A Novel Oxygenator-Right Ventricular Assist Device Circuit Using the SYNERGY Micropump as Right Heart Support in a Swine Model of Pulmonary Hypertension

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Abstract—

Objectives

As clinical experience with extracorporeal life support (ECLS) continues to grow, pulmonary hypertension (PH) remains a potential target for intervention and investigation. PH is a rare but severe, progressive disease that can lead to right heart failure and death. ECLS has the potential to ameliorate both the pulmonary and cardiac dysfunction associated with PH, and thus provide a life saving intervention in this disease.

Methods

In this study, we assessed the blood biocompatibility of the SYNERGY micropump in conjunction with a Quadrox D oxygenator in a novel oxygenator-right ventricular assist device (OxyRVAD) extracorporeal membrane oxygenation (ECMO) circuit in a swine model of acute PH. Four pigs were placed on OxyRVAD ECMO. PH was induced by banding the pulmonary artery. After banding, mean pulmonary artery pressure (mPAP) increased from 17 mmHg to 39 mmHg.

Results

All animals survived 6 hours without catastrophic biocompatibility issues. There were no significant differences in hemoglobin, plasma-free hemoglobin, or platelets from baseline. Platelet activation – assessed by plasma P-selectin – did not increase during the run. Indirect measurements of hemolysis were assessed by total bilirubin and lactate dehydrogenase. Total bilirubin did not change significantly. The average increase in lactate dehydrogenase was significant.Fibrinogen and D-dimer levels were significantly decreased from baseline.

Conclusion

OxyRVAD showed no catastrophic failures in this short-term test. Micropump OxyRVADs may have a role in the management of PH.

Keywords— extracorporeal membrane oxygenation, ECMO, SYNERGY micropump, OxyRVAD

I. INTRODUCTION

Extracorporeal life support (ECLS) is an important life-saving therapy for refractory cardiopulmonary failure.[1-2]Technological advances as well as growing clinical experience continues to improve outcomes and extend the range of ECLS applications. Miniaturized pumps now allow for smaller, lighter systems, opening up possibilities for life-saving interventions with ECLS in mobile emergency, pediatric, bridge-to-transplant, and even combat environments.[3-8] At the same time, novel circuit configurations allow for better physiologic optimization and broaden the scope of disease that can be managed effectively with ECLS.[9]

In this study, we assess the hematologic biocompatibility of the SYNERGY (HeartWare International, Inc., Framingham, MA) miniature blood pump in conjunction with a Quadrox D oxygenator (Maquet, Inc., Rastatt, Germany) in a novel oxygenator/right ventricular assist device (OxyRVAD) circuit in an acute pulmonary hypertension (PH) model. Hemolysis and coagulation system effects remain the principle safety concerns with new pump and oxygenator technology in ECLS circuits.[10] A prior study using the SYNERGY pump in a standard extracorporeal membrane oxygenation (ECMO) circuit in healthy swine found no discernable effect on measures of hemolysis or the coagulation system.[11] We built on these results by testing the SYNERGY micropump in an animal PH model and with a novel ECLS circuit designed to optimize therapy for PH and right heart failure. Plasma-free hemoglobin (PFH), total hemoglobin, platelets, P-selectin, total bilirubin, lactate

dehydrogenase, D-dimer, and fibrinogen were measured to assess blood biocompatibility.

II. MATERIAL AND METHODS

The study was performed under an approved protocol from the Columbia University Institutional Animal Care and Use Committee. A total of four (n = 4) animals underwent initiation of right atrial to pulmonary artery OxyRVAD using a SYNERGY-Quadrox circuit shown in **Figure 1**. Anticoagulation was maintained during the study with hourly boluses of unfractionated heparin.

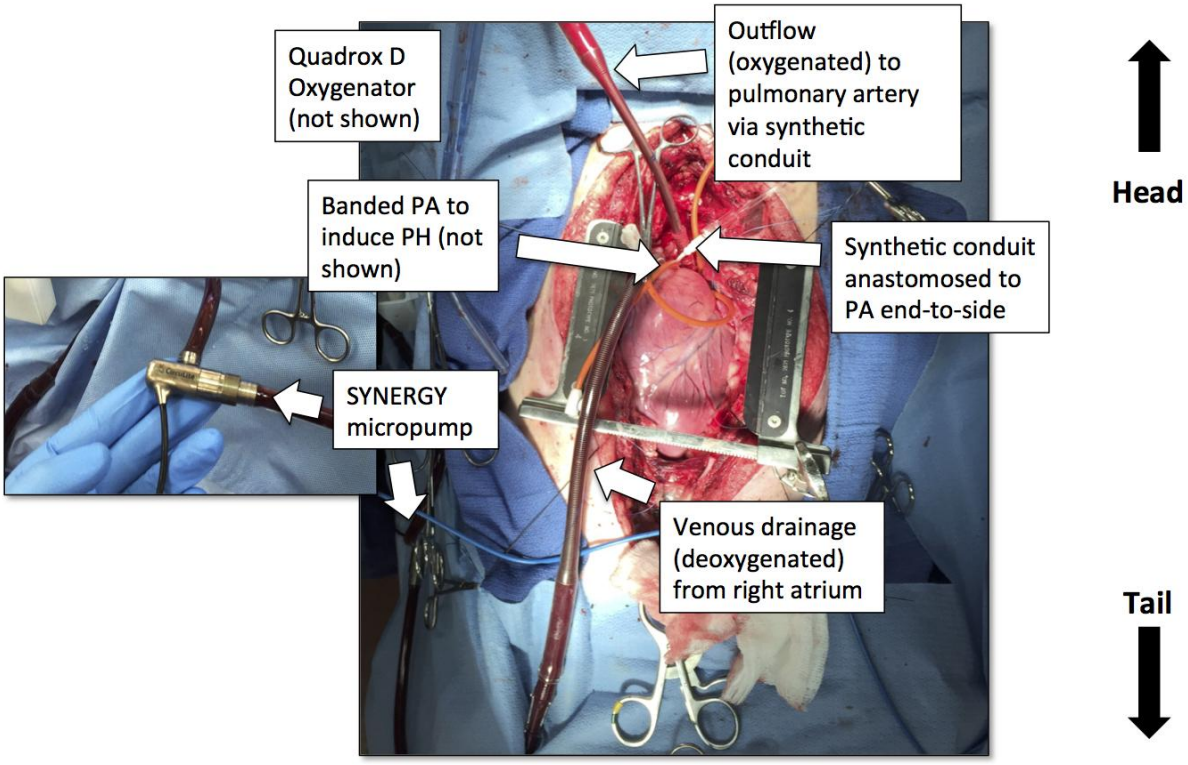

FIGURE 1. OXYRVAD ECMO CIRCUIT DESIGN

The four animals ranged in size from 56 to 62 kg. All animals were premedicated with intramuscular telazol (2.0–5.0 mg/kg). They were induced with 2% to 3% isoflurane by facemask, endotracheally intubated, and maintained on 0.75% to 3% isoflurane. Ventilation was provided through endotracheal intubation with 100% FIO_2at a rate between 4 and 10 breaths/min and tidal volumes between 3 and 12 mL/kg. Ventilator settings were adjusted to maintain an end-tidal CO_2pressure between 17 and 45 mmHg. Before cannulation, the SYNERGY-Quadrox ECMO circuit was primed with 500 mL of Ringer's lactate. The right femoral artery was cannulated with a 20 Ga arterial catheter for use in blood draws, arterial blood gases, and blood pressure monitoring.

The pigs were prepped and draped in a sterile fashion and a midline sternotomy was made. The pericardium was opened and the great vessels dissected. An intravenous bolus of 15,000 U of unfractionated heparin was administered. The right atrium was cannulated with a 23 Fr right angle venous drainage cannula and secured with a 3-0 Prolene pursestring suture and snare. The pulmonary artery was dissected away from surrounding tissue and controlled with umbilical tape. A 6 mm Hemashield (Boston Scientific, Natick, MA) graft was sewn to the pulmonary artery in an end to side fashion distal to the umbilical tape band. An 18 Fr Elongated One Piece Arterial cannula was inserted into the graft in a sleeve-like fashion and secured to the graft using silk ligatures. The cannulae were attached to the circuit via a Cobe E Pack 3/8-inch tubing (Sorin Group, Milan, Italy). Prior to initiating the ECMO circuit flow, the umbilical tape around the pulmonary artery was snared down gradually to induce pulmonary hypertension. Pulmonary vascular pressures were monitored via a pressure monitor placed transmurally in the right ventricle across the pulmonic valve. After banding, mean pulmonary artery pressure (mPAP) increased from 17 mmHg to 39 mmHg.

After induction of pulmonary hypertension, flow in the OxyRVAD ECMO circuit was initiated with the SYNERGY pump operating at 20,000 RPM and increasing slowly to 25,000–30,000 RPM per the manufacturer's recommendation, which provided an average of 2.29 ± 0.30 L/min of flow.Sweep gas was 100% oxygen and was maintained between 1.0 and 4.0 L/min of flow (**Table 1**). Minute ventilation was adjusted based on end-tidal CO_2monitoring, as well as swine arterial blood gas measurements. The ECMO run was 6 hours for each pig, and 1,000 U of unfractionated heparin were given hourly.

TABLE 1
EXTRACORPOREAL MEMBRANE OXYGENATION COMPONENT PARAMETERS

Table 1. ECMO Component Parameters							
Pump					**Oxygenator**		
					Pressure		
Hour	RPM	Pump flow	Sweep		Pre oxygenator	Post oxygenator	Delta
-0.5							
0	21,000	1.66	2.25		68.8	64.0	4.8
1	25,500	2.15	2.63		83.0	75.0	8.0
2	27,375	2.43	2.43		98.8	90.8	8.0
3	28,000	2.46	1.81		98.3	91.5	6.8
4	28,000	2.51	2.44		103.8	97.3	6.5
5	29,250	2.41	2.38		92.8	85.0	7.8
6	29,250	2.38	2.50		94.0	85.8	8.3
Average	26,911	2.29	2.36		91.3	84.2	7.1
SD	2,900	0.30	0.28		11.9	11.3	1.2

2.1 Blood Collection

Preoperative blood, hourly arterial blood gases, and whole blood at 2-hour intervals were collected from each animal by the femoral arterial line. Whole blood was collected in Vacutainer (Becton Dickinson, Franklin Lakes, NJ) K2EDTA tubes for hematology measurements, sodium citrate tubes for activated partial thromboplastin (aPTT) measurements, and serum separating tubes with silica clot activator for blood chemistry measurements. Blood was collected in citrate tubes and immediately spun down in a centrifuge for serum collection, storage, and freezing at −80°C in 1.8 mL Nunc CryoTubes (Thermo Fisher Scientific, Waltham, MA) for measurements of PFH, P-selectin, D-dimer, and fibrinogen.

Hematology and coagulation measurements were performed by the Columbia University Institute for Comparative Medicine Animal Diagnostic Laboratory and normalized for dilution effects.

2.2 Hematologic Analysis

Plasma-free hemoglobin, P-selectin, D-dimer, and fibrinogen levels were measured in serum samples from swine by sandwich enzyme-linked immunosorbent assay using the reagents and protocol supplied with the swine-specific kits (NeoBioLab, Cambridge, MA) according to the manufacturer's instructions. The final concentration of each protein was measured by spectrophotometry at a wavelength of 450 nm and expressed in nanograms per milliliter (ng/mL). A standard curve was plotted relating the intensity of the color to the concentration of standards. The protein concentration in each sample was interpolated from this standard curve.

2.3 Statistical Analysis

Continuous variables are shown as mean with standard deviation. Data were compared with nonparametric repeated measures analysis of variance using Friedman's test (SPSS Software v21.0, IBM, Armonk, NY). A p value of <0.05 was considered significant.

III. RESULTS AND DISCUSSION

All animals completed the study protocol for 6 hours. ECMO pump flow was maintained at an average of 2.29 ± 0.30 L/min throughout the study period, sweep gas flow was 2.36±0.28 L/min, and the SYNERGY pump was kept at a mean of 26,911 RPM (**Table 1**).

All study animals remained stable during the study period with mean arterial PaO_2 and $PaCO_2$ of 456.0 ± 47.7 mmHg and 33.0 ± 5.0, respectively (**Table 2**), and mean SpO2 of 98.3 ± 2.0%. Minute ventilation was adjusted to maintain end-tidal CO_2between 17 and 45 mmHg. These adjustments led to a 22% to 74% pre- and post-ECMO reduction in minute ventilation. Additionally, the pressure gradient across the oxygenator remained low throughout the study at 7.1±1.2 mmHg (**Table 1**). Oxygen transfer ranged from 48.0 to 103.0 mL/min throughout the study period (**Table 3**). We do not measure activated clotting times during ECMO runs but rather use aPTT times. In these four pigs, we measured aPTT, although were not able to titrate heparin dosing based on these results because of the time lag in processing the samples. We report the aPTT in **Table 4**.

TABLE 2
BLOOD GAS MEASUREMENTS

	Preoxygenator					Postoxygenator					Pig			
Hour	pH	$PaCO_2$	PaO_2	O_2 Sat (%)		pH	$PaCO_2$	PaO_2	O_2 Sat (%)		pH	$PaCO_2$	PaO_2	O_2 Sat (%)
-0.5											7.467	42.1	503.7	98.8
0	7.42	43.2	34.9	78.8		7.56	25.2	261.1	99.9		7.47	41.0	489.1	98.8
1	7.47	35.8	30.0	68.7		7.54	27.4	276.9	99.9		7.58	26.4	484.0	98.5
2	7.41	40.8	29.4	76.0		7.47	33.6	328.2	99.9		7.50	29.2	381.9	97.8
3	7.44	37.1	31.3	70.8		7.48	24.7	329.0	99.9		7.50	31.2	492.2	95.5
4	7.40	46.4	31.9	82.1		7.49	33.4	359.2	99.9		7.47	36.3	452.7	98.0
5	7.40	42.5	34.1	78.0		7.49	30.6	329.4	99.9		7.48	31.1	397.3	98.3
6	7.39	45.1	27.8	80.8		7.46	33.9	315.3	99.9		7.48	35.9	494.9	99.0
Average	7.42	41.3	31.3	76.0		7.50	29.8	314.1	99.9		7.49	33.0	456.0	98.0
SD	0.03	4.2	2.6	5.4		0.04	4.0	33.8	0.0		0.01	5.0	47.7	1.2

TABLE 3
O_2 TRANSFER VIA OXYGENATOR

Hour	Pre and Post Oxygenator O_2 content differential (mL O_2/L blood)	Blood flow (L/min)	O_2 transfer (mL/min)
0	28.9	1.66	48.0
2	42.4	2.43	103.0
4	35.6	2.51	89.2
6	41.8	2.38	99.5

TABLE 4
ANTICOAGULATION MEASUREMENTS

Hour	aPTT (seconds)
-0.5	19.58
0	121.53
2	72.00
4	36.58
6	34.25

3.1 Hematologic Parameters

Plasma-free hemoglobin and hemoglobin. There was no statistically discernible difference in hemoglobin concentration from baseline with levels ranging from 6.4 to 7.7 g/dL (p = 0.083). Similarly, the PFH did not increase from baseline, ranging from 3.5 to 6.4 ng/mL (p = 0.663) (**Figure 2**).

Platelets and P-selectin. Changes in platelet levels were not significant. Changes in P-selectin were significant but average levels decreased, not increased, during the 6-hour run. Total platelets ranged from 339,000 to 435,000/µL (p = 0.092) while P-selectin levels ranged from 40 to 61 ng/mL with an early peak at time 0 and subsequent fall near baseline for the remainder of the 6-hour run (p = 0.008) (**Figure 2**).

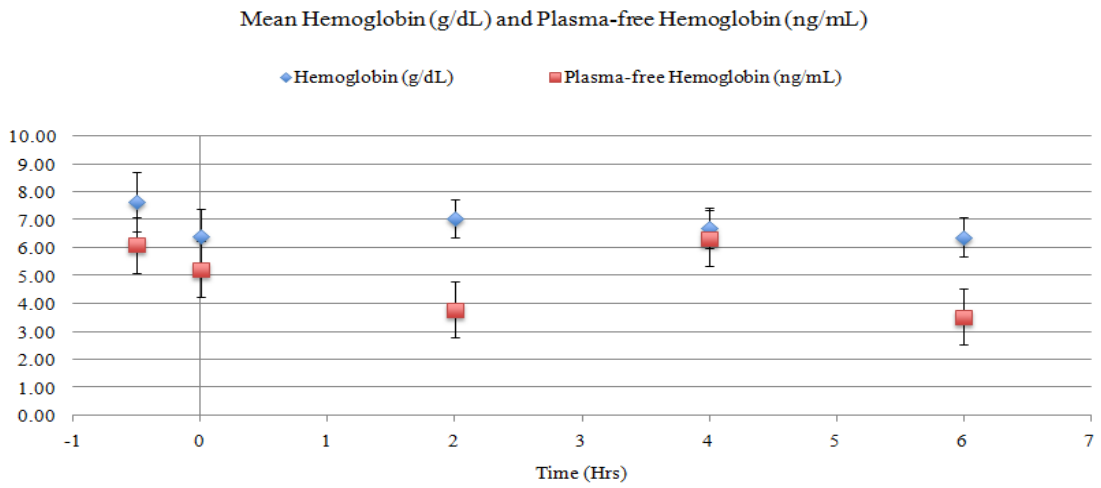

FIGURE 2. MEAN HEMOGLOBIN AND PLASMA-FREE HEMOGLOBIN

3.2 Total Bilirubin and Lactate Dehydrogenase

Indirect laboratory measurements of hemolysis were assessed by total bilirubin and lactate dehydrogenase. Total bilirubin ranged from 0.25 to 0.32 mg/dL (p = 0.101), and lactate dehydrogenase ranged from 497 to 965 U/L (p = 0.011) (**Figure 3**).

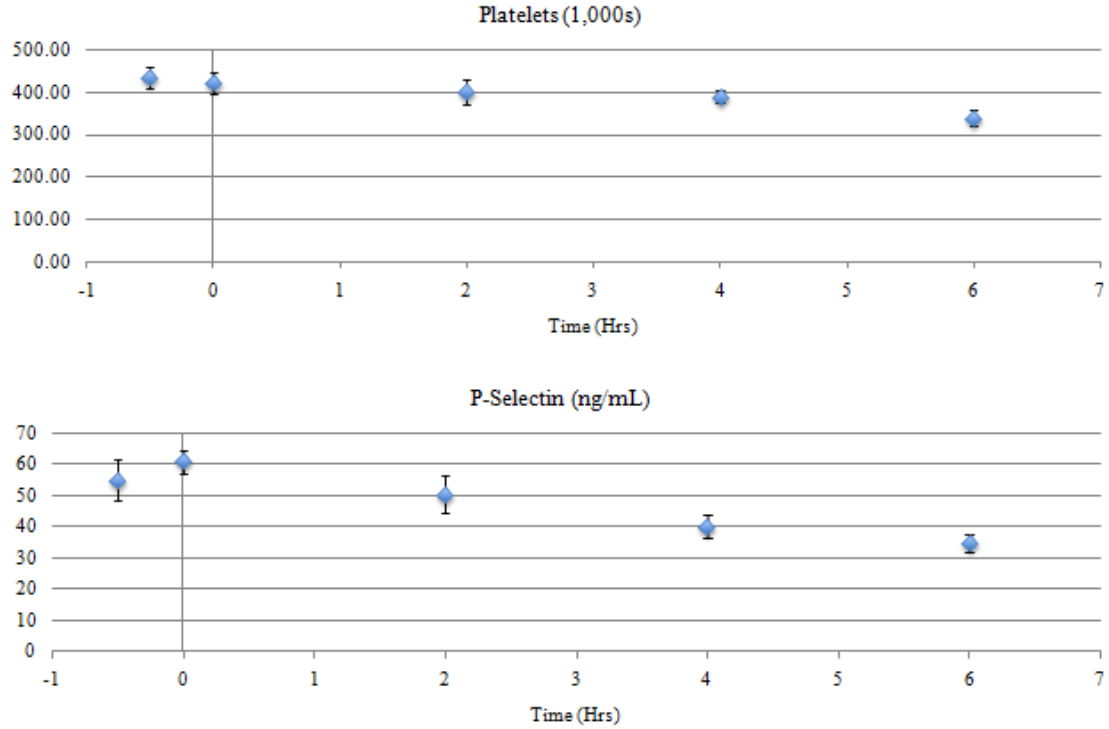

FIGURE 3. PLATELETS & P-SELECTIN

3.3 D-dimer and Fibrinogen

Effect on coagulation factors was measured by plasma levels of fibrinogen and D-dimer. Changes in both variables were significant. Fibrinogen levels ranged from 152 to 280 mg/dL (p = 0.027), and D-dimer levels ranged from 78 to 133 ng/mL (p = 0.013) (**Figures 4**).

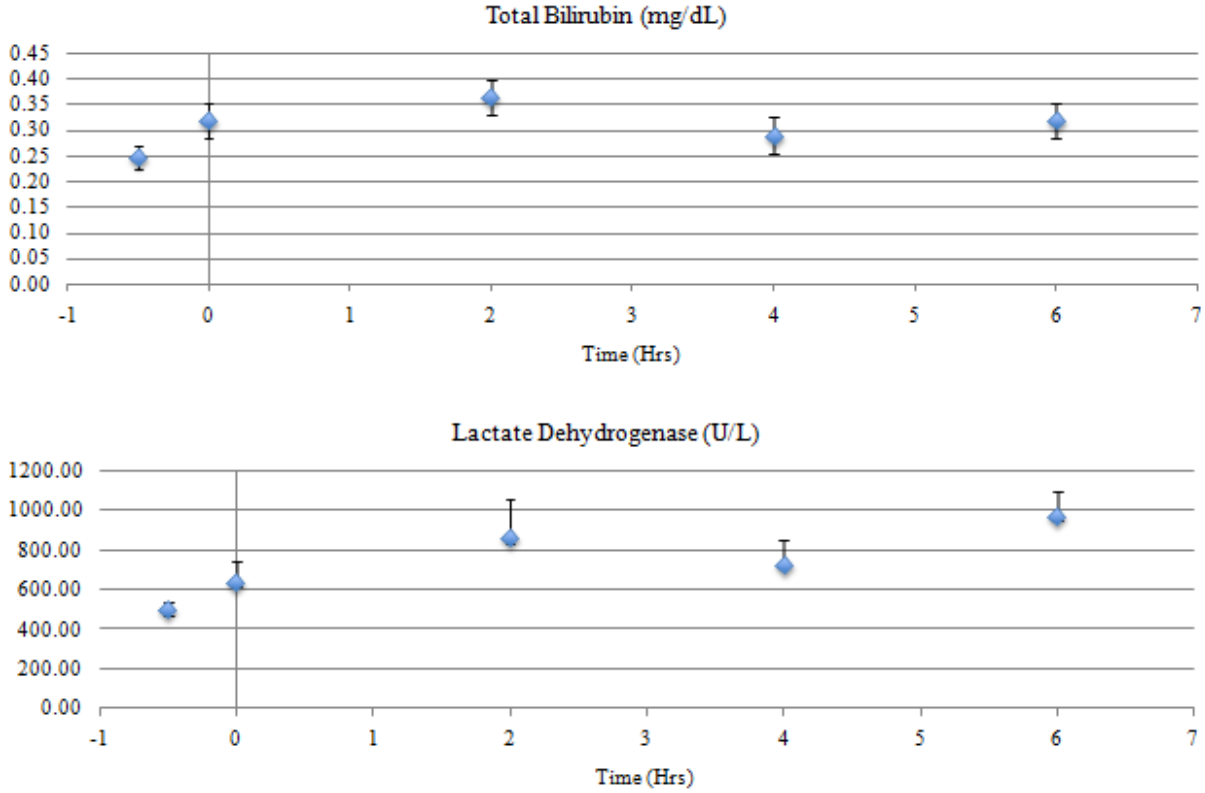

FIGURE 4. TOTAL BILIRUBIN & LACTATE DEHYDROGENASE

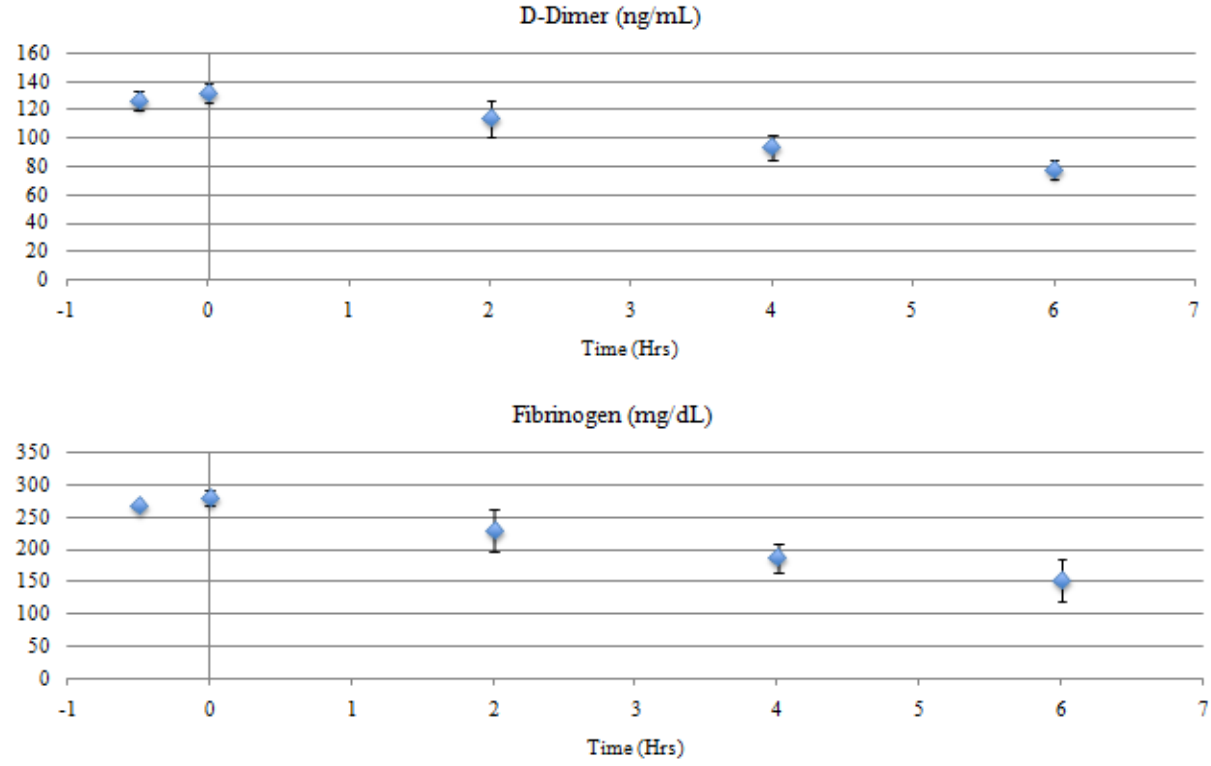

FIGURE 5. FIBRINOGEN& D-DIMER

IV. DISCUSSION

Since the first clinical case of extracorporeal membrane oxygenation (ECMO) in 1972 by Hill et al, progress in ECLS technology has led to novel circuit configurations and smaller pumps.[12] These advances have enabled clinicians to apply ECLS therapy to new clinical problems. Pulmonary hypertension remains an area of active investigation and, because of its unique cardiopulmonary consequences, a prime candidate in which to test many of these innovations.

The SYNERGY pump was originally developed to offer a low profile left ventricular assist device (LVAD) for use in patients with New York Heart Association Class IIIb or IVa heart failure. Its output is limited to a maximum of 4.25 L/min. Despite the SYNERGY's intended use as an LVAD, its output capacity and small size make it an excellent candidate for use in ECLS contexts where output demands are often lower and greater mobility offers profound clinical benefits. Patients with right heart failure, pediatric patients, and patients with chronic obstructive pulmonary disease (COPD), for example, typically have lower flow rate requirements in ECLS applications.[13-14] A pump that meets these output needs but features a low profile and lightweight design can potentially facilitate ambulation and participation in physical therapy, allow greater opportunity for health optimization among bridge-to-transplant patients, permit ECLS patients to leave the hospital and participate in activities of daily living, and enable mobile and combat environment applications of ECLS with maximal ease and speed.

To date, the SYNERGY pump has been used as a partial support LVAD for both bridge-to-transplant and destination therapy,[15] and has been implanted in both open procedures and percutaneously.[16] It has been studied in ovine models as a biventricular assist device.[17] Only one experiment has been published examining its use in an ECLS circuit to provide pulmonary support.[18] In that study there was no significant hemolysis or activation of the coagulation cascade when using the SYNERGY for standard venovenous ECMO in healthy swine.[19]Neither the SYNERGY pump nor any other micropump has been used as an OxyRVAD in an ECLS circuit to manage pulmonary hypertension. This study suggests that micropumps could find use in novel applications of ECLS with a specific focus on pulmonary hypertension.

The primary safety concerns with new ECLS technologies are hemolysis and effects on the coagulation system.[20-21]The increase in LDH observed in this study may be evidence of hemolysis during the 6-hour ECMO run. Alternatively, it may simply represent an increase to a new baseline level reflective of device use. LDH is a surrogate marker of hemolysis; however, it can be elevated in other conditions. In the case where there is indeed a meaningful degree of hemolysis, coincident rises in total bilirubin and plasma-free hemoglobin and decreases in blood hemoglobin levels are expected. In this experiment, total bilirubin, hemoglobin, and plasma-free hemoglobin did not change significantly from baseline, making the observed rise in LDH less consistent with hemolysis and more likely attributable to other causes.

P-selectin levels were significantly changed from baseline but trended downward to below baseline after an initial rise. P-selectin levels were measured as a marker of platelet activation, with greater platelet activation manifesting an increase in plasma P-selectin. While the change in P-selectin levels was significant, the downward change was unexpected and perhaps represents a chance observation.

The observed significant changes in fibrinogen and D-Dimer, in contrast, represent robust evidence of interaction with the fibrinolytic cascade. These observations are important, and they should be considered within the larger context of the ECLS literature. Effects on measures of fibrinolysis are a well-documented consequence of ECMO, with activation of the coagulation system frequently being attributed to the inflammatory effects of the membrane oxygenator rather than the pump.[22-25] The findings in this study mirror those in previous studies.

The limitations of this study include its small sample size, the use of healthy swine to study ECLS in a particular disease state, and that the pulmonary hypertension induced in this experiment was acute while clinically relevant group 1 PH is a chronic disease. The study is also limited in its inability to directly attribute observed hematologic effects to a cause, such as the pump, the oxygenator, the cannulae, or other factors. The small sample size makes the results vulnerable to the outsized influence of anomalous data from any one pig; this issue may be a factor in the LDH findings. By modeling acute PH rather than chronic PH, the results may be more applicable to acute PH states, such as those caused by pulmonary embolic phenomena. The use of better animal models of chronic PH for testing micropumps in ECLS remains an avenue for future investigation.

V. CONCLUSION

The SYNERGY micropump Quadrox D oxygenator OxyRVAD system was successfully tested in a swine model of pulmonary hypertension with stable pump flows and without catastrophic hematologic issues. Low levels of hemolysis,

platelet activation, and fibrinolysis demonstrate favorable biocompatibility of this system in this simulated condition. This study supports the idea of using micropump technology in combination with a gas oxygenator to alleviate the sequelae of PH and right heart failure.

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