Efficacy of Apneic Oxygenation with Extracorporeal Carbon Dioxide Removal for Ventilatory Support during Acute Respiratory Failure

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Abstract

Apneic oxygenation (AO) with extracorporeal carbon dioxide removal (ECCO_2R) was investigated as a gas exchange support technique during acute respiratory failure (ARF). The purpose of this work was to study the limitations of AO and ECCO_2R in the pig challenged with pulmonary artery infusions of E. Coli endotoxin as a model of ARF. Fourteen animals of 36.5 kg average weight were placed on AO with simultaneous ECCO_2R accomplished with a venovenous bypass through a membrane lung. Bypass blood flow rate remained constant at 1 L/min in all trials. Inlet gas fraction (FIO_2) was varied between 0.209 and 1.0. With ECCO_2R, arterial pCO_2 and pH were held to mean values of 36.9 mmHg and 7.41 respectively. Arterial pO_2 was directly related to the membrane lung FIO_2 and was inversely related to pulmonary shunt resulting from the ARF. AO with ECCO_2R was shown to be an easily manageable ventilatory support technique capable of meeting the gas exchange requirements of a porcine model of endotoxin induced respiratory distress.

Introduction

Patients with acute respiratory failure that has progressed to a point of severe hypoxia generally begin treatment with some form of mechanical ventilatory assistance. Although countless patients have survived this support technique, it is not without risk and potential for complicating the underlying pathology. Avoiding long term conventional positive pressure ventilation with high inspired fractions of oxygen can reduce the risk of progressive lung damage and the alteration of proper lung function. Using high positive end-expiratory pressure (PEEP) with artificial ventilation alters cardiac function and may aggravate the development of pulmonary shunt. Barotrauma and mechanical complications of conventional positive pressure ventilation may lead to poor tolerance and lack of improvement in the status of these patients.

If this modality of therapy fails to provide the ventilatory support required, it has been suggested that extracorporeal membrane oxygenation (ECMO) can be used to augment both oxygen delivery and removal of carbon dioxide. Studies indicate that ECMO may have particular importance in the treatment of the neonate in acute respiratory failure. ECMO, however, is not without significant risk. With the commonly used veno-arterial bypass technique the risks include arterial cannulation requirements, high blood flow, embolization, and reduction of blood flow to the lungs. As applied in the past, mechanical ventilation is continued and this in turn brings with it complications typical to those previously described. Continued high pressure inflation of lungs which contain non-compliant diseased areas tend to worsen pulmonary shunt and lead to localized alkalosis in those areas of greatest compliance receiving the majority of the ventilation.

Gattinoni et al. have described a new method of augmenting gas exchange in patients with acute respiratory failure. More commonly referred to as apneic oxygenation (AO) with extracorporeal CO_2 removal (ECCO_2R), it can be functionally described as a separation of the two major gas exchange processes of the lungs, namely oxygenation and carbon dioxide elimination. Oxygen requirements can be met by apneic oxygenation which is the bulk movement of oxygen into the alveoli from a column extending to a source outside of the patient. This continued movement of
oxygen is the result of consumption by the pulmonary blood flow and is possible without lung motion. In clinical practice, however, the technique involves periodic positive pressure lung inflations at very low frequencies (2 to 3 breaths per minute) in order to limit the loss of lung volume due to alveolar collapse.\textsuperscript{14,16} Carbon dioxide elimination is performed with a low flow veno-venous bypass through a membrane lung. It has been suggested that this technique obviates many of the risks and potential complications of both conventional positive pressure ventilation and ECMO by keeping positive pressure ventilation to a minimum and using a less invasive and atraumatic low flow veno-venous bypass.\textsuperscript{12,16,17}

The purpose of the present study was to determine the efficacy of this support technique in a pig model of progressive E. Coli endotoxin induced respiratory failure. Eight pigs were studied without the infusion of endotoxin to determine the hemodynamic and respiratory consequences of AO with ECCO\textsubscript{2}R and six additional pigs were studied following endotoxin infusion to evaluate the limitation of the technique to provide adequate gas exchange during respiratory failure.

Materials and Methods

Animal preparation and surgery
The fourteen pigs used for this study were of 36.5 kg average weight. Each animal was premedicated with 0.01 mg/kg Atropine Sulfate, induced with 30 mg/kg Ketamine Hydrochloride and 1.65 mg/kg Morphine Sulfate, and intubated. Sodium Pentobarbital was infused at 4 mg/kg/hr into an ear vein for anesthesia maintenance. Metocurine Iodide was given (0.01 mg/kg) as required to maintain paralysis. Artificial ventilation was established with a volume ventilator\textsuperscript{a} set at an initial tidal volume of 13 ml/kg, and a frequency of 15 breaths/min. Inspired fraction of oxygen, end tidal fraction of oxygen (F\textsubscript{et}O\textsubscript{2}), and airway pressure were monitored at the distal tip of the endotracheal tube. A standard electrocardiogram was monitored. The right femoral artery was cannulated for arterial blood pressure measurement and arterial blood gas sampling. A small anatomy (15 cm injection port) 7F Swan-Ganz thermodilution catheter\textsuperscript{b} was inserted in the right femoral vein and flow directed into the pulmonary artery. This catheter was used to sample mixed venous blood and to measure pulmonary artery pressure, central venous pressure, pulmonary capillary wedge pressure, blood temperature, and cardiac output via the thermodilution technique. Blood gases were determined with a standard blood gas analyzer. The external jugular veins were exposed bilaterally for cannulation. A 22F venous cannula was introduced into the right jugular vein and advanced 25 cm to a level below the right atrium. A 20F venous cannula was introduced into the left jugular vein and advanced 10 cm toward the superior vena cava.

Extracorporeal circuit
The extracorporeal circuit consisted of a 1/4" polyvinyl chloride tubing segment extending from the right external jugular vein catheter to a 500 ml collapsible reservoir. From this reservoir, the blood was pumped with a clinically standard non-occluded roller pump\textsuperscript{c} through a 3/8" tubing segment into one of two membrane lungs\textsuperscript{d,e}. The blood returned to the animal through the left external jugular vein via another 1/4" tubing segment. The integral heat exchanger of each membrane lung maintained the extracorporeal circuit blood normothermic by means of a thermostatically controlled water bath. The circuit was prepared by flushing 2–3 minutes with 100% carbon dioxide and priming with one liter of heparinized (2 U/ml) Plasmalyte\textsuperscript{f}. Shortly before extracorporeal circulation was to be initiated, the prime was displaced with heparinized (4 U/ml) donor pig blood. The pH and PCO\textsubscript{2} of this final blood prime was adjusted to near normal venous blood gas values with Sodium Bicarbonate injection and room air ventilation. The flow rate through the membrane lung was monitored by first passing the gas through a precision rotameter\textsuperscript{g}. A gas blender\textsuperscript{h} was used to adjust the gas mixture of the membrane lung from an F\textsubscript{IO}2 of 0.209 (room air) to 1.0 (100% oxygen). The actual F\textsubscript{IO}2 was confirmed using an oxygen analyzer\textsuperscript{i}.

Experimental protocol
Prior to cannulation for veno-venous bypass, a baseline data set was obtained. Two hundred U/kg heparin were administered and activated clotting time determinations were used thereafter to ensure clotting times of 2–3 X the baseline value. Immediately after cannulation, another data set was obtained and venovenous bypass was initiated. The extracorporeal circulation was begun slowly (100–200 ml/min), and over a period of 30 minutes was increased to 1 L/min which was then kept constant for the remainder of the exper-

\textsuperscript{a} Model 607, Harvard Instruments, Millis, MA 02054
\textsuperscript{b} Model 93A-095-7F, American Edwards, Santa Ana, CA 92711
\textsuperscript{c} Model 7400, Sarns, Ann Arbor, MI 48103
\textsuperscript{d} M-2000, Shiley Inc., Irvine, CA 92714
\textsuperscript{e} Capiox II 33, Terumo Corp., Tokyo, Japan
\textsuperscript{f} 2B-25-44, Travenol Laboratories, Deerfield, IL 60015
\textsuperscript{g} Model 10A3555, Fisher, Pittsburgh, PA 15219
\textsuperscript{h} Model 5100, Bird Corp., Palm Springs, CA, 92263
\textsuperscript{i} Model OM-11, Beckman, Fullerton, CA 92634
Hemodynamic and respiratory function measurements

Each data set consisted of mean arterial and pulmonary artery pressures, central venous pressure, pulmonary capillary wedge pressure, heart rate, cardiac output, arterial and venous blood gases, blood temperature, hematocrit, F_iO_2, F_eO_2 (membrane lung), PEEP, lung peak airway pressure (obtained at the initiation of each positive ventilation period), and pulmonary shunt. Pulmonary shunt (%) was calculated as SHUNT = (C_O_2 - C_VO_2) / (C_O_2 - C_CO_2) where C_AO_2 = arterial oxygen content (ml/dL), C_VO_2 = venous oxygen content (ml/dL), and C_ENDO_2 = end capillary oxygen content (ml/dL). The C_VO_2 was estimated from the alveolar oxygen tension as determined by the measurement of F_endO_2. To derive blood oxygen contents, O_2 saturation was calculated with the method of Lutz and hemoglobin concentrations were estimated as one-third of the hematocrit value. Statistical evaluation was performed with the Student’s t-Test and p values of < 0.05 were considered significant.

Results

Table 1 compares the hemodynamic and blood gas data obtained during the control period prior to cannulation, immediately after cannulation and prior to the initial apneic oxygenation state. This pre-apnea data collection was taken at a constant veno-venous bypass flow of 1 L/min but prior to any ventilation of the membrane lung. The post-cannulation data does not differ significantly from the pre-cannulation data. The pre-apnea data differs, however, with respect to the mean arterial pressure, the mean pulmonary artery pressure, and the arterial pO_2. Also shown is a comparison of the hematocrit before and after the initiation of bypass. Hematocrit was not significantly altered by the initiation of the bypass.

Table 2 compares the mean hemodynamic and respiratory data at the conclusion of each apneic state for all pigs without endotoxin. The only significant hemodynamic difference between apneic states was with mean pulmonary artery pressure which declined with increasing F_eO_2. The respiratory variables which showed significant difference between treatments were pAco_2 and F_eO_2. The F_eO_2 at the conclusion of each apneic state varied directly with the F_eO_2 of the gas ventilating the membrane lung (Figure 1). This relationship was always observed, with or without endotoxin infusion.

Figure 2 demonstrates the time course of the mean pulmonary artery and peak airway pressure changes which occurred after the initiation of the endotoxin infusion. The control value for each parameter (immediately prior to the start of the infusion but while on apneic oxygenation) is shown at time zero. The effect

Figure 1: Graph depicting change in membrane lung inlet oxygen fraction and resulting post-apnea end-tidal oxygen fraction.
Table 1
Comparison of hemodynamic and blood gas data prior to the apneic periods

<table>
<thead>
<tr>
<th></th>
<th>Pre-cannulation</th>
<th>Post-cannulation</th>
<th>Pre-apnea</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP, mmHg</td>
<td>57.8 (7.7)</td>
<td>58.2 (6.8)</td>
<td>72.5 (10.2)**</td>
</tr>
<tr>
<td>MPAP, mmHg</td>
<td>11.4 (4.1)</td>
<td>12.9 (5.1)</td>
<td>22.6 (5.7)**</td>
</tr>
<tr>
<td>HR, /min</td>
<td>120.4 (15.8)</td>
<td>127.2 (18.0)</td>
<td>129.4 (22.5)</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>5.7 (1.1)</td>
<td>5.1 (1.2)</td>
<td>5.1 (1.6)</td>
</tr>
<tr>
<td>CVP, mmHg</td>
<td>2.3 (2.9)</td>
<td>2.8 (3.4)</td>
<td>2.5 (3.2)</td>
</tr>
<tr>
<td>paH</td>
<td>7.33 (.05)</td>
<td>7.34 (.04)</td>
<td>7.34 (.06)</td>
</tr>
<tr>
<td>paO₂, mmHg</td>
<td>83.8 (10.2)</td>
<td>82.8 (11.1)</td>
<td>69.9 (11.1)*</td>
</tr>
<tr>
<td>paCO₂, mmHg</td>
<td>39.2 (6.2)</td>
<td>37.8 (6.0)</td>
<td>40.1 (4.9)</td>
</tr>
<tr>
<td>HCT, %</td>
<td>28.3 (2.1)</td>
<td>28.3 (2.1)</td>
<td>29.0 (1.8)</td>
</tr>
</tbody>
</table>

Values are means ± (S.D.) for 14 pigs. MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; HR, heart rate; CO; cardiac output; CVP, central venous pressure; paH, arterial pH; paO₂, arterial pO₂; paCO₂, arterial pCO₂; HCT, hematocrit. *Significant difference from pre-cannulation (P < 0.05). **Significant difference from pre-cannulation (P < 0.01).

Table 2
Comparison of end apneic state hemodynamic and blood gas data

<table>
<thead>
<tr>
<th></th>
<th>FₐO₂ = 0.209</th>
<th>FₐO₂ = 0.60</th>
<th>FₐO₂ = 1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP, mmHg</td>
<td>73.3 (12.3)</td>
<td>76.0 (13.1)</td>
<td>78.2 (12.7)</td>
</tr>
<tr>
<td>MPAP, mmHg*</td>
<td>14.0 (4.9)</td>
<td>10.3 (3.2)</td>
<td>8.6 (2.8)</td>
</tr>
<tr>
<td>HR, /min</td>
<td>99.3 (27.2)</td>
<td>84.3 (17.7)</td>
<td>78.9 (16.9)</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>4.2 (1.1)</td>
<td>3.9 (1.0)</td>
<td>3.7 (1.0)</td>
</tr>
<tr>
<td>CVP, mmHg</td>
<td>1.3 (1.4)</td>
<td>1.4 (1.1)</td>
<td>1.4 (1.3)</td>
</tr>
<tr>
<td>paH</td>
<td>7.46 (.09)</td>
<td>7.47 (.10)</td>
<td>7.48 (.10)</td>
</tr>
<tr>
<td>paO₂, mmHg**</td>
<td>72.7 (23.4)</td>
<td>227.7 (53.3)</td>
<td>420.6 (64.3)</td>
</tr>
<tr>
<td>paCO₂, mmHg</td>
<td>34.5 (7.0)</td>
<td>33.1 (6.8)</td>
<td>32.5 (7.3)</td>
</tr>
<tr>
<td>FₐO₂, %**</td>
<td>26.9 (7.3)</td>
<td>50.7 (8.7)</td>
<td>70.3 (10.6)</td>
</tr>
</tbody>
</table>

Values are means ± (S.D.) for 8 pigs. MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; HR, heart rate; CO; cardiac output; CVP, central venous pressure; paH, arterial pH; paO₂, arterial pO₂; paCO₂, arterial pCO₂; HCT, hematocrit; FₐO₂, end tidal oxygen fraction. *Significant difference between states (P < 0.05). **Significant difference between states (P < 0.01).

Figure 2: Time course of mean pulmonary artery pressure (open circles) and peak airway pressure (closed circles) following onset of endotoxin infusion shown at time zero. Plotted are means ± S.D. of the endotoxin infusion was characterized by progressive elevations in mean pulmonary artery pressure and lung peak airway pressure. Significant difference from the control (p < 0.05) begins at 76 minutes for mean pulmonary artery pressure and at 139 minutes for peak airway pressure.

The relationship between pulmonary shunt, mean pulmonary artery and peak airway pressures, and arterial pO₂ for each apneic state during endotoxin infusion was analyzed. The data indicates that at a membrane lung FₐO₂ of 0.40, as the shunt progressed beyond 40%, the corresponding pO₂ values fell below 80 mmHg (Table 3). As the pulmonary distress worsened (increased mean pulmonary artery and peak airway pressures) a membrane lung FₐO₂ of 0.60 was required to maintain the pO₂ above 80 mmHg. The point at which the pO₂ fell below 80 mmHg when the membrane lung was ventilated with an FₐO₂ of 1.0 was not observed over the duration of the endotoxin infusion. This level of FₐO₂ was effective for the degree of pulmonary distress which occurred over the exper-
Table 3
Extent of lung distress at an arterial pO2 of 80 mmHg

<table>
<thead>
<tr>
<th>F102 = 0.40</th>
<th>F102 = 0.60</th>
<th>F102 = 1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIME, minutes</td>
<td>190</td>
<td>300</td>
</tr>
<tr>
<td>SHUNT, %</td>
<td>41</td>
<td>41</td>
</tr>
<tr>
<td>MPAP, mmHg</td>
<td>37</td>
<td>40</td>
</tr>
<tr>
<td>PAWP, cmH2O</td>
<td>22</td>
<td>27</td>
</tr>
</tbody>
</table>

Values are means within time course of the endotoxin infusion for 6 pigs. MPAP, mean pulmonary artery pressure; PAWP, peak airway pressure.

Discussion

Veno-venous cannulation is one of several access techniques that has been used in the extracorporeal support of respiratory failure. Proposed advantages of this technique over others include little change in cardiovascular hemodynamics, uniform distribution of arterialized blood, absence of major artery cannulations, and pre-oxygenation of the pulmonary blood flow.8-10,19,10 The presence of the cannulae did not significantly alter the cardiovascular hemodynamics of the animals (Table 1). The positioning of the cannulae proved to be repeatable between animals as confirmed by random necropsy. Venous drainage to the membrane lung was always sufficient to support the 1 L/min blood flow rate used for these studies.

The data collected after the bypass was initiated but prior to the first apneic state showed a significant elevation in mean arterial and pulmonary artery pressures and a significant reduction in pao2 (Table 1). Although the increase in mean arterial pressure remained for all animals studied, the elevation of mean pulmonary artery pressure and reduction of pao2 was transient. We believe these changes to be the result of a reaction to the donor pig blood added to the circuit to prevent bypass induced hemodilution. Despite this initial reaction, low flow veno-venous bypass could be maintained for several hours with hemodynamic stability.

The hemodynamic and respiratory state of the animals not receiving endotoxin showed improvement during apneic oxygenation compared with the pre-apneic data (Table 2). Of the hemodynamic variables, only the pulmonary artery pressure significantly differed between apneic states. As the membrane lung F102 increased the pulmonary artery pressure declined.

It is probable that this decrease is the direct result of relief of pulmonary vasoconstriction as more favorable oxygenation conditions were achieved. The ventilatory status during apnea of the eight animals without endotoxin would best be described as respiratory alkalosis. This is the result of excessive CO2 removal by the membrane lungs during this first phase of the investigation. However, the mean pCO2 and pH of all 14 pigs (with and without endotoxin) were held to 36.9 mmHg and 7.41 respectively. The use of ECCO2R was shown to be an effective adjunct to apneic oxygenation and is capable of maintaining carbon dioxide within normal ranges with little or no ventilation.

The rise in F102 as the F102 of the membrane lung was increased is clearly shown (Figure 1). The measurement of F102 in this study is a direct indicator of the alveolar pO2 (PAO2). The PAO2 and the resulting affect on pao2 are in direct relationship with the F102 status of the membrane lung. Manipulation of the nitrogen content of the blood via the membrane lung will bring about changes in the nitrogen content of the alveolar space thereby affecting the alveolar oxygen concentration.13,18,21,22 At steady state, changes in nitrogen content will be responsible for the alterations in pao2 observed. It must be noted, however, that as the F102 through the membrane lung is increased, the alveolar pO2 is less than expected theoretically. This observation is most likely the result of ventilation/perfusion inequalities in the various alveolar units.

Infusion of E. Coli endotoxin resulted in a progressive elevation of both mean pulmonary artery pressure and peak airway pressure (Figure 2). These results are consistent with the findings of others23-25 and are the result of a loss in pulmonary cell membrane integ-
rity and progressive development of perivascular edema. Pulmonary mechanics and function following the endotoxin infusion are characterized by decreasing lung compliance, decreasing functional residual capacity, decreasing $p_aO_2$, and increasing pulmonary shunt. As a result of these progressive and deteriorating changes, it is possible to determine the effectiveness of AO with ECCO$_2$R with varying degrees of pathology in our model. Table 3 indicates the level of shunt, mean pulmonary artery pressure, and peak airway pressure at which hypoxemia, defined here as a $p_aO_2$ of 80 mmHg or less, begins. Our data presented here suggests that an $FiO_2$ in excess of 0.40 would be required to support lung injury characterized by a pulmonary shunt in excess of 40%, a mean pulmonary artery pressure over 37 mmHg, and a peak airway pressure in excess of 22 cmH$_2$O. As the level of pulmonary distress worsens, as evidenced by the increased mean pulmonary artery and peak airway pressures, a higher $FiO_2$ (0.60) is required to support the oxygenation requirements of the model. Hypoxia was not observed with an $FiO_2$ of 1.0 over the duration of the study periods. The resulting level of alveolar oxygen concentration using an $FiO_2$ of 1.0 was always capable of supporting the animals. AO with ECCO$_2$R could readily maintain arterial $p_aO_2$ at or above normoxic levels following respiratory failure in this study. In previous unpublished experiments with higher rates of endotoxin infusion, however, we have seen that lung pathology can eventually progress to a point where an $FiO_2$ of 1.0 cannot meet the ventilatory needs of the animal. Therefore, a definite limit to the effectiveness of the technique does exist.

Several key features of the efficacy of AO with ECCO$_2$R for this pig model can be developed from these findings. First, there is very little hemodynamic consequence to the prolonged application of this support technique. Second, higher alveolar oxygen concentrations will support more advanced pulmonary distress (Figure 3). The results of this investigation indicate that AO with ECCO$_2$R can support pulmonary shunt in excess of 50% with alveolar oxygen concentrations controllable by $FiO_2$ manipulation of the membrane lung (Figure 1). Controlling $p_aO_2$ with the membrane lung $FiO_2$ obviates any requirement to expose the lung to extremely high oxygen partial pressures at the alveolar level to provide gas exchange. Third, AO with ECCO$_2$R not only satisfies oxygenation requirements over a wide range of lung conditions but also eliminates carbon dioxide sufficiently to keep $p_aCO_2$ and pH within normal limits. AO with ECCO$_2$R has been shown to be an easily manageable respiratory support technique capable of meeting the gas exchange requirements in a porcine model of endotoxin induced respiratory failure.

References

Questions from the Audience

Question—Sandra Pfefferkorn: How long were you able to maintain successful pig models with this particular technique? Did you have a time limit?

Answer: We had three different apneic states that we applied to the animals three different times for a total of nine states. Each state was the five minute ventilation period, 20 minute apneic period and then a data collection. In fact the total period was about 30 minutes, so that was four and a half hours that our experiments were designed. Now I will say that we did quite a few pilot experiments, and we in fact supported pigs for up to eight hours with this particular technique, with no lung motion at all. Absolutely none. Those were not equally induced respiratory models, but it speaks well of the ability of the technique with no lung motion at all to be able to support, at least, a viable pig.

Question—Pfefferkorn: Were you able to do the veno-venous bypass without heparin, or did you use heparin?

Answer: We did use heparin. We anticoagulated the pigs with approximately 200 units per kilogram and had no difficulty whatsoever, and had no evidence of a problem with heparinization. We did supplement the heparin. We did use ACTs to monitor that.

Question—Pfefferkorn: With the size of the pigs being 40 kilos, and one liter flow, can you extract data from that into a human model of a 70 kilo man with respiratory failure? Would the flows be comparable?

Answer: Yes, that would. In fact, the clinical trials that have been done with patients in Italy have been done with very low flow veno-venous bypass. Typically between one and one and a half liters per minute of flow and have been very successful. All of the clinical trials have used two SciMed membrane lungs in parallel. They have had no difficulty at all with CO₂ removal. And, yes, it has been done with very low flows. It appears to be an attractive feature of this particular technique.

Question—Tom Utsey: Would you clarify, just briefly, the apneic phase with regard to the endotracheal end of the experiment? You mentioned no air flow. Did you have any at all, or did you just use very low IMVs?

Answer: During the apneic periods, which were 20 minutes in length, there was no lung motion at all. Oxygen was delivered from an oxygen filled spirometer and we were able to have, on that spirometer, a constant pressure of 8 cm of water in the airway. This was a solid column of oxygen directed from the spirometer through the endotracheal tube into the trachea and down into the alveoli. Now, of course, depending on what the membrane lung was doing at the time with respect to its ventilation, that would determine what the alveolar content would be. In other words, with 100 percent ventilation of the membrane lung, we could wash out a great deal of the nitrogen of the alveolar space and elevate the entire oxygen. With room air going through the membrane lung, we would be actually washing in nitrogen into the alveolar space and decreasing that content. So we had the ability to actually change the alveolar content and the environment for the pig, depending upon the respiratory distress, and on what the pig needed.