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Long-term Animal Model of Veno-Venous Extracorporeal Membrane Oxygenation with Atrial Septal Defect as a Bridge to Lung Transplantation

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Abstract

This study evaluated the effectiveness of an atrial septal defect (ASD) with veno-venous extracorporeal membrane oxygenation (vvECMO) as a bridge to transplantation. Sheep (56 ± 3 kg; n = 7) underwent a right sided thoracotomy to create the ASD (diameter = 1 cm) and place instrumentation and a pulmonary artery (PA) occluder. After recovery, animals were placed on ECMO, and the PA was constricted to generate a two-fold rise in right ventricular systolic pressure. Sheep were then maintained for 60 hours on ECMO, and data were collected hourly. Five sheep survived 60 hours. One sheep died due to a circuit clot extending into the RV, and another died presumably due to an arrhythmia. Mean right ventricular pressure (mRVP) was 19±3 mmHg at baseline, averaged 27±7 mmHg over the experiment, but was not statistically significant (p = 0.27) due to one sheep without an increase. Cardiac output (CO) was 6.8±1.2 L/min at baseline, averaged 6.0±1.0 L/min during the experiment, and was statistically unchanged (p = 0.34). Average arterial oxygen saturation and pCO_2 over the experiment were 96.8 ± 1.4% and 31.8 ± 3.4 mmHg, respectively. In conclusion, an ASD combined with vvECMO maintains normal systemic hemodynamics and arterial blood gases during a long-term increase in right ventricular afterload.

Keywords

right ventricular failure; pulmonary failure; ECLS; lung transplant; septostomy

Introduction

Lung disease is the cause of one in seven deaths in the United States, totaling 400,0000 Americans each year [1]. The burden caused by pulmonary pathologies can also be inferred by the fact that between 10 and 30% of heart failure admissions in the US are the result of cor pulmonale, and the NIH pulmonary hypertension registry reports that 50% of death results from right ventricular failure [2]. Currently, the only treatment option for chronic irreversible pulmonary failure is lung transplantation. After transplantation, right ventricular strain normally decreases, and remodeling processes reestablish normal right ventricular

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physiology spontaneously [3]. Unfortunately, the demand for donor lungs has steadily outgrown the supply. This mismatch between the demand and available donor organs leads to the fact that approximately one fourth of patients on the lung transplant waiting list die per year in the US [4].

Unlike renal or cardiac replacement therapy, the current methods for supporting patients with end stage lung disease are not sufficiently refined to act as a long-term bridge to transplantation. An atrial septostomy is occasionally applied to unload the RV and bridge patients suffering from right ventricular failure to lung transplantation [5, 6]. Right to left atrial shunting increases cardiac output resulting in increased oxygen delivery despite mild arterial desaturation. Due to the desaturation, patients with severely impaired gas exchange are not considered suitable candidates for atrial septostomies, limiting the application to a small group of patients.

Hypothetically, patients suffering from gas exchange deficiency could be supported by veno-venous extracorporeal membrane oxygenation (vvECMO) to condition the venous blood prior to the septostomy. Recent major advances in ECMO technology have enabled patients to be supported with relative safety for several weeks up to months facilitating even extubation [7, 8]. The possibility of extubation is of particular importance, since a spontaneously breathing and alert transplant candidate is considered the ideal recipient, because of a less severe level of physical deconditioning in particular of respiratory muscles.

Previous studies conducted at our institution have shown the effectiveness of an atrial septostomy combined with vvECMO in an acute large animal model [9, 10]. This large animal study was designed to evaluate the long-term effectiveness of this new approach as a bridge to lung transplantation for respiratory and right ventricular failure.

Methods

All animals received care compliant with the “Principles of Laboratory Animal Care” formulated by the National Society for Medical Research and the “Guide for the Care and Use of Laboratory Animals” prepared by the National Academy of Sciences and published by the National Institutes of Health. The study was approved by the University of Michigan Committee on Use and Care of Animals (UCUCA).

Surgical Preparation

Adult male sheep (56±3kg, n=7) were anesthetized using a standard protocol as previously described and used by our laboratory [11]. Antibiotic prophylaxis was performed no more than the day of surgery with two intravenous doses of 1g of Nafcillin (Sandoz, Inc., Princeton, NJ-USA), and 120mg of Gentamycin (APP Pharmaceutical, LLC., Schaumburg, IL-USA). The ventilator (Narkomed 600, North American Draeger., Telford, PA-USA) was set initially at a tidal volume of 10mL/kg and a frequency of 12–15 breaths/min. It was adjusted as needed to maintain the arterial pCO_2 between 35–45mmHg with a peak inspiratory pressure less than 30cmH_2O. Venous access was achieved with a 9Fr percutaneous sheath introducer (Arrow International, Inc., Reading, PA-USA). A pulmonary artery catheter (Edwards Lifesciences, LLc., Irvine, CA-USA) was positioned in the outflow tract of the right ventricle to measure continuous right ventricular pressure. Arterial access was established by carotid catheterization using PVC tubing (Abbott Critical Care Systems., North Chicago, IL-USA). The arterial catheter was connected to a fluid coupled pressure transducer (Abbot Critical Care Systems., Chicago, IL-USA) to monitor arterial pressure which was displayed continuously (Marquette Electronics., Milwaukee, WI-USA).

Surgery

A right sided thoracotomy was performed, including partial resection of the fourth rib. A perivascular flow probe (24PAX model, Transonic Systems., Ithaca, NY-USA) was placed around the ascending aorta and attached to a flow meter (T206, Transonic Systems., Ithaca, NY-USA) to measure continuous cardiac output (CO). A 20mm diameter vascular occluder (Access Technologies., Skokie, IL-USA) was positioned around the pulmonary artery to establish right ventricular afterload. In all sheep, the vascular occluder was inflated until there was a 50% decrease in CO and the right ventricular systolic pressure was doubled. This degree of acute reduction in CO and increase in right ventricular afterload is lethal according to our previous experiments. The degree of inflation was noted for use after recovery (mean volume of inflation: 2.01 ml ± 0.30 ml), and the occluder was then deflated.

The atrial septal defect (ASD) was performed on a beating heart through a double purse string suture on the right atrial appendage by digital perforation of the fossa ovalis and the membranous part of the atrial septum. A modified 27Fr dual lumen cannula (Avalon Laboratories, Rancho Dominguez, CA-USA) was introduced through the right jugular vein to establish drainage from the inferior vena cava and reinfusion directly into the right atrium. The catheter's drainage port from the superior vena cava was blocked to limit recirculation.

Chest tubes (36Fr) were placed and attached to a dry suction water seal chest drainage chamber (Atrium Medical Corporation., Hudson, NH-USA) to enable fluid drainage and lung expansion by applying 20mmH_2O negative pressure to the pleural cavity. An intercostal block was performed by injecting a long lasting local anesthetic 0.5% Bupivacaine (Hospira, Inc., Lake Forrest, IL-USA) into the fourth and adjacent intercostal spaces. The chest was closed in 3 layers. The sheep was then moved to a custom-built cage that allowed sitting and standing but not turning around. During recovery and the further experimental course the postoperative analgesic protocol consisted of intramuscular injection of 60mg ketorolac (Hospira, Inc., Lake Forest, IL-USA), and 0.6mg buprenorphine (Buprenex® Reckitt Benckiser Pharmaceuticals Inc., Richmond, VA-USA) every 4–6 hours. The intercostal block with Bupivacaine was repeated as needed, but was not necessary more than twice. Extubation was accomplished 3–5 hours postoperatively. A heparin drip 80U/h (Multi-Phaser NE-1000, New Era Pump System Inc., Wantagh, NY-USA) was started six hours postoperatively to achieve an activated clotting time between 200–300 seconds. Maintenance fluid was given at a rate between 50–200mL/h, as guided by the central venous pressure (CVP), the oral fluid intake of the animal, and clinical conditions. The CVP alone was not considered reliable due to the presence of the double lumen cannula in the right atrium.

ECMO Circuit

The ECMO circuit consisted of a centrifugal pump (Biomedicus 520 D, Medtronic Minnianapolis, MN-USA), heater unit (ECMO-Temp®, Zimmer, Dover, Ohio-USA), oxygenator (Capiox® SX, Terumo, Ann Arbor, MI-USA), 3/8″ S-50 HL medical grade tubing (Tygon® Saint-Gobain Performance Plastics., Akron, OH-USA), and the previously described dual lumen cannula. The circuit was primed with 1L Lactated Ringer solution mixed with 50mL of 8.4% sodium bicarbonate solution (Hospira Inc., Lake Forrest, IL-USA). Prior to initiating vvECMO, 0.5g i.v methylprednisolone (Pfizer, New York, NY-USA) was administered to reduce the inflammatory response to the foreign surfaces of the circuit. vvECMO flow was then initiated and maintained at 1.0–3.5L/min according to the arterial blood gases. Pure oxygen was delivered to the oxygenator at a flow rate of 2–6L/min based on arterial blood gases. The centrifugal pump was kept between 2000–3000rpm.

Experimental Procedure

Veno-venous ECMO was initiated after a 12–18 hour postoperative period if the animal was standing and alert. It was initiated prior to that point (n=3) if postoperative arterial pO_2 fell below 60mmHg. A full hemodynamic and blood gas data set (see Table I) was then taken to establish the sheep's baseline condition prior to reapplying the pulmonary artery band. The band was re-inflated to the level recorded during surgery. Blood gases and hemodynamics were then recorded every hour after surgery (see Table 1). Plasma free hemoglobin and blood chemistry were measured daily.

The condition of the vascular occluder was tested daily by deflating the balloon for a period of 5 minutes while recording right ventricular pressures and then re-inflating it with the same amount of volume guided by simultaneous RV pressure measurement. The degree of gas exchange support by vvECMO was tested by daily withholding the O_2 supply to the oxygenator for up to 2 minutes causing severe dyspnea in each sheep. The sheep were ate and drank freely over the 60 h experiment. All animals breathed spontaneously in addition to support via vvECMO. A face mask was attached in 3 animals for short periods if the oxygen saturation fell below 90% under physical activity (e.g. standing up). At the end of the experiment the sheep were euthanized using Fatal-Plus (Vortech Pharmaceuticals, Ltd, Dearborn, MI) and a gross necropsy was performed. The patency and size of the ASD was measured during necropsy.

Data Analysis and Statistical Evaluation

Each sheep's hemodynamic and blood gas data was averaged over 12 hour intervals. Data for these periods were then averaged for all sheep. Data is presented as an average of this data ± standard error. Arterial oxgen delivery (DO_2) was calculated as:

$$DO_2 = CO[(1.34^{*}Hb^{*}SO_2)/100 + k^{*}PO_2], \quad (1)$$

in which CO is the cardiac output in ml/min, Hb is the hemoglobin concentration in g/dL, SO_2 is the fractional arterial oxyhemoglobin saturation, and k is the oxygen solubility in blood (3×10^{-5} ml O_2/ml blood/mm Hg), and PO_2 is the oxygen partial pressure in blood.

To examine the statistical effect of time on all data, linear models with correlated error structures (given the repeated measures) were fitted to the observed data using IBM SPSS 19 (Chicago, IL). The sheep/experiment number was the subject; the fixed, repeated variable was the experimental time; and the dependent variables were MAP, CO, mRVP, PO_2, PCO_2, Hb, and DO_2. Alternative covariance structures were compared using information criteria (e.g., AIC, BIC). In all cases, an autoregressive covariance structure was found to have the best fit. A Bonferroni correction was applied to the contrasts to prevent increases in Type I error rates. A p-value of 0.05 or less was considered statistically significant.

Results

All seven sheep survived creation of the ASD, placement on vvECMO, and pulmonary artery banding. One sheep experienced circuit failure and death after 20 h of ECMO support due to massive circuit thrombus formation despite adequate heparin delivery (see *Necropsy*). There was no obvious cause for this, as ACTs were always over 220 seconds in this sheep. In another animal, sudden death occurred at 20 hr. Necropsy showed a dislocation of the cannula into the right ventricle, presumably evoking a malignant arrhythmia as the cause of death. The remaining five sheep survived the entire experimental period of 60 h. All surviving sheep developed slight facial edema most likely due to cannulation of both jugular veins. No hemorrhage or other bleeding issues occurred, and no transfusion of red blood cells or platelets were necessary.

Hemodynamics

The hemodynamic picture overall is of an animal that had slightly elevated cardiac output and mean arterial pressure post-operatively with a return to normal values within 12 hours. Even with excellent pain management, this is common amongst post-operative sheep adjusting to the recovery room and recovery cages. Cardiac output (CO) was 6.8±1.2 L/min at baseline (Figure 1). It remained in a normal range for the duration of the experiment, averaging 6.0 ± 1.0 L/min thereafter, and did not vary significantly with time (p=0.34). Mean arterial pressure averaged 93±8mmHg at baseline and remained in the normal range thereafter, averaging 81±8 mmHg. These changes approached but were not statistically significant (p = 0.09). The HR averaged 127±9 beats/min at baseline and varied between 119±7 and 149±8 thereafter ($p < 0.05$). There was a small trend towards increased HR at 60 hours, but there were no significant differences at any time when compared to baseline (p = 0.11 to 0.99). Mean right ventricular (mRVP) pressure was 19 ± 3 mmHg at baseline. Four of five sheep demonstrated a consistent increase in mRVP, but the fifth demonstrated a decrease in mRVP after banding. For this reason, mRVP did not increase significantly overall following PA banding (p = 0.27, Figure 2), despite a trend towards increasing pressure. The mean RVP over the experimental period was 27±7 mmHg.

Gas exchange

The mean arterial oxygen partial pressure (PaO_2) was 93±4 mmHg at baseline, fell to 78±5 mmHg 12 hours after PA banding and was relatively constant thereafter. Although on average PaO_2 declined after PA banding, this trend was not consistent, and there was no significant change in PaO_2 over the experiment (p = 0.19). Despite this small drop, the average oxygen saturation was maintained greater than 95% at all experimental times. Hemoglobin fell slightly from 9.3 ± 0.7 g/dl to 8.9 ± 1.0 g/dl after 12 hours and then fell steadily until stabilizing after day 3 (Figure 4). As a result of hemodilution, arterial oxygen delivery (DO_2) fell from 845±78 at baseline to 598±45 at 24 hours (Figure 4). Thereafter, it was stable. The mean arterial carbon dioxide partial pressure ($paCO_2$) averaged 30.3±2.2 mmHg at baseline, 30.3±1.6mmHg after 12hr, and 31.8 ± 3.4 mmHg over the entire period after PA banding (Figure 3). This change was small and clinically insignificant, but did approach statistical significance (p = 0.08). Withholding the O_2-supply to the oxygenator leaded to severe dyspnea in all animals.

Necropsy

The correct positioning of the ECMO cannula was affirmed in all but one animal. In this latter animal the cannula was found in the right ventricle, as discussed previously. In the other premature death, clots were found around and in the cannula, as well as in the right atrium, right ventricle, and pulmonary artery. The pulmonary artery occluder was also affirmed functional in every animal. The ASD diameter averaged 1 ± 0.2 cm. A slight interstitial edema was found in every animal combined with slight pleural effusions. The lungs appeared normal and no signs of embolism were found in the liver, kidneys, and intestine. The brain was not examined.

Discussion

Due to the consistent shortage of available donor lungs, much effort has been spent developing feasible therapies and devices to support patients on the waiting list. A bridge to lung transplant should provide full gas exchange at rest and possibly with moderate exertion and alleviate right ventricular strain. Moreover, it must do this for a few weeks to months. The ideal bridge to lung transplantation device should also be wearable to offer mobility and potentially home use. Unfortunately, no available method or device has met these criteria to date. One current technique is pumpless arteriovenous CO_2 removal (AVCO2R) using the

Novalung interventional lung assist device (iLA). The iLA is a relatively low resistance (5–6 mmHg/(L/min)) oxygenator connected to cannulas in a femoral artery and vein. Thus, blood flow is driven by the arterial-venous pressure gradient [11]. However, this promising device requires a mean arterial blood pressure of greater than 70 mmHg, and the patient's circulation has to tolerate an arterio-venous shunt volume of 1.0 – 2.5 L/min in order to achieve adequate gas transfer. Thus, the iLA does not offer right ventricular unloading or support. Moreover, very little oxygen transfer is achieved. Therefore, the iLA is mostly used in patients with an intolerable CO_2 retention, but with acceptable oxygenation. One other major drawback of the iLA is that ambulatory use is impossible due to femoral cannulation.

Another possible solution may be a thoracic artificial lung consisting of a low resistance oxygenator connected in parallel to the lung via the pulmonary artery and the left atrium. This creates a low resistance blood flow path with gas exchange that can unload the RV and reduce RV strain. Recent, highly positive results achieved by long term large animal models [12] lead to the introduction and initial experience of a paracorporeal artificial lung in humans with successful support periods over several weeks [13]. The struggle with a centrally attached artificial lung is that it requires an invasive thoracotomy in severely ill patients, exposing this particular patient population to a considerable risk of anesthesia and major cardiac surgery. In addition, the formation of intrathoracic adhesions due to induced injuries results in a surgically difficult lung transplantation.

Another rather invasive method to support pulmonary and right ventricular failure is veno-arterial ECMO which is occasionally used as a bridge to lung transplantation [7]. However, for most adult patients with unresponsive severe respiratory failure, veno-venous support is the method of choice. The veno-venous configuration contains numerous advantages in comparison to the veno-arterial configuration. Examples are the lower incidence of neurologic complications, the lack of arterial compromise, the potential for a single venous cannula for drainage and reinfusion, and the preservation of pulsatile perfusion. Today's ECMO technology allows even the application in an extubated and alert patient. However, vvECMO does not provide circulatory support.

Early experimental studies in the mid 1960s and clinical observations in the mid 1980s have suggested that an inter-atrial shunt might be beneficial for the treatment of right ventricular failure [14, 15]. Therefore, despite causing a slight hypoxemia, atrial septostomies are occasionally utilized to bridge patients to lung transplantation [6]. In isolated severe hypertension, the drop in arterial oxygenation can be offset by the increase in cardiac output provided by unloading the RV. However, if respiratory deficit is also present, the resultant hypoxia may be too severe. Previous acute and non recovery experiments conducted in our laboratory proved that a one cm diameter atrial septal defect permitted enough shunting to maintain normal cardiac output while vvECMO maintained normal arterial blood gases over a period of four hours.

This study was designed to prove this concept in an alert large animal model. In summary, our results indicate that right to left atrial shunting in combination with vvECMO established with a double lumen cannula for drainage and reinfusion is capable of supporting right ventricular function, maintaining normal cardiac output, and maintaining near-normal gas exchange in a chronic, awake animal model. Cardiac output was maintained at a normal level for sheep of this weight despite a significant reduction in pulmonary artery flow over a period of 60 hours. One big advantage of this approach is that you do not need to be restrictive in ASD creation, since oxygenized right atrial blood is supplied by vvECMO support.

Unfortunately, there was no reliable method applicable to determine the shunt fraction in order to show the significance of the ASD, and its impact on maintaining cardiac output. An echocardiography in awake and standing sheep is extremely unreliable according to our experiences, because of the angle and shape of the sheep's chest which is longitudinal oval compared to humans which are transversely oval with better echo access to the heart Also the possibility to use venous and arterial blood gases in order to calculate the shunt fraction is not sufficiently reliable, since the shunt fraction in a standing sheep is depending on many factors like phase of inspiration, phase of cardiac cycle, thoracic pressure and so on. Last but not least a veno-venous ECMO was in place with arterial return to the right atrium complicating the possibility to use blood gases. However, according to our previous studies using an extracardial interatrial shunt the shunt fraction increases with banding of the pulmonary artery (9,10). The patency of the ASD was verified during necropsy showing a mean ASD diameter of 1 cm. Some reports describe the use of special stents to keep an interatrial communication open performing an ASD in patients suffering from arterial pulmonary hypertension [5]. This is also recommended especially in adult patients because of a thick muscular septum. In our experiment stenting the ASD would be closer to the clinical setting, however we considered stenting for a 60 h period as not necessary according to our previous studies.

Oxygen delivery under the aid of extracorporeal veno-venous support fell significantly over the first 24 hours of the experiment. However, this drop in oxygen delivery was due to hemodilution during ECMO rather than a drop in cardiac output. Blood transfusions in the first 24 hours of ECMO support would likely have eliminated this issue. Arterial PCO_2 remained at normal levels over the course of the experiment. Ultimately, ECMO should be able to maintain sufficient gas transfer clinically.

However, there are also obstacles associated with ECMO therapy. According to the mainly pediatric orientated Extracorporeal Life Support Registry (ELSO), out of approximately 40,000 ECMO runs, an average of 2.7 complications occurred with an overall survival rate of 76%. The incidence of complications in this study confirms the experience of ELSO registry. Two animals out of seven experienced complications more or less associated with ECMO therapy during our experiment. There are hints that pumpless technologies like the paracorporeal artificial lung attached in parallel to the lung from the pulmonary artery to the left atrium might cause lesser blood damages and complications. However, these paracorporeal artificial lung experiments were performed without high right ventricular afterload.

Potential Limitations

The presented support mode was intended for patients suffering from chronic pulmonary hypertension caused predominantly from pathologies in the peripheral vascular tree and consecutive RV failure. Our model, however, is more similar to acute RV failure similar to a severe pulmonary embolism. However, this new approach is designed for critically ill patients, who have suffered an acute exacerbation of their disease state leading to a severe deterioration of pulmonary hypertension and RV failure. Additionally, we believe the model used here is more challenging, as the RV has not yet accommodated to the high afterload and is thus more prone to failure. Different results may be achieved utilizing animals with chronic pulmonary hypertension and a partially compensated right ventricle. Another limitation of this study is the induced respiratory distress caused by the thoracotomy. A closed chest atrial septostomy would be preferable and better simulate the clinical application. Use of the thoracotomy likely included increase blood loss, inflammation, and post-operative weakness in these animals that detrimentally affected outcomes.

Lastly, there was no reliable means available to document the shunt fraction and volume unloading of the RV. Transthoracic echocardiography is extremely difficult to perform in sheep, and intracardiac echocardiography was not available. Also, the use of venous and arterial blood gases to calculate the shunt fraction was not possible, due to the return of inadequately mixed venous and oxygenated ECMO blood to the right atrium. However, our previous studies using an extracardial interatrial shunt indicate that the shunt fraction increases with banding of the pulmonary artery (9,10). Accordingly, the ASD was patent at necropsy, with a mean diameter size of 1 cm.

The next phase of this work will be to perform longer term studies using closed-chest, catheter-based septostomies and intracardiac echocardiography for more detailed analysis of right ventricular function. The first successful patient reports have demonstrated the effectiveness of this approach, albeit without detailed description of the physiology [16].

Conclusions

The combination of an ASD with VV ECMO is sufficient to unload the right ventricle sufficiently to maintain normal cardiac output and provide sufficient gas exchange in a long-term awake animal. This procedure has promise as a clinical bridge to lung transplant.

Acknowledgments

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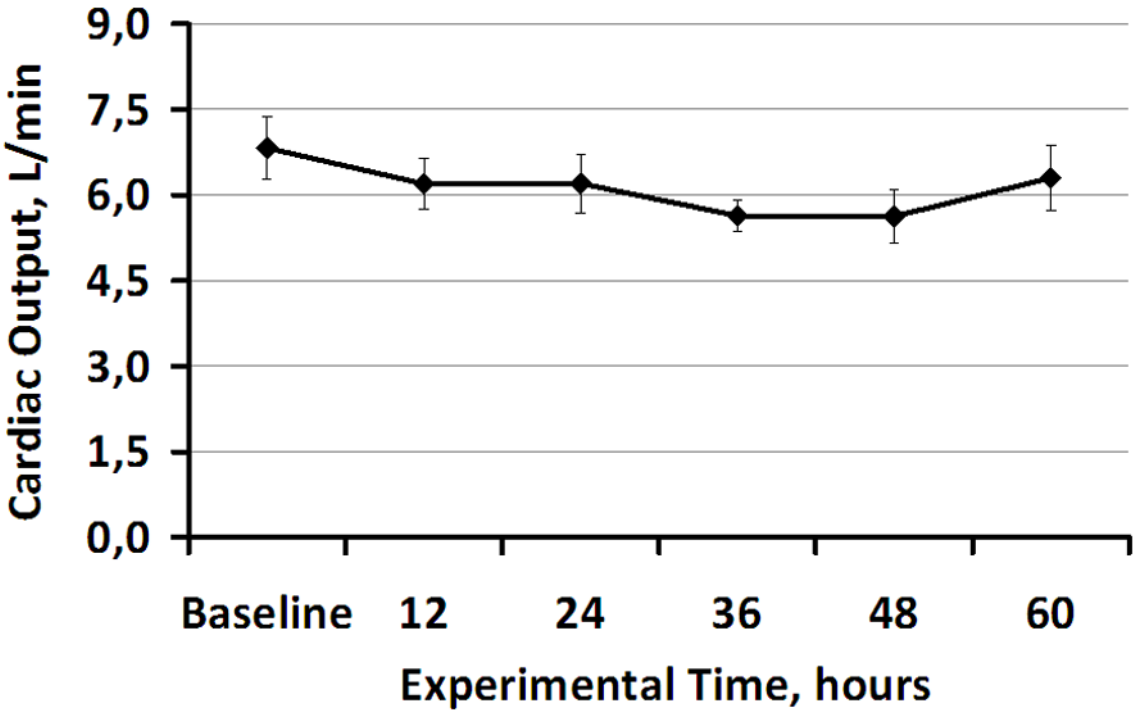

Fig. 1.
Cardiac output vs. experimental time. Note that a physiologic CO is maintained throughout the experiment.

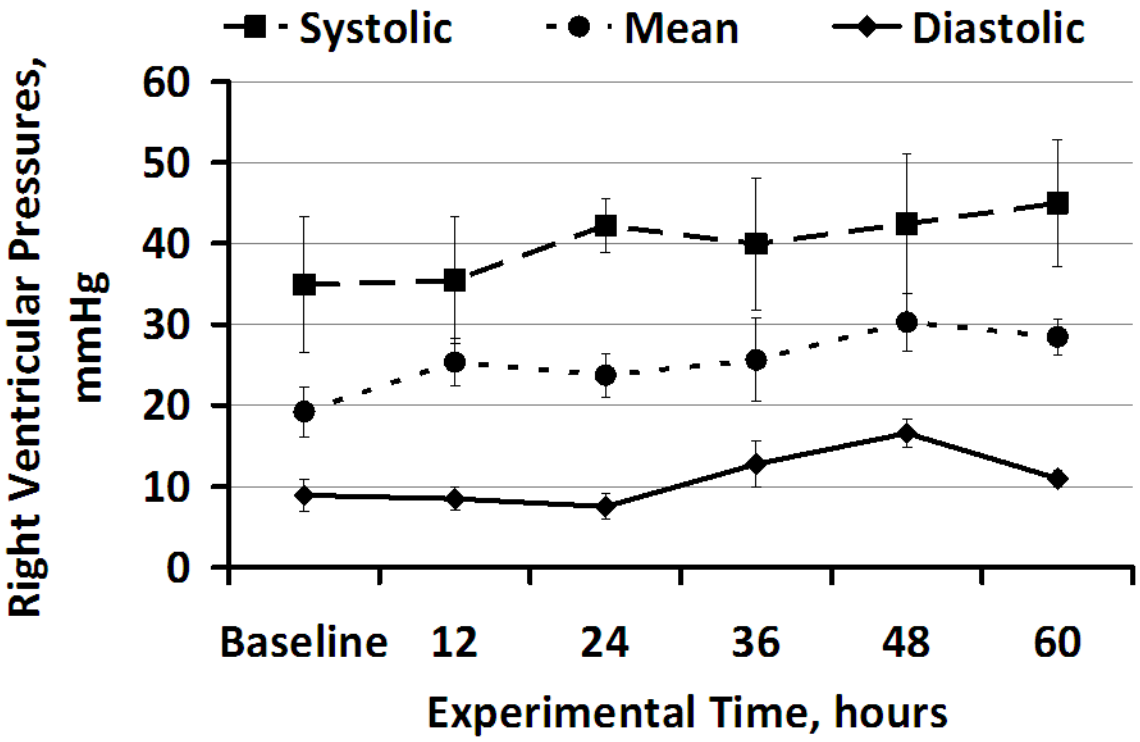

Fig. 2.
Right ventricular pressures during the course of the experiment. Note that they remained elevated despite interatrial shunting.

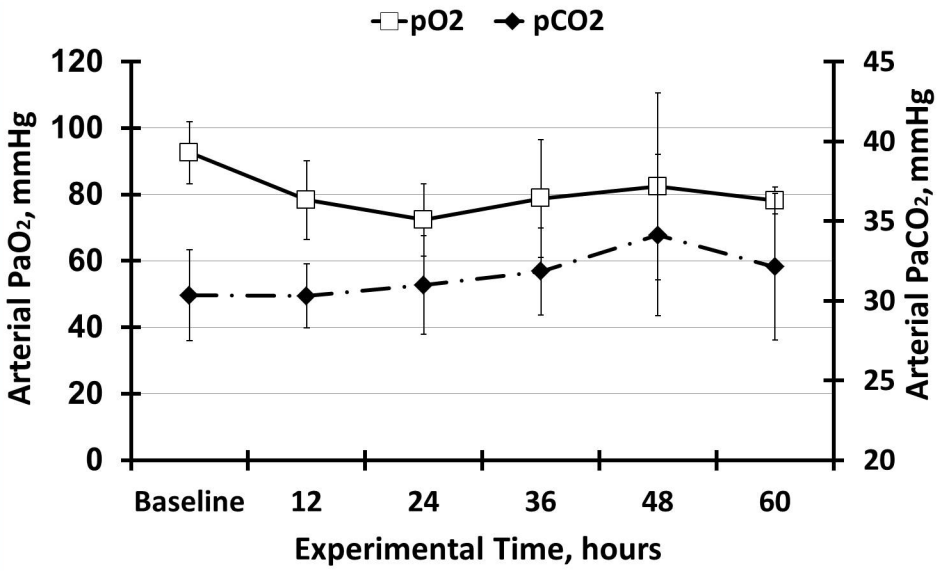

Fig. 3.
Arterial blood gases vs. experimental time. Arterial PCO_2 is maintained at normal levels, while there is a small decrease in PO2.

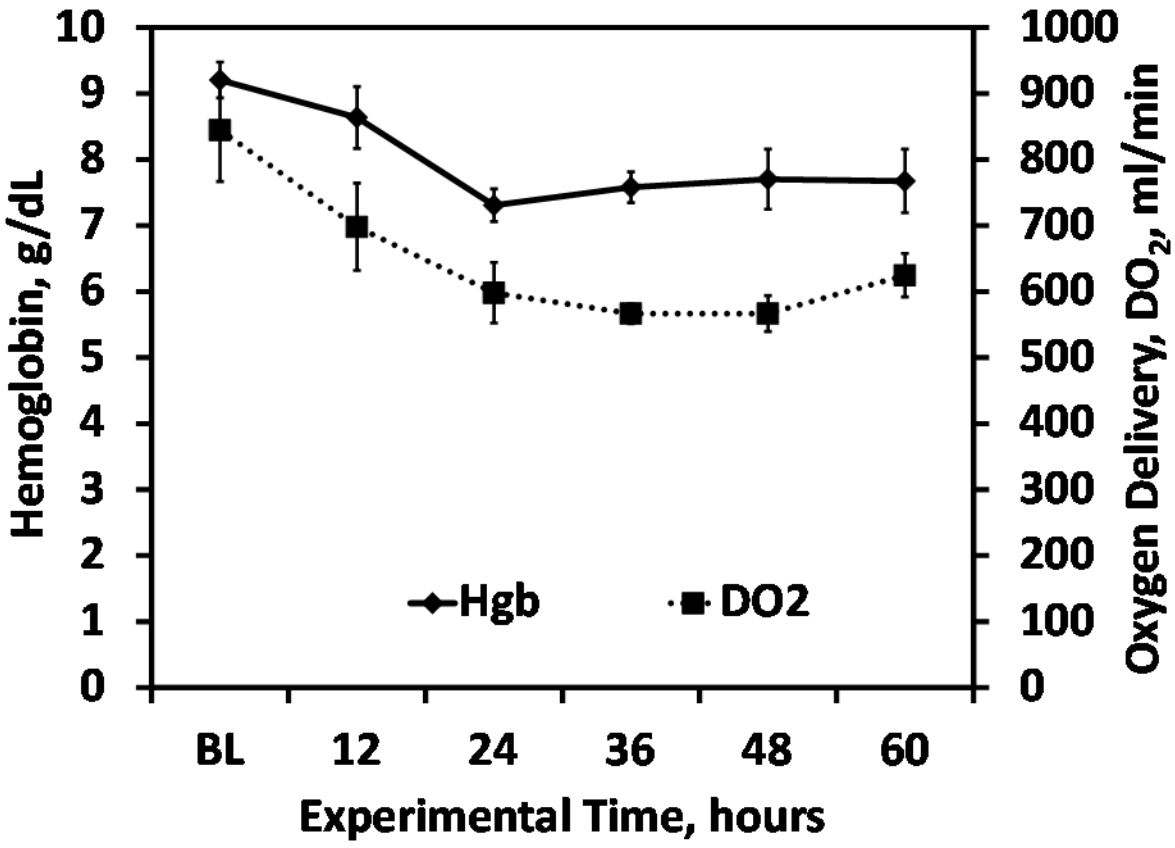

Fig. 4.
Oxygen delivery (DO_2) and arterial hemoglobin concentration (Hgb) vs. experimental time in hours. The drop in hemoglobin is primarily responsible for the fall in DO_2.

Table 1

Experimental Data Set

VARIABLE	DESCRIPTION	FREQUENCY
Hemodynamics	• Systolic, diastolic and mean arterial pressure (MAP) • Central venous pressure (CVP) • Heart rate and respiratory rate • Right ventricular systolic, diastolic and mean pressure • Cardiac output • ECMO blood flow	Continuously monitored, recorded every hour
Blood gases (arterial and venous)	• pH • PCO_2 and PO_2 • Hemoglobin (Hb)	Monitored and recorded every hour
Blood test	• Complete blood chemistry and plasma free hemoglobin • Activated coagulation time (ACT's)	Daily Hourly