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LUNG PHYSIOLOGY DURING ECS RESUSCITATION OF DCD DONORS FOLLOWED BY IN-SITU ASSESSMENT OF LUNG FUNCTION

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Abstract

Extracorporeal cardiopulmonary support(ECS) of donors following cardiac death(DCD) has been shown to improve abdominal organs for transplantation. This study assesses whether pulmonary congestion occurs during ECS with the heart arrested and describes an in-vivo method to assess if lungs are suitable for transplantation from DCD donors following ECS resuscitation. Cardiac arrest was induced in 30 kg pigs, followed by 10min. of warm ischemia. Cannulas were placed into right atrium (RA) and iliac artery, and veno-arterial ECS was initiated for 90min with lungs inflated, Group 1 (n=5) or deflated Group 2 (n=3). Left atrial pressures were measured as a marker for pulmonary congestion. After 90 min of ECS, lung function was evaluated. Cannulae were placed into the pulmonary artery (PA) and left ventricle (LV). A second pump was included, and ECS was converted to a bi-VAD system. The RVAD drained from the RA and pumped into the PA, and the LVAD drained the LV and pumped into the iliac. This brought the lungs back into circulation for a 1hr assessment period. The oxygenator was turned off, and ventilation restarted. Flows, blood gases, pulmonary artery and left atrial pressures, and compliance were recorded. In both groups: LA pressure was <15mmHg during ECS. During the lung assessment period, PA flows were 1.4–2.2 liter/min. PO₂ was >300mmHg, with normal PCO₂. ECS resuscitation of DCD donors is feasible and allows for assessment of function prior to procurement. ECS does not cause pulmonary congestion, and lungs retain adequate function for transplantation. Compliance correlated with lung function.

Keywords

DCD; NHBD; Lung Transplantation; ECMO; ECS

Lung transplantation is a successful treatment for patients with end stage pulmonary disease; however there is a critical shortage of available organs for transplantation. Currently in the U.S. there are 2,324 patients on the waiting list with 1405 transplants in 2006.¹ The vast majority of lung transplantations is from brain dead donors with functional circulation. The use of lungs from donors following cardiac death (DCD)--also known as non-heart beating donors (NHBD)--could increase the number of available organs.

The use of extracorporeal cardiopulmonary support (ECS) on the donor after cardiac death has been shown experimentally and clinically to increase the number and the quality of abdominal organs at our institution.^{2–4} ECS resuscitation of DCD organs is also currently being used in a few centers around the world to resuscitate kidneys and livers with excellent results.^{5–10}

Lungs from DCD donors may also be appropriate for transplantation. However, there is no current technique to evaluate their function prior to procurement. The first lung transplant was performed in 1963 by Dr. Hardy and was from a non-heart beating donor.¹¹ Since then, successful clinical application of lung transplantation from DCD donors has only been reported in small patient groups.^{12–14} A group in Madrid, Spain recently published promising results from 17 lung transplants from donors following cardiac death resuscitated on ECS.¹² However, they did report higher rates of primary graft dysfunction. Aside from this report, DCD lungs resuscitated with ECS have not been considered for procurement due to concerns with pulmonary congestion that may occur with the arrested heart. This is similar to what can happen during application of veno-arterial extracorporeal membrane oxygenation (ECMO) in a patient with severe cardiomyopathy.¹⁵ Furthermore, there has been no previously described method to assess lung function from a DCD donor prior to procurement.

The experiments described here used a swine model of DCD to investigate if pulmonary congestion occurs during ECS resuscitation. In addition, lung function was assessed *in-situ* in the donor to determine quality prior to procurement.

Materials and Methods

Animals and Anesthesia

Eight swine weighing of 27.6 kg±1.2 kg were used. Animals were treated according to guidelines in *Guide for the Care and Use of Laboratory Animals* (US National Institutes of Health publication No.85–23, National Academy Press, Washington DC, revised 1996), and all methods were approved by the University of Michigan Committee for the Use and Care of Animals.

Anesthesia was induced with 3 mg/kg of telezol (Tiletamine HCL and Zolazepam HCL, Fort Dodge Animal Health, Fort Dodge, IA) and 6 mg/kg of xylazine (VEDCO, St Joseph, MO). Anesthesia was maintained with inhaled isoflurane (Hospira, Inc, Lake Forest, IL). Arterial and central venous pressures were monitored via the carotid and jugular.

Surgical instrumentation

A median sternotomy was performed, and a flow probe (Transonic Systems Inc, Ithaca, NY) was placed around the pulmonary artery (PA). Catheters were placed into the PA and left atrium (LA) for blood samples and pressure measurement. Baseline arterial PO₂ and PCO₂ were measured using an ABL 5 blood gas analyzer (Radiometer, Copenhagen) and PA pressure and flow and LA pressure were recorded for calculating pulmonary vascular resistance.

Baseline lung compliance was obtained by slowly inflating the lungs with a ventilator (Nellcor Puritan Bennett 840 series ventilator, Tyco Health, Carlsbad Ca.). This measure served as means to assess donor lung quality prior to transplantation. A peak pressure of 30 cm H₂O was set at a respiratory rate of four breaths/min, resulting in inspiratory plateau pressures of 30 cm H₂O for 10 seconds. The tidal volume was measured, and compliance was calculated as tidal volume divided by 30 cm H₂O. A 14 French cannula (Biomedicus, Medtronic, Minneapolis MN) was placed in the distal retroperitoneal iliac artery as our ECS reinfusion line. A 24 French cannula (DLP, Medtronic) was placed into the right atrium(RA) to mimic a clinical jugular venous drainage line.

Cardiac arrest was induced by infusing pancuronium (Hospira, Inc, Lake Forest, IL) and removing ventilator support. The pig was anticoagulated with 150U/kg of heparin before removal of the ventilator. After cardiac arrest, we allowed 10 minutes of warm ischemia prior to commencing ECS. Cardiac arrest typically took 8 to 17 minutes and was indicated by clinical asystole, the absence of a pulse when the arterial tracing was less than 20mmHg and the difference between systole and diastole less than 10mmHg. Figure 1 gives the timeline for the experiment.

ECS Resuscitation

The ECS circuit (Figure 2a) consisted of ¼ inch R3603 TYGON tubing (Fisher Scientific, Pittsburgh, PA), 3/16 inch Nalgene 50 Silicone tubing (Nalge Company, Rochester, NY), a Cobe roller pump (Lakewood, Colorado), and a Capiox SX25 oxygenator (Terumo, Elkton, MD). The circuit was primed with 500mls of lactated Ringer's solution with 50mEq of bicarbonate. ECS flows were measured by a T208 Transonic tubing flow meter (T208, Transonic systems, Ithaca, New York).

Following warm ischemia, ECS was started. ECS flows were maintained between 40ml/kg/min to 80ml/kg/min, aiming to maximize flows without causing cavitation. The heart was maintained in the arrested state by administration of 1.5 grams of lidocaine and ligation of the coronary arteries. During this period, LA pressures were recorded every fifteen minutes after initiating ECS as a surrogate marker for pulmonary congestion. During ECS resuscitation, pigs were divided into two groups. In Group 1 (static hold, n=5), the lungs were kept inflated at 20 cm H₂O with air to prevent atelectasis. In Group 2 (deflated, n=3), the lungs remained deflated.

Lung Function Assessment

After 90 minutes of ECS, the pigs were converted to bi-ventricular(Bi-VAD) assist support to bring the lungs back into circulation and assess their function (Figure 2b). A 22 French canula (DLP, Medtronic) was placed into the PA. A 28 french cannula (DLP, Medtronic) was placed into the left ventricle(LV). The ECS roller pump was switched to drain from the RA and infuse into the PA, thus acting as an RVAD. A second pump with a built in reservoir (M-Pump, MC3, Ann Arbor, MI) drained from the LV and infused into the iliac artery, thus acting as an LVAD. PA flows controlled by the RVAD were maintained low in the beginning of this period and increased up to the point where cavitation started to occur in the system and this was the maximum flow. LVAD flow rates were equivalent to RVAD flow rates. With the lungs back into circulation, the oxygenator was turned off. Ventilation recommenced with pure oxygen, a respiratory rate of 6–12, peak inspiratory pressures of 20–30 cmH₂O and a positive end-expiratory pressure PEEP of 5cmH₂O. At 10, 20, 30, 45 and 60 minutes, blood samples were obtained from the PA and LA to determine pO₂ and pCO₂ to assess ventilation and oxygenation. PA flow was measured and PA and LA pressures obtained every 10 minutes. Lung compliance was again performed using the previous methods. The experiment concluded after 60 minutes of ventilation.

Wet-Dry Ratio and Histology

The lingula of each lung was removed, weighed, and dried in an oven (Stabletemp, OakLon) at 38–40 C for one week. It was then re-weighed, and the wet-dry ratio was calculated. Similar samples were acquired from normal swine that did not undergo this procedure and wetdry ratios were determined. Wedge biopsies of the lung were procured and fixed in 10% formalin. They were processed in standard fashion and stained with hematoxylin and eosin.

Statistical Analysis

A mixed model analysis was utilized with SPSS (Chicago, IL) for analyzing between study times and groups. The subject variable was swine number, and the fixed independent factors were the time, group, and the interaction variable time. Post-hoc multiple comparison between times was performed using Bonferroni corrected confidence intervals for all variables. Wet to dry ratio was compared using ANOVA, with Tukey's multiple comparison method. All figures are presented using standard error of the mean.

Results

Extracorporeal Support (ECS)

In both groups ECS was successful. Figure 3 shows mean arterial pressure (MAP) and ECS flows in both groups for 90 minutes. Flows for Group 1 (static hold) ranged from 1.08 ± 0.07 to 1.41 ± 0.07 L/min, this translates (44.3 to 57.6 ml/kg/min). Flows for Group 2 (deflated) ranged from 0.99 ± 0.24 to 1.78 ± 0.11 L/min (41.2 to 74.2 ml/kg/min). MAP during ECS for Group 1 was between 27.4 ± 2.7 and 58.0 ± 10.2 mmHg. MAP for Group 2 was between 27.0 ± 10.21 and 59.7 ± 5.8 mmHg. Group 2 had statistically higher flows than Group 1 ($p < 0.05$), but MAP were similar ($p = 0.52$)

Left atrial (LA) pressure in Group 1 was 7.2 ± 0.6 mmHg when ECS and increased significantly to 14.6 ± 1.0 mmHg at the end of 90 minutes ($p < 0.05$). LA pressure in Group 2 was 3.0 ± 2.0 mmHg at the beginning of ECS and increased significantly to 9.0 ± 2.0 mmHg (Figure 4). LA pressure was consistently higher in Group 1 compared to Group 2 ($p < 0.003$). The hematocrit for all animals during this stage was 24.8% to 26.9% with no significant difference between the groups.

Bi-VAD Lung Assessment

PA flows in Group 1 (static hold) were 1.96 ± 0.24 L/min at baseline and ranged from 1.41 ± 0.11 to 1.61 ± 0.08 L/min during the assessment period (Figure 5). In Group 2 (deflated), PA flow was 2.15 ± 0.08 L/min at baseline and ranged from 1.53 ± 0.13 to 1.69 ± 0.18 L/min during the assessment period. In both groups PA flows were significantly decreased compared to baseline ($p < 0.05$), but there was no statistical difference between the groups.

Pulmonary vascular resistance (PVR) in Group 1 was 6.52 ± 2.93 mmHg/L/min at baseline and ranged from 11.72 ± 3.05 to 14.38 ± 3.23 mmHg/L/min during the assessment period (Figure 6). In Group 2, PVR was 4.81 ± 0.66 mmHg/L/min at baseline and ranged from 7.48 ± 0.89 to 12.19 ± 5.70 mmHg/L/min during the assessment period. In both groups PVR was significantly increased compared to baseline ($p < 0.003$) but there was no statistical difference between the two groups.

Average arterial PO_2 s were greater than 300 mmHg at all time points for both groups with no significant difference between the groups ($p = 0.5$) (Figure 7). Group I mixed venous PO_2 ranged from 30.9 ± 1.4 to 40.3 ± 4.3 mmHg. In Group 2, mixed venous PO_2 ranged from 29.1 ± 1.3 to 41.4 ± 12.0 mmHg. There was no statistical difference between the two groups (Figure 7). Average PCO_2 during this period remained within the normal range at all time points for both groups with no statistical difference between the groups (Figure 8). The hematocrit for all animals during this part ranged from 24.4% to 21.5% with no significant difference between the groups.

Compliance

Compliance remained near baseline in most sheep (Figure 9). Only two (1b and 2b) showed a marked decrease of compliance to below 20 ml/cmH₂O. Characteristics of these two animals

were compared to those with compliance above 20 ml/cm H₂O during the assessment period. Compliant lungs (>20ml/cm H₂O) had much better lung function parameters including PVR, PO₂ and PCO₂ compared to the poorer compliant lungs (<20ml/cm H₂O)(Table 1).

Lung Tissue

The wet to dry ratio was 4.94±0.16 for the normal control samples, 5.59±0.19 for Group 1, and 5.65±0.09 for Group 2. There was no statistical difference between the two groups but both were statistically larger than normal lungs. Lung histology of all animals were normal

Discussion

In the past decade, a few institutions have used veno-arterial extracorporeal circulation to restart perfusion of abdominal organs from DCD or non-heart beating donors.^{3–8, 16} ECS is applied while the organs are still within the body for periods ranging from 30 minutes to 4 hours prior to procurement. ECS has been used to cool the abdominal organs in an effort to limit ischemic injury.^{6,16} ECS at normal body temperature has also been instituted and shown experimentally to improve abdominal organ function compared to organs from donors not resuscitated with ECS.^{2,17–19} The mechanism for this has not been fully understood. However, normothermic ECS has experimentally been shown to increase the energy profile¹⁷ and antioxidants level in the harvested organs.¹⁸ Finally, normothermic ECS may allow ischemic preconditioning and subsequently cause the organ to be more resistant to reperfusion injury on implantation.¹⁹

In the studies described above, the aorta was occluded during ECS with a balloon to improve circulation to the abdominal organs. This effectively prevented blood flow to the thoracic organs and prevents resuscitation of the heart. In this study, resuscitation of the heart was eliminated. But the lungs should have received flow from the bronchial artery. Bronchial artery flow during cardiopulmonary bypass has been shown to participate in respiratory exchange, and is able to support metabolism in the lung parenchyma.²⁰ Several studies have suggested that bronchial flow during cardiopulmonary bypass plays a role in preventing lung dysfunction after bypass,^{21,22} by mediating reperfusion injury and decreasing lung edema.²³ These studies suggest that allowing bronchial flow to occur during ECS resuscitation may improve the quality of the donor lungs.

Left sided distension of the heart during ECS support of patients with profound cardiac dysfunction is common.²⁴ Likewise, there are concerns that left atrial distension could cause pulmonary congestion during ECS resuscitation in a DCD donor when the heart is arrested. Left atrial distension can occur from aortic regurgitation through an incompetent aortic valve in a dilated and arrested heart. It can also occur from blood return through the thesbian veins and from bronchial artery flow. In clinical ECMO, left sided decompression is accomplished using direct venting, balloon atrial septostomy or placement of a transseptal atrial cannula.^{24–28} It can also be managed by increasing the ECMO pump flow, thereby draining the right heart more effectively and decreasing pulmonary blood flow.²⁹ In a non-beating, dilated heart with incompetent mitral and pulmonic valve, retrograde flow through the pulmonary artery may occur, effectively decompressing the pulmonary vasculature and left heart and preventing pulmonary congestion. Although it was not specifically evaluated, there were small amounts of retrograde flow (50–150ml/min) through the pulmonary artery during the ECS period. This may explain why left atrial pressures remained low in our model during 90 minutes of ECS resuscitation. Lungs from DCD donors have been described to be more tolerable of warm ischemia than abdominal organs.³⁰ Lung parenchymal cells are close to sources of oxygen in the alveolar spaces and respiration can occur through passive diffusion.³¹ Indeed, experiments have shown inflation or ventilation with oxygen or air can sustain and improve lungs from DCD donors.^{31–33} In this limited study, static inflation of room air during ECS resuscitation did not seem to be necessary for maintaining lung function.

A significant obstacle to using lungs from DCD donors is the inability to assess function prior to transplantation. Being able to adequately assess function is vital prior to transplanting a life sustaining organ such as the lung. Steen *et al.* have developed a very elegant method to assess lung function prior to transplantation.³⁴ Following procurement from a DCD donor and cold storage, the heart lung block is placed into a modified heart-lung machine to be assessed ex-vivo prior to implantation. Reperfusion is accomplished via the PA using a perfusate with deoxygenated blood while ventilating the lungs. Thus, gas exchange and pulmonary hemodynamics can be evaluated prior to transplantation. Steen's group went on further to show that non-acceptable donor lungs could be successfully reconditioned to a better state and subsequently transplanted with good function.^{35,36}

In this study, a simple method was used to assess lung function prior to procurement in a DCD donor that is already on ECS resuscitation for the abdominal organs. By transitioning from veno-arterial ECS to a RVAD/LVAD circulation system, one can bring the lungs back into circulation. With the lungs back in circulation and the oxygenator turned off, the DCD donor's body acts as the deoxygenator. With the ventilator turned on, deoxygenated blood will be pumped through the lungs for assessment. Moreover, dynamic compliance could be used to simplify assessment of lung quality. A less compliant lung (<20ml/cmH₂O) likely predicts poor function and a more compliant lung (>20ml/cmH₂O) may predict good function.

Conclusions

This study suggests that lungs do not become significantly congested over 90 minutes during ECS when the heart is arrested even without an aortic occlusive balloon. This study also indicates that lung function is suitable for transplantation after ECS with or without inflation. Lastly, this study indicates that compliance of the donor lung may be an effective tool to determine viability after ECS support. This work is further evidence of the promise of extracorporeal support expanding the donor organ pool.

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Figure 1. Timeline of experiment. Surgical instrumentation and baseline measurements, induction of Cardiac Arrest and 10 minutes of Warm Ischemia (WI). Veno-Arterial Extracorporeal Support (V-A ECS) for 90 minutes and BiVAD circulation with lung function assessment.

Figure 2a.
Veno-Arterial Extracorporeal Support of the Donor following cardiac death.

Figure 2b.
BiVAD (RVAD/LVAD) assessment period.

Figure 3.
Mean Arterial Pressure and Flows during Veno-Arterial Extracorporeal Support of DCD donor.

Figure 4.
Left Atrial (LA) Pressure during Veno-Arterial Extracorporeal Support of DCD

Figure 5.
Pulmonary arterial(PA) blood flow achieved during BiVAD assessment period.

Figure 6.
Pulmonary Vascular Resistance (PVR) during BiVAD assessment period.

Figure 7.
Arterial and Mixed Venous pO₂s during the BiVAD assessment period.

Figure 8.
Arterial pCO₂ during the BiVAD assessment period.

Figure 9.
Compliance at baseline and at time = 30 mins during biVAD assessment period.

Table 1

Comparison of lung characteristics between relatively compliant and non-compliant lungs (>20ml/cm H₂O vs. <20ml/cm H₂O).

Compliance @ 30 min	PVR (SEM) mmHg/L/min/kg	PO2 (SEM) mmHg	PCO2 (SEM) mmHg
> 20 ml/cmH20 (n=6)	9.2 (1.9)	493 (17.9)	36.3 (1.8)
< 20 ml/cmH20 (n=2)	19 (5.0)	240 (25.8)	49.6 (2.2)