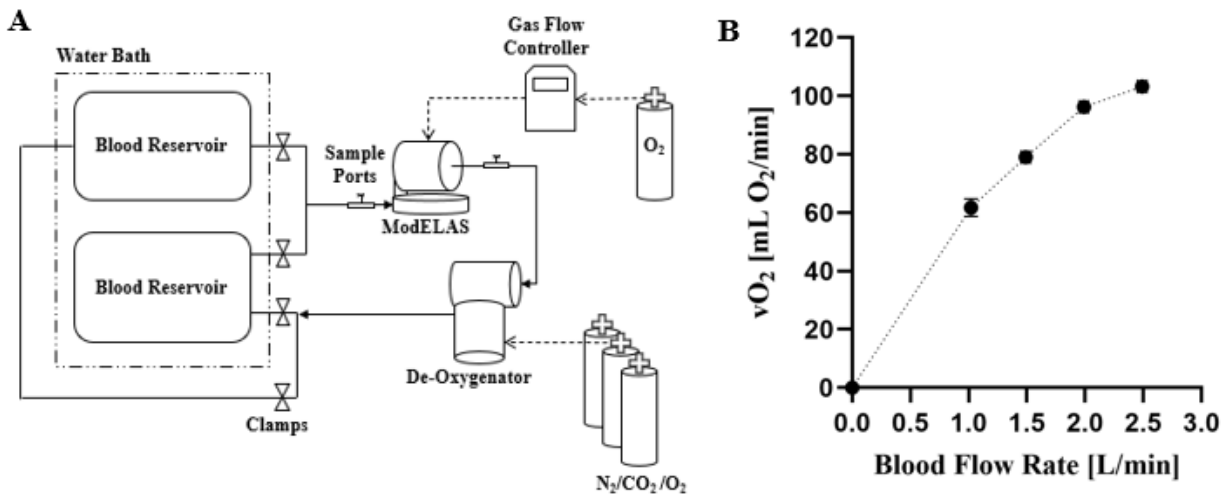
### 3.2 In-Vitro Oxygenation

Oxygenation rates of the HFM bundle were evaluated in bovine blood collected from the abattoir (Thoma Meat Market, Saxonburg, PA). Post-collection, blood was treated with heparin (15 IU/mL) and gentamicin (0.1 mg/mL), filtered (40  $\mu$ m filter, Pall Biomedical Inc., Fajardo, PR), and adjusted to a hemoglobin (Hb) of  $12 \pm 1$  g/dL with phosphate buffered saline (PBS). The test circuit (Figure 3.2A) was composed of two compliant blood reservoirs submersed in a heated water bath, an Affinity oxygenator, and the ModelAS. The heated water bath maintained blood temperature at  $37 \pm 2^\circ$ . Blood was circulated through a single reservoir and brought to venous conditions (oxygen saturation ( $SO_2$ ) =  $65 \pm 5\%$  and partial pressure of  $CO_2$  ( $PCO_2$ ) =  $45 \pm 5$  mmHg) using a blend of  $N_2$ ,  $CO_2$ , and  $O_2$  gases flowed through the Affinity oxygenator. Once conditioned, blood was directed from the conditioned reservoir through the ModelAS and collected in the second reservoir. During this time gas flow through the Affinity was ceased and pure

oxygen sweep gas passed through the ModelAS at a flow rate of 5 L/min with a GR series mass flow controller (Fathom Technologies, Georgetown, TX). Blood samples were taken from the inlet and outlet of the test device at blood flow rates of 1-2.5 L/min in 0.5 L/min increments. An ultrasonic flow probe (Transonic System Inc., Ithaca, NY, USA) monitored blood flow rate. Three repeated measurements were taken at each blood flow rate. Blood samples were analyzed with a RAPIDPoint 405 blood gas analyzer (Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA). Oxygenation rates were calculated using the equation:

$$\dot{V}_{O_2} = Q[\alpha_{O_2}\Delta P_{O_2} + 10C_tHb\Delta S] \quad [1]$$

where  $\dot{V}_{O_2}$  is the oxygenation rate (mL  $O_2$ /min),  $Q$  is the volumetric blood flow rate (L/min),  $\alpha_{O_2}$  is the solubility of oxygen in blood ( $3E-5$  (mL  $O_2$ )(mL blood) $^{-1}$ (mmHg) $^{-1}$ ),  $\Delta P_{O_2}$  is the  $O_2$  partial pressure differential across the device (mmHg),  $C_t$  is the binding capacity of Hb for  $O_2$  ( $1.34$  (mL  $O_2$ )(g Hgb) $^{-1}$ ), Hb concentration is in units of g/dL, and  $\Delta S$  is the fractional oxygen saturation differential (%) across the device. Oxygenation rates for the ModelAS are displayed in Figure 3.2B.



*Figure 3.2: A: Circuit for measuring in vitro oxygenation rates in blood. The clamps at the inlet and outlet of the blood reservoirs controls which reservoir the blood leaves from and returns to. Blood is recirculated through one reservoir until conditioned. Once conditioned, blood is directed from the conditioned reservoir, through the test device, and returned to the second empty reservoir. B: In Vitro oxygenation rates for the ModELAS over varying blood flow rates.*

Oxygenation increased with increasing blood flow rate and reached a maximum of 107 mL/min at the highest blood flow rate of 2.5 L/min. This oxygenation rate fulfills the performance specification of achieving approximately 90% of the oxygenation needs of a 25 Kg child.

### 3.3 In-Vitro Hemolysis

Hemolysis testing was performed at 2.5 L/min with bovine blood collected from the abattoir (Thoma Meat Market, Saxonburg, PA). Blood was treated in the same manner as in the oxygenation experiments, except diluted to a hematocrit of  $30 \pm 2\%$  with PBS according to ASTM F1841-97. The ModELAS was evaluated in parallel with a control circuit consisting of a Lilliput 2 oxygenator (Sorin Group, Mirandola, Italy) and a Centrimag blood

pump (Abbott Laboratories, Chicago, IL, USA). Each circuit consisted of the device connected to a compliant reservoir (MVR800, Medtronic, Minneapolis, MN, USA) submerged within a heated water bath. The water bath maintained a blood temperature of  $37 \pm 2^\circ\text{C}$  over the course of the experiment. A hoffman clamp at the outlet of the device was used to adjust the pressure differential across the device to 100 mmHg. Blood was circulated for a total of 6 hours during which measurements of hematocrit and plasma free Hb (PfHb) were collected every 30 minutes. A normalized index of hemolysis value (NIH) was calculated according to previously published methods (Figure 3.3).<sup>23</sup> 3 experiments were performed comparing the ModELAS and the control device.

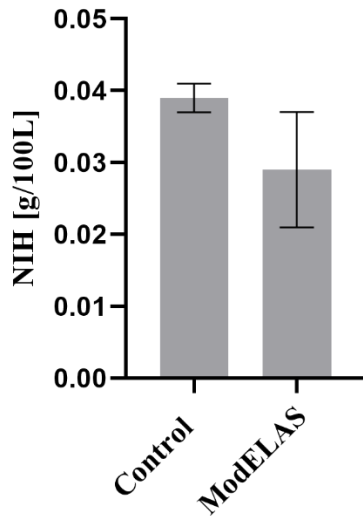


Figure 3.3: NIH values for the control and the ModelAS circuit.

An unpaired t-test showed there is no difference ( $p > 0.05$ ) between the NIH calculated for the control and ModelAS circuits. The mean NIH of the ModelAS device is  $0.029 \pm 0.008$ . This value is 28% smaller than the NIH of the only similar device in development, the PediPL, at the same flow rate.<sup>24</sup>

#### 4. In-Vivo Studies

The ModelAS can accommodate three levels of respiratory support using different HFM bundles mounted on a universal centrifugal pump platform. The adult application has been tested in 6-hour,<sup>18</sup> 5-day,<sup>20</sup> and month-long studies<sup>19</sup> in an ovine model. The ECCO<sub>2</sub>R application has been validated in 7-day ambulatory sheep studies.<sup>21</sup> Finally, the pediatric application has undergone acute testing in a sheep model,<sup>22</sup> the details of which are reviewed below.

### 4.1 Completed Pediatric In-Vivo Work

#### 4.1.1 Methods

The goal of these pediatric ovine studies was to evaluate acute in-vivo device performance as well as develop an ideal surgical strategy for future chronic studies. A total of 6 healthy sheep (23.3-32.2 kg) underwent clinical trials at the Center for Preclinical Studies at the McGowan Institute for Regenerative Medicine. All animals received human care according to a protocol approved by the University of Pittsburgh's Institutional Animal Care and Use Committee.

A subcutaneous injection of atropine (0.05 mg/kg) and an intravenous injection of ketamine (3.9-5.3 mg/kg) were used to induce anesthesia. Inhaled isoflurane (1.5-3%) maintained anesthesia throughout the study duration and ventilator settings were adjusted to maintain normal physiologic blood gas values. Mean arterial pressure (MAP) was monitored throughout the study via an arterial line in the carotid artery. Central venous pressure (CVP) and maintenance drips were monitored and provided through a venous line in the jugular vein. MAP, CVP, and heart rate (HR) were recorded every 15 minutes throughout the study duration.

A heparin bolus of 300 IU/kg was administered prior to cannulation to achieve an activated clotting time (ACT) of greater than twice the baseline of the animal. The venous cannula was placed in the right atrium and the arterial cannula was placed in the pulmonary artery. Cannulation of the right atrium and pulmonary artery were achieved through a left thoracotomy for the first two trials. Surgical access to the heart was achieved via a right thoracotomy after venous.



*Table 4.1: Summary of Pediatric Acute Clinical Trials*

Trial	Surgical Access	Cannula Type	Device	Flow Rate	Duration (hrs)	Comment
1	Left Thoracotomy	18 Fr Straight (venous) 16 Fr Straight (arterial)	P-PAL	1.0-2.5	4.5	N/A
2	Left Thoracotomy	22 Fr Right Angle (venous) 16 Fr Straight (arterial)	P-PAL	1.0-1.4	4	Venous Cannula Occlusion
3	Right Thoracotomy	22 Fr Right Angle (venous) 16 Fr Straight (arterial)	P-PAL	1.0-2.5	6	N/A
4	Right Thoracotomy	22 Fr Right Angle (venous) 16 Fr Straight (arterial)	P-PAL	1.0-2.4	6	Increased Bundle Resistance
5	Right Thoracotomy	22 Fr Right Angle Metal Tip (venous) 18 Fr Straight (arterial)	ModELAS	1.0-2.5	6	N/A
6	Right Thoracotomy	22 Fr Right Angle Metal Tip (venous) 18 Fr Straight (arterial)	ModELAS	1.0-2.5	6	N/A

occlusion occurred in trial 2. A targeted ACT of 1.5-2 times baseline was maintained over the study duration via continuous heparin administration through the venous line.

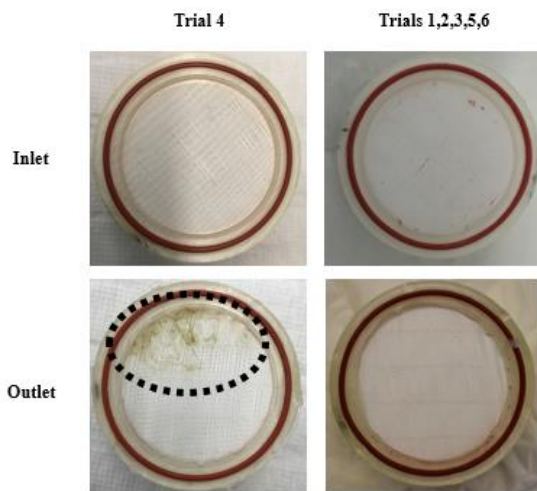
Cannulas were connected to a device primed with 1 U/mL heparinized saline. Trials 1-4 were completed with a P-PAL and trials 5-6 were completed with a ModELAS. A period of 10 minutes was allowed to pass after the initiation of blood and sweep gas flow (mix of 5% CO<sub>2</sub> and 95% O<sub>2</sub> at 3-5 L/min) before samples were collected for gas exchange. Pressure drop across the HFM bundle was measured continuously (PCU-2000, Millar, TX). The impeller rotation rate was modulated to attain targeted blood flow rates of 1, 1.5, 2, and 2.5 L/min over the course of three repeated measurements. Device inlet and outlet samples were evaluated for blood gas tensions and hematocrit for each measurement. Blood samples for Pfhb analyses<sup>23</sup> were taken at baseline, pump on, and every hour after until study termination. All studies were electively terminated after data collection was completed. The heart and lungs were

examined for gross anomalies upon study completion. The device was removed and passively washed with saline to remove blood while retaining intra-device thrombus.

#### **4.1.2 Results**

Table 4.1 summarizes the cannulas, cannulation strategy, device type used, flow rates experienced, duration, and complications of each trial. Surgical access to the heart and cannula selection was refined over the series of acute studies. In trial 2 flow rate was limited by venous cannulation occlusion due to suction onto the right atrial wall. Pivoting from a left to right thoracotomy allowed for better cannula placement and subsequent studies were free from suck-down events. The final iteration of cannula selection, a 22 Fr right angle metal tip venous and a 18 Fr straight arterial, provided improved venous drainage and arterial return and eased cannula tunneling. Future studies will therefore use a right thoracotomy for surgical access to the heart with venous drainage achieved via a 22 Fr right angle metal tip cannula and arterial return via an 18 Fr arterial cannula.

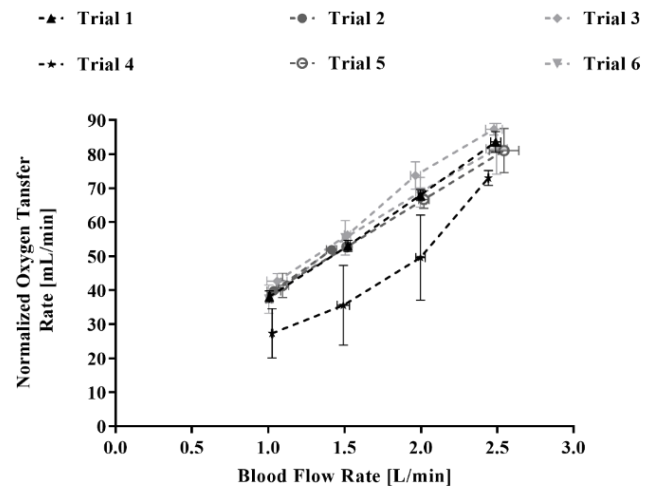
The venous cannula occlusion that occurred in trial 2 limited the device flow range to 1.0-1.4 mL/min. The necropsy revealed right atrium bruising indicating cannula suction onto the right atrium wall. No other trial exhibited device related trauma to the heart or lungs. In trial 4, thrombus formed throughout the HFM bundle resulting in decreased oxygenation and increased HFM bundle resistance (11 mmHg/L/min to 120 mmHg/L/min). It was suspected that improper priming of the device before implantation was responsible. No other devices exhibited thrombus formation within the HFM bundle (Figure 4.1) or pumping compartments.



*Figure 4.1: Photographs of a bundle inlet and outlet face representative of typical study (trials 1-3, 5, and 6) and that of trial 4. Black dotted oval indicates the area of clot formation in the fourth trial.*

The maximum oxygenation rate of the completed trials was  $83.7 \pm 3.5$  mL/min at 2.5 L/min blood flow rate (Figure 4.2).

The in-vivo oxygenation rate was limited by intraoperative anemia most likely resulting from surgical hemodilution and red blood cell sequestration. The mean Hb experienced across all animal studies was  $6.2 \pm 0.3$  g/dL and blood exiting the device was 100% saturated with the exception Trial 4 (due to intra-bundle thrombus formation). The oxygenation rates experienced in-vivo are therefore not representative of the full capabilities of the device. In chronic studies it is expected that Hb values will return to near baseline as recovery progresses. A two-way ANOVA showed there was no effect of test device (P-PAL or ModELAS) on oxygenation rate ( $p > 0.05$ ).



*Figure 4.2: In-vivo oxygenation rates.*

Device support was hemodynamically well-tolerated (Table 4.2). Baseline data is the average of vital signs taken during the 30 minutes prior to device implantation and final data is a summary of all data points taken in the last hour of the study. Baseline and final MAP, CVP, and HR values were compared using a paired samples t-test for each animal. Statistical significance was considered for a p value less than 0.05.

Table 4.2: Baseline and Final Animal Hemodynamics

Trial No.	MAP (mmHg)		CVP (mmHg)		HR (beats/min)	
	Baseline	Final	Baseline	Final	Baseline	Final
1	65 ± 5	54 ± 1	9 ± 2	9 ± 1	95 ± 13	88 ± 2
2	89 ± 5	64 ± 10*	8 ± 1	5 ± 1	81 ± 5	80 ± 1
3	52 ± 6	5 ± 4	6 ± 2	4 ± 1	94 ± 4	97 ± 2
4	62 ± 14	53 ± 5	11 ± 2	7 ± 1*	93 ± 5	95 ± 8
5	68 ± 15	49 ± 6	7 ± 2	5 ± 1	89 ± 15	102 ± 5
6	61 ± 21	41 ± 1	5 ± 4	10 ± 1	92 ± 19	95 ± 1

\* p<0.05, considered significant between baseline and final values

Baseline and final HR were not significantly different for any animal. The MAP of trial 2 statistically decreased and the MAP of trial 5 statistically increased. In trial 4 the CVP statistically decreased. These significant changes in MAP and CVP were not consistent and concerning trends were not observed.

PfHb levels greater than 50 mg/dL are considered clinically relevant levels of hemolysis.<sup>25</sup> PfHb for all trials remained below 20 mg/dL (Figure 4.3).

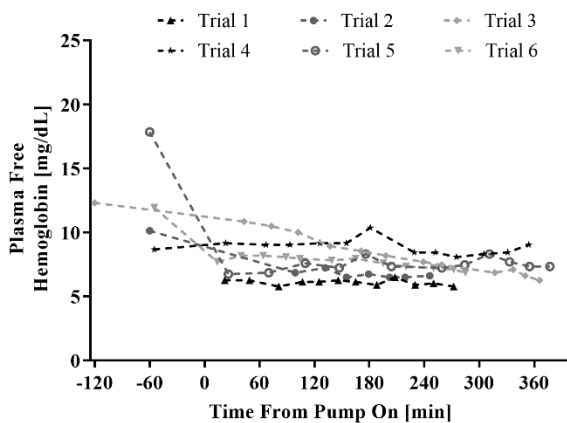
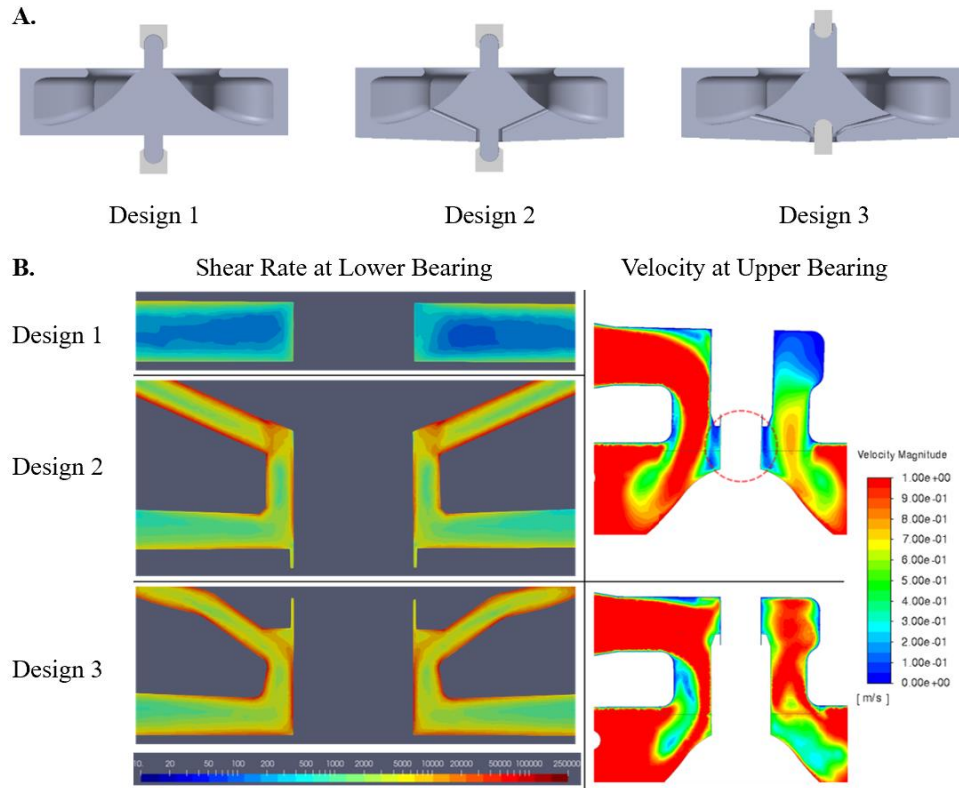


Figure 4.3: In vivo PfHb generated by the test devices.

#### 4.2 Impeller Modifications for Future In-Vivo Month-Long Pediatric Studies

The adult application of the MODELAS underwent month-long chronic studies<sup>19</sup> after the acute pediatric in-vivo tests were completed. The two-pivot bearing design underwent evolution over the course of these trials, resulting in a total of 3 designs being tested (Figure 4.4). The impeller design utilizes permanent magnets imbedded within the impeller coupled to an external motor plate.

In the first impeller design, the design also used in the pediatric in-vivo studies, pivots were located at either end of the impeller shaft and nested in ultra-high molecular weight polyethylene cups embedded into the impeller housing. Wear studies showed that both the bearing and cups withstand at least 30 days of use without deformation (data not shown). In in-vivo studies thrombus generation at the pivot sites resulted in increases in motor torque greater than 50% and clinically significant levels of hemolysis within 2-3 weeks of support. The ceramic bearings were replaced with smoother zirconium bearings to reduce surface roughness and frictional heating. Thrombus formation and hemolysis persisted despite the change of bearing material.



*Figure 4.4: A: Cross section view of the impeller bearing designs. B: CFD predicted shear rates (left column) and velocities (right column) for the lower and upper bearings respectively. Colored spaces indicate blood filled pathways on a cross sectional view of the device bearings. Colors correlate to the displayed scales in each image.*

Six cylindrical ports ~0.8 mm in diameter were included in the impeller (Design 2) to draw blood away from the lower pivot and eliminate the stagnation present in the first impeller design. CFD analysis showed that these “wash-out holes” passively flushed blood away from the lower bearing and increased modeled shear rates. These changes reduced lower bearing thrombus generation and ameliorated clinical levels of hemolysis. An increase in motor torque (< 20%) still developed over 2-3 weeks of support and upper bearing thrombus formed in the area of stasis depicted in Figure 4.4 (encircled in red).

The pivot-cup bearing orientation was inverted and the geometry of the washout holes was modified in Design 3 to eliminate flow separation and increase shear at both the upper and lower bearings. 4 of 5 in-vivo trials with this final pivot-bearing design completed the month-long trial without increases in torque and none of the trials experienced clinical levels of hemolysis. The third impeller design will be utilized in planned month long pediatric in-vivo studies as a result of its improvement to device reliability.

## 5. Conclusion

Acute and chronic respiratory failure remain a global health concern for the pediatric population. When conventional therapies fail, IMV and ECMO are employed to bridge patients to recovery or transplant. The supply and demand chain for donor lungs is unbalanced, with the number of waitlisted patients outnumbering available organs. Patients therefore may rely on IMV or ECMO for extended periods of time. These therapies, however, have historically been related with poor transplant outcomes. Patients able to participate in physical therapy while on ECMO have improved post-transplant outcomes compared to sedated counterparts. A push towards reducing the complexity and size of circuit components has evolved to enable patients on ECMO to ambulate with greater safety and less difficulty. Our group has developed an integrated pump-lung device, the ModELAS, intended to ease patient ambulation while providing support to three patient populations.

The pediatric application of the ModELAS was designed to provide 90% of the respiratory support required for a patient between 5 and 25 kg. This corresponds to an oxygenation rate of 35-106 mL/min at blood

flow rates ranging from 1.0 to 2.5 L/min. In-vitro testing of the device showed that the designed centrifugal pump and HFM bundle were able to provide the required pressure head and oxygenation rate for in-vivo use while maintaining an acceptable level of hemolysis. 6-hour acute studies were then performed to determine implantation and cannulation strategies. The device was hemodynamically well tolerated with no clinical hemolysis or concerning trends in MAP, CVP, or HR. A right thoracotomy with a 22 Fr right angled metal tipped venous cannula and 18 Fr straight arterial cannula will be used for future chronic studies.

A course of month-long studies with the adult application of the ModELAS have been performed since the acute pediatric studies. The centrifugal pump in the ModELAS underwent 2 design iterations during the adult studies. The final iteration of the impeller, with which 4 of 5 animal studies completed a month long in-vivo trial, will be used in planned pediatric chronic studies. The pediatric and adult configurations of the ModELAS are identical except for the fiber bundle size. It is therefore believed that the month-long studies of the pediatric configuration ModELAS will demonstrate similar device reliability to that of the adult configuration.

## References

1. Moore BJ, Freeman WJ, Jiang HJ. *Costs of Pediatric Hospital Stays, 2016*. Agency for Healthcare Research and Quality; 2019:12. <https://www.hcup-us.ahrq.gov/reports/statbriefs/sb250-Pediatric-Stays-Costs-2016.pdf>
2. Khemani RG, Markovitz BP, Curley MAQ. Characteristics of Children Intubated and Mechanically Ventilated in 16 PICUs. *Chest*. 2009;(136):765-771. doi:10.1378/chest.09-0207
3. *International Summary - January 2017*. Extracorporeal Life Support Organization; 2017:1-34. Accessed December 15, 2021. <https://www.else.org/portals/0/files/reports/2017/international%20summary%20january%202017.pdf>
4. *International Summary - October 2021*. Extracorporeal Life Support Organization; 2021.
5. Thompson K, Staffa SJ, Nasr VG, et al. Mortality after Lung Transplantation for Children Bridged with Extracorporeal Membrane Oxygenation. *Annals ATS*. Published online October 7, 2021:AnnalsATS.202103-2500C. doi:10.1513/AnnalsATS.202103-2500C
6. Field-Ridley A, Dharmar M, Steinhorn D, McDonald C, Marcin JP. Intensive Care Unit-Acquired Weakness (ICU-AW) is Associated With Differences in Clinical Outcomes in Critically Ill Children. *Pediatr Crit Care Med*. 2016;17(1):53-57. doi:10.1097/PCC.0000000000000538
7. Rehder KJ, Turner DA, Hartwig MG, et al. Active Rehabilitation During Extracorporeal Membrane Oxygenation as a Bridge to Lung Transplantation. *Respiratory Care*. 2013;58(8):1291-1298. doi:10.4187/respcare.02155
8. Hayes D, Kukreja J, Tobias JD, Ballard HO, Hoopes CW. Ambulatory venovenous extracorporeal respiratory support as a bridge for cystic fibrosis patients to emergent lung transplantation. *Journal of Cystic Fibrosis*. 2012;11(1):40-45. doi:10.1016/j.jcf.2011.07.009
9. Turner DA, Cheifetz IM, Rehder KJ, et al. Active rehabilitation and physical therapy during extracorporeal membrane oxygenation while awaiting lung transplantation: A practical approach\*. *Critical Care Medicine*. 2011;39(12):2593-2598. doi:10.1097/CCM.0b013e3182282bbe
10. Mohite P, Sabashnikov A, Reed A, et al. Extracorporeal Life Support in “Awake” Patients as a Bridge to Lung Transplant. *Thorac Cardiovasc Surg*. 2015;63(08):699-705. doi:10.1055/s-0035-1546429
11. Fuehner T, Kuehn C, Hadem J, et al. Extracorporeal Membrane Oxygenation in Awake Patients as Bridge to Lung Transplantation. *Am J Respir Crit Care Med*. 2012;185(7):763-768. doi:10.1164/rccm.201109-1599OC
12. Turner DA, Rehder KJ, Bonadonna D, et al. Ambulatory ECMO as a Bridge to Lung Transplant in a Previously Well Pediatric Patient With ARDS. *Pediatrics*. 2014;134(2):e583-e585. doi:10.1542/peds.2013-3435
13. Schmidt F, Jack T, Sasse M, et al. Back to the roots? Dual cannulation strategy for ambulatory ECMO in adolescent lung transplant candidates: An alternative? *Pediatric Transplantation*. 2017;21(4):e12907. doi:10.1111/ptr.12907
14. Scott S, Escobar M, Brown C, et al. THE USE OF VA ECMO AS A BRIDGE TO PEDI- ATRIC HEART-LUNG TRANSPLANT: A CASE REPORT. *Critical Care Medicine*. 2020;48(1):80.

- doi:10.1097/01.ccm.0000619136.93084.d6
15. Hayes D, Galantowicz M, Preston TJ, et al. Cross-country transfer between two children's hospitals of a child using ambulatory extracorporeal membrane oxygenation for bridge to lung transplant. *Pediatr Transplantation*. 2013;17(5):E117-E118. doi:10.1111/petr.12098
  16. Orizondo RA, May AG, Madhani SP, et al. In Vitro Characterization of the Pittsburgh Pediatric Ambulatory Lung. *ASAIO Journal*. Published online December 2017. doi:10.1097/MAT.0000000000000711
  17. Madhani SP, Frankowski BJ, Federspiel WJ. Fiber Bundle Design for an Integrated Wearable Artificial Lung. *ASAIO Journal*. 2017;63(5):631-636. doi:10.1097/MAT.0000000000000542
  18. Madhani SP, Frankowski BJ, Burgreen GW, et al. In vitro and in vivo evaluation of a novel integrated wearable artificial lung. *The Journal of Heart and Lung Transplantation*. 2017;36(7):806-811. doi:10.1016/j.healun.2017.02.025
  19. Orizondo RA, Omecinski KS, May AG, et al. Month-long Respiratory Support by a Wearable Pumping Artificial Lung in an Ovine Model. *Transplantation*. 2021;105(5):999-1007. doi:10.1097/TP.0000000000003481
  20. Madhani SP, Frankowski BJ, Ye SH, et al. In Vivo 5 Day Animal Studies of a Compact, Wearable Pumping Artificial Lung: *ASAIO Journal*. Published online December 2017;1. doi:10.1097/MAT.0000000000000740
  21. May AG, Orizondo RA, Frankowski BJ, et al. In vivo testing of the low-flow CO2 removal application of a compact, platform respiratory device. *ICMx*. 2020;8(1):45. doi:10.1186/s40635-020-00329-9
  22. May AG, Orizondo RA, Frankowski BJ, Wearden PD, Federspiel WJ. Acute In Vivo Evaluation of the Pittsburgh Pediatric Ambulatory Lung: *ASAIO Journal*. 2019;65(4):395-400. doi:10.1097/MAT.0000000000000918
  23. Svitek RG, Frankowski BJ, Federspiel WJ. Evaluation of a Pumping Assist Lung That Uses a Rotating Fiber Bundle. *ASAIO J*. 2005;51(6):773-780. doi:10.1097/01.mat.0000178970.00971.43
  24. Wu ZJ, Gellman B, Zhang T, Taskin ME, Dasse KA, Griffith BP. Computational Fluid Dynamics and Experimental Characterization of the Pediatric Pump-Lung. *Cardiovasc Eng Tech*. 2011;2(4):276-287. doi:10.1007/s13239-011-0071-5
  25. Brogan T. *Extracorporeal Life Support: The ELSO Red Book*. 5th ed. (Brogan T, Lequier L, Lorusso R, MacLaren G, Peek GJ, eds.). ELSO and Seminars in Perinatology; 2017.