Original Article

Pumpless Arterial-Venous Extracorporeal CO$_2$ Removal During Acute Lung Injury

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ABSTRACT

Acute Respiratory Distress Syndrome (ARDS) is associated with high morbidity and mortality. It has been shown that extracorporeal CO$_2$ removal (ECCO$_2$R) can be used to supplement mechanical ventilatory support for ARDS patients. This makes it possible to reduce the amount of positive pressure ventilation, thus reducing cardiovascular compromise and barotrauma, promoting lung rest and healing.

We have been evaluating a pumpless arterial-venous ECCO$_2$R circuit with a priming volume of approximately 150 ml. A 0.8 m$^2$ hollow fiber membrane oxygenator was studied in 5 dogs (average weight = 27.8 kg) anesthetized with sodium pentobarbital. A femoral artery and vein were cannulated with 17 Fr cannulae. The blood flow through this circuit averaged 1.11 l/min or approximately 23% of the animal's cardiac output. Acute lung injury was induced with oleic acid, (100 mg/kg). Following lung injury, the pulmonary shunt increased by 69% over baseline, while the pulmonary artery pressure increased from 12.7 to 18.7 mmHg. Despite this lung injury, pumpless arterial-venous ECCO$_2$R was able to support all of the animal's CO$_2$ exchange without ventilating the native lungs, which were held inflated with oxygen at 5 cmH$_2$O.

The results of this study indicate that a small, highly efficient, low resistance gas exchanger can completely supplant the need for artificial ventilation during pumpless arterial-venous bypass, even with severe respiratory distress. This simple method of ventilatory support should prove to be an important adjunct to positive pressure ventilation.

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INTRODUCTION

Adult Respiratory Distress Syndrome is a multifactorial disease associated with high morbidity and mortality (1). It has been proposed that extracorporeal CO₂ removal (ECCO₂R) combined with low frequency positive pressure ventilation (LFPPV) could be an adjunctive form of therapy for this population of patients by allowing a decrease in the amount of positive pressure ventilation necessary to support the patient (2). This will also decrease the amount of cardiopulmonary complications concomitant with the generation of high intrathoracic pressure. Thus, ECCO₂R should allow for lung rest and healing, by providing for most of the CO₂ removal and reducing the need for frequent lung inflation (3,4).

The concept of ECCO₂R with LFPPV is certainly not new. It was first proposed by Kolobow et al., in 1978 (5) and has subsequently been studied by several investigators.Gattinoni, et al. (6), studied ECCO₂R with a veno-venous bypass system using two 3.5 m² membrane gas exchangers aligned in series. Blood was drained by a cannula inserted into the inferior vena cava, and then returned to the external jugular vein. The extracorporeal blood flow averaged 1.45 l/min, while the gas exchanger was ventilated with warm humidified oxygen at a rate of 20-30 l/min. The native lungs were ventilated at a rate of 2-3 breaths per minute, while the peak ventilating pressure was limited to 35 cmH₂O. The results of this study revealed that the pao₂ increased significantly with initiation of ECCO₂R, while the static compliance of the lung also improved. This group also saw an improvement in ventilation/perfusion matching. In addition, the patients in this study were seen to have a decrease in pulmonary artery pressures, and a fall in cardiac indices (6).

A similar technique was performed by Hickling, et al. (7). These investigators presented a case study of a 33 year old female with Guillain Barré syndrome who subsequently developed ARDS. The patient’s condition worsened rapidly, and criteria were met for entry into an extracorporeal membrane oxygenation (ECMO) trial. The patient at this point had a predicted mortality of greater than 90%. This decline in the patient’s condition occurred while the patient was on a maximum amount of mechanical ventilatory support. The patient had bilateral femoral venous cannulae inserted for extracorporeal blood flow. ECCO₂R was initiated using a centrifugal pump and two 3.5m² silicone membrane gas exchangers. Blood and gas flows averaged 1 l/min and 10 l/min, respectively. The patient improved fairly rapidly during the early phases of ECCO₂R. This was evidenced by the improvement in chest radiographs, which showed decreased lung consolidation. After approximately 72 hours of ECCO₂R, the patient had a pao₂ of 92 mmHg with a fraction of inspired oxygen (FiO₂) of 0.28 to both the gas exchangers and mechanical ventilator. The mean pulmonary artery pressure of this patient decreased from a mean of 66 mmHg to a mean of 18 mmHg over the course of the trial of ECCO₂R. Although the treatment seemed to be successful, the patient expired from a massive intracerebral hemorrhage during her course of extracorporeal circulation (7).

A recently published multicenter randomized clinical trial of ECCO₂R-LFPPV concluded that it provided no significant improvement in patient survival or hospital stay as compared to mechanically ventilated controls (8). Despite this apparently disappointing outcome, several aspects of the procedure and components of the ECCO₂R circuit used in this study could be modified and perhaps improved. This and most of the early ECCO₂R studies have utilized one or more adult sized oxygenators with membranes made of silicone, or polypropylene. The surface area of these oxygenators have usually been between 2-3.5 m² (7-9) requiring large priming volumes. Most of the systems used in the noted studies typically require a pump, are labor intensive, and require a large volume to prime the circuit.

Barthalemy, et al, studied ECCO₂R in a pumpless system using sheep as the experimental model (10). These investigators employed a 2 m³ hollow fiber gas exchanger for ECCO₂R while oxygenation was accomplished by inflating the lungs with 100% oxygen at a constant pressure of 12-15 cmH₂O. With this experimental arrangement it was possible to satisfy all of the gas exchange requirements of the sheep which remained apneic for 5-24 hours. This system was able to remove carbon dioxide at 100-125 ml/min with blood flows ranging from 1 to 2 l/min and gas flows between 4-10 l/min.

The purpose of the present study was to evaluate a newer generation pediatric hollow fiber membrane oxygenator for use in a pumpless arterial-venous (A-V) ECCO₂R system with a low priming volume. There are many theoretical advantages to this approach over those from earlier investigations. The first is the use of a small, highly efficient, hollow fiber membrane oxygenator with a circuit of 1/4” tubing. This allows for a much smaller priming volume. In addition, since the system does not employ any type of mechanical pump, several potential problems are avoided such as the risk of tubing rupture or spallation. Also, there will be less risk of air entry into the system because at no time is a negative pressure generated in the system by a pump. If feasible this configuration could easily be adapted into the intensive care setting.

MATERIALS AND METHODS

A-V ECCO₂R Circuit: The system employed in this study was a relatively simple circuit with a Minimax Plus® pediatric hollow fiber membrane oxygenator, in an arterial-venous shunt made of 1/4” polyvinyl chloride tubing (Figure 1). The left femoral artery and right femoral vein were cannulated with 17 Fr. Biomedicus percutaneous perfusion cannulae®. The arterial cannula was connected to the inlet of the gas exchanger. A flow probe (Bio-Probe Tx40P)® was placed proximal to the oxygen-
A sampling and pressure monitoring port was placed just before the flow probe. Blood pressure was measured at both the inlet and outlet of the gas exchanger to determine the blood flow resistance across the oxygenator. Blood was returned via the femoral venous cannula attached to the arterial outlet of the oxygenator. The circuit was made as compact as reasonable requiring a total priming volume of 150 ml. Temperature and gas sampling probes were placed on both the gas inlet and exhaust ports of the oxygenator. The fractions of oxygen in the insufflating and exhaust gases (FiO₂ and FeO₂, respectively) as well as the fraction of carbon dioxide in the exhaust gas (FeCO₂) were analyzed at each data sampling interval using a gas analyzer (Datex Ultima). The dogs' inspired and expired gases were similarly analyzed. All gas flows into the gas exchanger were measured with a precision pneumotachograph (Fleisch #0) and exhaust volumes were calculated for BTPS conditions at the temperature of the blood exiting the oxygenator.

A heater-cooler unit was used in conjunction with the integral heat exchanger of the Minimax-Plus oxygenator to maintain the temperature of the blood going through the oxygenator at a constant 37 degrees C. Oxygenator inlet and outlet gas temperatures were continuously measured via small wire temperature probes inserted into the gas supply line, and the oxygenator exhaust port. A six centimeter piece of 1/4" tubing was attached to the exhaust port so that exhaust gas sampling and temperature monitoring would not be contaminated with room air.

**Surgical Preparation:** All animals used in this study received humane care in compliance with the “Guide for the Care and Use of Laboratory Animals”, published by the National Institutes of Health (NIH Publication No. 85-23, revised 1985). Anesthesia was induced with sodium pentobarbital (25 mg/kg) and maintained by a continuous infusion at 6 mg/kg/hr. Doxacurium (0.16 mg/kg) was used intermittently as a paralytic agent. The animals were intubated and mechanically ventilated with a Bear I volume ventilator. The average weight of the animals tested was 26.7 kg. The following settings were used throughout the experiments as our control ventilator settings:

- Tidal Volume (TV) 15 ml/kg
- Ventilator Rate (f) 14 breaths per minute (BPM)
- Ventilator FiO₂ 0.40
- Positive End Expiratory Pressure (PEEP) 5 cm H₂O

If these settings proved to be inappropriate, adjustments were made in the tidal volume to deliver an adequate minute ventilation. Any base deficit greater than 2.5 meq/l was immediately corrected with appropriate quantities of sodium bicarbonate.

The right femoral artery was cannulated for continuous arterial blood pressure measurement and arterial blood gas and pH analysis. A 7 Fr oximetric, balloon tipped, pulmonary artery catheter was advanced through the right external jugular vein into the pulmonary artery for measuring cardiac output, pulmonary artery pressure and pulmonary capillary wedge pressure measurements, as well as taking mixed venous blood samples.

After a control data set was taken, the dog was heparinized with 100 IU/kg sodium heparin, and activated clotting times (ACTs) maintained at 250-350 seconds. At this point, the left femoral artery and vein were cannulated with 17 Fr percutaneous cannulae. These cannulae were allowed to back bleed from the animal to remove any air, and clamped. The cannulae were then connected air free to the ECCO₂ R circuit.

**Experimental Protocol and Data Measurements:** A full set of data was taken no sooner than 15 minutes after each manipulation of the experimental state in order to achieve steady state. Blood gas samples were drawn and analyzed at 37° C with a Radiometer ABL-2. All blood gases and pH were temperature corrected to the temperature of the blood measured at the time.
of sampling. The arterial and venous blood samples were also analyzed with a Co-Oximeter (IL 282)* for oxygen saturation and hemoglobin determinations.

Prior to opening the cannulae and allowing blood to flow through the circuit, a full set of control data was taken. These data sets included heart rate, cardiac output, arterial and pulmonary artery pressures, blood gases and pH. The experiment was started by manipulating the mechanical ventilator and the ECCO₂R system settings. For ECCO₂R, gas flow through the membrane was kept constant at 6 l/min. Four experimental states were studied both before and after the induction of lung injury with oleic acid. These states are summarized in Table 1.

After the final data collection for the fourth state, acute lung injury (ALI) was induced. This was accomplished by one or more bolus injections of 100 mg/kg oleic acid. A minimum of an hour and 30 minutes was allowed for the animal to reach a new steady state before the experiment continued. Following ALI, the same experimental conditions as described in Table 1 were repeated with the only difference being that the FIO₂ of the dog and the gas exchanger was set at 1.0.

RESULTS

Physiological Impact of AV-ECCO₂R: Table 2 summarizes the hemodynamic impact of initiating blood flow through the A-V circuit. In the steady state, there were no significant changes in mean arterial pressure, mean pulmonary arterial pressure or heart rate. There was a large and significant increase in the cardiac output. Figure 2 shows the immediate impact of opening the AV circuit on arterial blood pressure. The initial fall in blood pressure was compensated and returned to normal within three minutes. After reaching steady state, the average blood flow through the gas exchanger was 1.11 ± 0.15 l/min almost exactly the increase in the cardiac output measured by thermodilution (Figure 2). This indicates that there was no significant change in the systemic vascular resistance in response to opening the shunt.

The ECCO₂R circuit was capable of removing CO₂ at 141.3 ml/min (STPD). Figure 3 compares the rate of CO₂ removal at the native lung during State 1 with removal at the membrane lung during State 4. Table 3 lists various hemodynamic measurements made during the course of the experiment. The numbers represent the mean values of all five animals with one standard deviation in parentheses. There was no significant difference in any of these parameters between the four states before lung injury. Figures 5 and 6 plot the blood gases during the

Table 1: Description of the Four Experimental States

<table>
<thead>
<tr>
<th>STATE</th>
<th>Mechanical Ventilation</th>
<th>ECCO₂R</th>
<th>FIO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TV = 15 ml/kg f=14</td>
<td>No</td>
<td>0.40</td>
</tr>
<tr>
<td>2</td>
<td>TV = 15 ml/kg f=14</td>
<td>Yes</td>
<td>0.40</td>
</tr>
<tr>
<td>3</td>
<td>TV = 15 ml/kg f=7</td>
<td>Yes</td>
<td>0.40</td>
</tr>
<tr>
<td>4</td>
<td>None</td>
<td>Yes</td>
<td>1.00</td>
</tr>
</tbody>
</table>

TV - tidal volume, f - ventilatory frequency

Table 2: Hemodynamic consequences of Pumpless AV Bypass

<table>
<thead>
<tr>
<th>MAP (mmHg)</th>
<th>PAP (mmHg)</th>
<th>Heart Rate (min⁻¹)</th>
<th>Cardiac Output (l/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Bypass</td>
<td>85.3(11)</td>
<td>12(1.6)</td>
<td>152(9.9)</td>
</tr>
<tr>
<td>Post-Bypass</td>
<td>82.7(9)</td>
<td>12.7(2.7)</td>
<td>157(7.7)</td>
</tr>
</tbody>
</table>

Data are MEAN ± S.D. * indicates significant difference from Pre-Bypass (p < 0.05) by Students t-test. MAP - mean arterial pressure, PAP - mean pulmonary artery pressure

Figure 2: The cardiovascular impact of opening the arterial-venous shunt through the gas exchanger. Part - arterial blood pressure.

* Instrumentation Laboratory Inc, Lexington, MA, 02173
Figure 3: Comparison of the rate of CO₂ removal at the native lung (State 1) and at the membrane lung during LFPPV-ECCO₂R (State 3).

Table 3: Hemodynamic Parameters during the Four States Studied

<table>
<thead>
<tr>
<th>STATE</th>
<th>MAP (mmHg)</th>
<th>PAP (mmHg)</th>
<th>Heart Rate (min⁻¹)</th>
<th>Cardiac Output (l/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-ALI</td>
<td>1</td>
<td>82.7 (9)</td>
<td>12.7 (2.7)</td>
<td>157 (7.7)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>84.7 (5)</td>
<td>13 (1.4)</td>
<td>161 (8.6)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>93 (7)</td>
<td>12.7 (1.7)</td>
<td>145 (12.8)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>90 (7.3)</td>
<td>13.7 (1.9)</td>
<td>137.7 (16)</td>
</tr>
<tr>
<td>Post-ALI</td>
<td>1</td>
<td>63 (7.3)*</td>
<td>18.7 (4.2)*</td>
<td>149.7 (22)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>64 (5)*</td>
<td>19 (5.4)*</td>
<td>154 (22.7)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>70.7 (6.2)*</td>
<td>19 (5.4)*</td>
<td>155.7 (25.3)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>74 (4.3)*</td>
<td>21.1 (6.2)*</td>
<td>153.7 (26.4)</td>
</tr>
</tbody>
</table>

Data are MEAN ±S.D.* indicates significant difference from corresponding Pre-ALI state (p < 0.05) by Students t-test. MAP - mean arterial pressure. PAP - mean pulmonary artery pressure.

Acute Lung Injury: Acute lung injury caused a significant decrease in arterial blood pressure, cardiac output and paO₂ (Table 3 and Figure 5). There was also a significant increase in paCO₂ in the ventilator only state (Figure 6). As was the case before ALI, ECCO₂R was capable of completely supporting the gas exchange requirements of the animal when combined with apneic oxygenation. There were no significant differences between paO₂ during any of the four states.

DISCUSSION

Despite considerable research involving techniques of ventilatory support for patients with ARDS, mortality remains high. Many studies have demonstrated that therapies aimed at maintaining gas exchange can cause further pulmonary damage. ECCO₂R with LFPPV has been shown to allow lung rest while supporting the patient in respiratory failure. When applied as veno-venous ECCO₂R, a spontaneously breathing subject will reduce breathing in proportion to the amount of CO₂ removed, responding to a decrease in paCO₂ without any adverse cardiopulmonary impact (11). Among the most significant obstacles in the widespread use of ECCO₂R for the treatment of ARDS are the side effects known to be associated with extracorporeal bypass and its relative complexity compared to mechanical ventilation. The typical ECCO₂R setup is labor intensive and expensive. Most of the ECCO₂R studies have used systems incorporating a pump, heat exchanger, and 1 or 2 large adult membrane oxygenators. These circuits are frequently cumbersome, require large volumes to prime and need a lot of physical space within the intensive care unit. Those systems incorporating two oxygenators in parallel may require as much as 1200 ml to prime. The complications associated with use of a pump such as hemolysis, cavitation or spallation with interrupted blood return, mechanical breakdown and tubing rupture are all potential concerns. Bleeding is also a frequently cited complication requiring discontinuation of ECCO₂R (8). The AV circuit as used in this study with the Minimax Plus addresses many of these problems. The small
circuit with minimal membrane surface area and low priming volume should serve to reduce blood-foreign material contact and enhance long-term biocompatibility.

The priming of the entire circuit with mounting at the bedside resulted in a total circuit prime of 150 ml, allowing for a crystalloid / blood free prime. This equates to less than 1/10th the prime volume of many of the circuits currently described.

Despite the relatively low flows and small membrane surface area, the pumpless arterial-venous ECC0 R system that we used was capable of adequately providing all of the CO2 exchange both before and after pulmonary injury. This system transferred CO2 at rates up to 160 ml/min. The paCO2 and pvCO2 were not significantly different between ventilator only and ECC0 R only pre-injury. Post-injury, the paCO2 and pvCO2 were slightly lower with ECC0 R only, compared to the ventilator only.

Cardiac output slightly decreased at the start of ECC0 R but increased as ventilator support was withdrawn. The typical blood flow through the membrane in this study was approximately 23% of the animals' native cardiac output which has been described as the ideal blood flow rate for CO2 elimination (13). One potential concern of this technique is the potential for arterial “steal” that the AV shunt might cause, diverting blood from peripheral vascular beds. Also, whether patients with compromised cardiac function can compensate properly for the initiation of the bypass. Thus, the ability to regulate or restrict flow through the circuit should be investigated in future studies.

Hemolysis was not measured in this study, but Awad, et al, reported little hemolysis in their study of prolonged pumpless arterial-venous perfusion for up to seven days in sheep (14). They also reported no plasma breakthrough, no failure to transfer CO2 and no need to replace any of the oxygenators due to failure over their seven day run in sheep (14). Oxygenator failure over a prolonged period remains a concern, however, with the potential of plasma breakthrough. As new membrane fibers are developed, this problem may be resolved in future devices.

Various coagulopathies are common with long term ECC0 R, as is complement activation and thrombocytopenia. These symptoms are also part of the pathology of ARDS itself. Bleeding was not a problem in this study. The fact that the prime was so small and resulted in no administration of blood products should decrease the risk of coagulopathy. Some of these complications are associated with the biocompatibility of the circuit and its materials. Important advances have been made in recent years to improve the biocompatibility of bypass components. Foremost among these is the ability to coat oxygenators and tubing with heparin. The use of a heparin bonded circuit in ECC0 R including an oxygenator with a small membrane area should reduce the need for sys-
temic anticoagulation, but also reduce complement activation and platelet loss.

Cost and invasiveness of ECCO₂R make centers hesitant to initiate this mode of therapy. The circuit used in this study is of simple design with no mechanical pumps and should be no more labor intensive than continuous arterial-venous hemofiltration. Circuit cost should also be substantially less than a standard ECCO₂R /ECMO circuit, even if heparin bonded. If a circuit is capable of being less costly, more biocompatible and uncomplicated, the tendency toward earlier initiation of ECCO₂R could decrease the morbidity and mortality associated with ARDS. For these reasons, further investigation of AV-ECCO₂R is warranted.

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