
Evaluation of Two Microporous Polypropylene Membrane Lungs for Extracorporeal Carbon Dioxide Removal during Apneic Oxygenation

Philip D. Beckley and Richard D. Tallman, Jr.

Division of Circulation Technology, School of Allied Medical Professions
The Ohio State University
Columbus, Ohio

Abstract

Five Capiox II 33 (Terumo Corporation) and nine M-2000 (Shiley Incorporated) microporous polypropylene membrane lungs were evaluated for dynamic operating characteristics during apneic oxygenation. Particular emphasis was placed on carbon dioxide and oxygen transfer (VCO_2 and VO_2 respectively). The lungs were incorporated into extracorporeal venovenous bypass circuits used with the pigs of 36.5 kg average weight. VCO_2 was determined by analyzing outlet gas composition and VO_2 was determined with the Fick technique. Blood flow rate was held constant at 1 L/min in all trials. Peak VCO_2 occurred at gas flow rates of 4 L/min and 6 L/min for the Capiox II 33 and M-2000 respectively. Both lungs eliminated CO_2 in quantities sufficient for complete ventilatory support during apneic oxygenation over the 5–8 hour experiments. VO_2 for the Capiox II 33 was 18.2 and 45.6 ml/min with an inlet oxygen saturation of 70% and FiO_2 of 0.209 and 1.0 respectively. Under the same conditions, the VO_2 for the M-2000 was 27.2 and 43.1 ml/min. Both lungs operated with low gas inlet pressures over the gas flow rates used and the blood path pressure drop averaged 42.2 and 20.7 mmHg for the Capiox II 33 and M-2000 respectively.

Introduction

Gattinoni et al.¹⁻⁴ have reported clinical trials of a ventilatory support technique for patients in acute respiratory failure. Identified as low frequency positive pressure ventilation (LFPPV) with extracorporeal CO_2 removal (ECCO₂R), it is best characterized as a separation

of the gas exchange functions of the lungs.⁵⁻⁸ Oxygenation of the patient occurs primarily via apneic oxygenation with periodic inflations of the lung at low frequencies (2 to 3 breaths per minute). Carbon dioxide elimination is achieved via a low-flow venovenous extracorporeal bypass through a membrane lung. It is suggested that LFPPV with ECCO₂R minimizes many of the complications and risks associated with conventional positive pressure ventilation or high-flow venoarterial extracorporeal membrane oxygenation.^{5,7,8}

Artificial lungs constructed of silicone rubber membrane material have been used in the clinical trials. Kolobow⁹ introduced a silicone rubber spiral coiled membrane lung specifically constructed for removal of carbon dioxide. Microporous membrane lungs, however, offer promise in this technique due to their low resistance to carbon dioxide transfer and are perhaps ideally suited for ECCO₂R.¹⁰⁻¹² In addition to efficient CO_2 removal, the membrane lung chosen for this application should also have the capability of transferring oxygen in amounts sufficient to augment the apneic oxygenation process, have minimal blood and gas path resistance, be easily manageable as an extracorporeal device, and be able to perform over long periods of ventilatory support.

This study describes the evaluation of two microporous polypropylene membrane lungs used for ECCO₂R in a pig model of acute respiratory failure. The lungs were specifically evaluated with respect to their efficiency of carbon dioxide elimination, augmentation of oxygen transfer, and physical dynamic properties.

Materials and Methods

Animal preparation and surgery

Fourteen pigs of 36.5 kg average weight were used for this study. Each animal was premedicated with 0.01 mg/kg Atropine Sulfate, induced with 30 mg/kg

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Direct communications to: Philip D. Beckley, M.S. Circulation Technology 1583 Perry Street Columbus, OH 43210

Ketamine Hydrochloride and 1.65 mg/kg Morphine Sulfate, and intubated. Maintenance anesthesia was accomplished with a 4 mg/kg/hr infusion of Sodium Pentobarbital. Metocurine Iodide was given (0.01 mg/kg) as required to maintain paralysis. Ventilation was established with a volume ventilator^a set at an initial tidal volume of 13 ml/kg and a frequency of 15 breaths/min. An electrocardiogram, arterial pressure, central venous pressure, and pulmonary arterial pressure were monitored. Cardiac output was determined via the thermodilution technique with a 7F Swan-Ganz catheter^b. Arterial and mixed venous blood gases were obtained from the arterial pressure and Swan-Ganz catheters respectively. The external jugular veins were cannulated bilaterally for veno-venous bypass. 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

Nine of the membrane lungs used in this study were of the flat plate design with a surface area of 2.3 M² ^c and five were of the hollow fiber configuration with a surface area of 3.3 M² ^d. Both membrane materials were microporous polypropylene. Each will hereafter be referred to as the M-2000 and the Capiox II 33. The extracorporeal circuit consisted of a 1/4" polyvinyl chloride tubing segment connecting the right jugular vein catheter to a 500 ml capacity collapsible reservoir. The blood was pumped from this reservoir into the membrane lung with a clinically standard non-occluded roller pump^e through a 3/8" tubing segment. The blood returned to the animal through the left jugular vein via another 1/4" tubing segment. The integral heat exchanger of each membrane lung maintained the extracorporeal circuit blood normothermic. In all cases the circuits were flushed for 2–3 minutes with 100% carbon dioxide and primed with one liter of heparinized (2 U/ml) Plasmalyte solution^f. Prior to the initiation of the veno-venous bypass, this prime was displaced with heparinized (4 U/ml) donor pig blood and the pH and pCO₂ of this final blood prime was adjusted to near normal venous blood gas values with NaHCO₃ injection and brief ventilation with room air. The ventilation flow rate through the membrane lung was

monitored by passing the gas source through a precision rotameter^g. A gas blender^h was used to adjust the ventilating gas mixture from an F_iO₂ of 0.209 (room air) to 1.0 (100% oxygen). Membrane lung gas inlet fraction of oxygen (F_iO₂) was confirmed and gas outlet of carbon dioxide (F_eCO₂) was determined with an oxygen analyzer and carbon dioxide analyzer respectively.^{i,j} Membrane lung blood inlet and outlet and gas inlet pressures were monitored. Blood inlet and outlet gas partial pressures and pH were obtained and determined with a standard blood gas analyzer.

Experimental protocol

Prior to cannulation for veno-venous bypass 200 U/kg Heparin was administered and activated clotting time determinations were used to ensure clotting times of 2–3 X the baseline value throughout the experiment. After cannulation, the extracorporeal circulation was begun slowly (100–200 ml/min) and over the course of 30 minutes was increased to 1 L/min which was then kept constant for the remainder of the experiment. The pigs were mechanically ventilated for 5 minutes with a randomly assigned inspired fraction of oxygen of 0.209, 0.40, 0.60, or 1.0. Following each ventilation period, the pig was placed on apneic oxygenation by attaching the endotracheal tube to a spirometer filled with 100% oxygen. Simultaneously, the F_iO₂ was adjusted to ventilate the membrane lung with an oxygen fraction identical to that which was previously delivered with mechanical ventilation. A constant airway pressure of 7–8 cmH₂O was maintained during this period of apnea. Data was collected after 20 minutes of apneic oxygenation. This data collection was followed by the next F_iO₂ assignment. Eight pigs were studied as normal respiratory function models and six pigs were studied with varying degrees of respiratory distress induced by infusion of E. Coli endotoxin^k infused into the jugular vein at a rate of 7.5 microg/kg/hr.

Membrane lung function measurements

Each data set consisted of arterial and venous blood gases and pH, blood temperature, hematocrit, membrane lung F_iO₂ and F_eCO₂, membrane lung inlet and outlet blood gases and pH, blood inlet and outlet pressure, gas inlet pressure, and membrane lung gas flow rate. Carbon dioxide transfer (VCO₂, ml/min) was calculated as $VCO_2 = (GFR)(F_eCO_2)$ where $GFR =$

a Model 607 Harvard Instruments, Millis, MA 02054
b Model 93A-095, American Edwards, Santa Ana, CA 92711
c M-2000, Shiley Inc., Irvine, CA 92714
d Capiox II 33, Terumo Corp., Tokyo, Japan
e Model 7400, Sarns, Ann Arbor, MI 48103
f 2B-25-44, Travenol Laboratories Deerfield, IL 60015

g Model 10A3555, Fisher, Pittsburgh, PA 15219
h Model 5100, Bird Corp., Palm Springs, CA 92263
i Model OM-11 Beckman, Fullerton, CA 92634
j Model LB-2, Beckman, Fullerton, CA 92634
k 055:B5, Sigma, St. Louis, MO 63178

membrane lung gas flow rate (ml/min) and $F_e\text{CO}_2$ = fraction of carbon dioxide in the exit gas. Oxygen transfer (VO_2 , ml/min) was calculated as $\text{VO}_2 = (C_o\text{O}_2 - C_i\text{O}_2)(\text{BFR})$ where $C_o\text{O}_2$ = outlet oxygen content (ml O_2 /ml blood), $C_i\text{O}_2$ = inlet oxygen content (ml O_2 /ml blood), and BFR = membrane lung blood flow rate (ml/min) which was held constant at 1000 ml/min. Blood oxygen saturations were calculated with the formula provided by Lutz¹³ for porcine blood. Hemoglobin concentrations were calculated as one-third of the hematocrit value. Gas transfer data obtained was converted to standard temperature and pressure (STP). The forcing function for carbon dioxide diffusion or log mean $\Delta p\text{CO}_2$ ¹⁴ was calculated as $\text{LM}\Delta p\text{CO}_2(\text{mmHg}) = (\Delta P1 - \Delta P2) / \ln(\Delta P1 / \Delta P2)$ where $\Delta P1$ = the difference between the $p\text{CO}_2$ at the blood inlet and gas exit (mmHg), and $\Delta P2$ = the difference the $p\text{CO}_2$ at the blood outlet and gas inlet (mmHg). The mass transfer coefficient was calculated as U (ml/min/mmHg) = $\text{VCO}_2 / \text{LM}\Delta p\text{CO}_2$.

Results

Figures 1 and 2 present the relationship between the forcing function for carbon dioxide ($\text{LM}\Delta p\text{CO}_2$) and the resulting carbon dioxide transfer for the Capiox II 33 and M-2000 respectively. Two mass transfer coefficient values (5.0 and 10.0 ml/min/mmHg) are shown for reference. Gas flow rate for this data ranged from 3 to 10 L/min. As a group, the data for the M-2000 is right shifted (lower values of mass transfer coefficient) when compared to the Capiox II 33. While the higher mass transfer coefficients were associated with lower

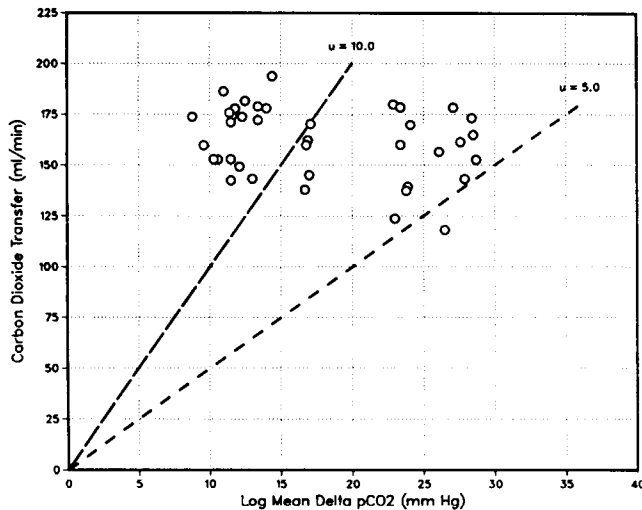


Figure 1: Relationship between forcing function for carbon dioxide and resulting carbon dioxide transfer for the Capiox II 33. Two mass transfer coefficients are plotted for reference. Gas flow rate range = 3–10 L/min.

gas flow rates for both lungs, this relationship was much more consistent with the Capiox II 33. Peak $\dot{\text{V}}\text{CO}_2$ occurred at gas flow rates of 4 L/min and 6 L/min for the Capiox II 33 and M-2000 respectively.

Figure 3 depicts the change in $p\text{CO}_2$ which occurred between the inlet and outlet of the devices as a function of the inlet $p\text{CO}_2$. A comparison was made between the two membrane lungs at 8 L/min gas flow. Data was also obtained at a lower gas flow (4 L/min) with the Capiox II 33. In all cases, as the inlet $p\text{CO}_2$ increased,

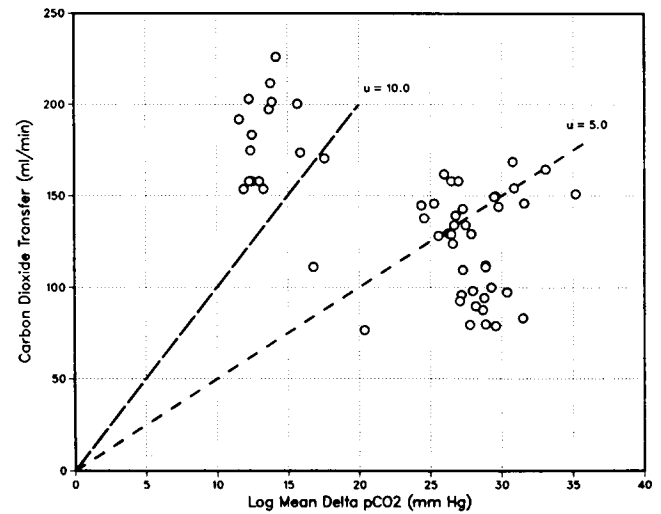


Figure 2: Relationship between forcing function for carbon dioxide and resulting carbon dioxide transfer for the M-2000. Two mass transfer coefficients are plotted for reference. Gas flow rate range = 3–10 L/min.

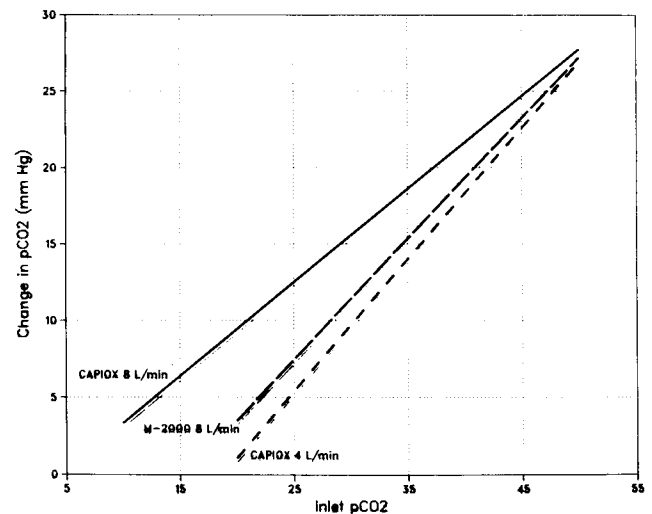


Figure 3: Linear regression data for the change in $p\text{CO}_2$ from lung inlet to outlet as a function of inlet $p\text{CO}_2$; gas flow rate, and membrane.

Capiox 8 L/min: $m = 0.61$, $b = -2.75$, $r = 0.95$, $p < 0.01$
M-2000 8 L/min: $m = 0.79$, $b = -12.3$, $r = 0.88$, $p < 0.01$
Capiox 4 L/min: $m = 0.86$, $b = -16.1$, $r = 0.95$, $p < 0.01$

the change in pCO₂ increased as well. The change in pCO₂ developed by the M-2000 was consistently below the Capiox II 33 at any given inlet pCO₂. As gas flow rate was decreased, the change in pCO₂ for a given inlet pCO₂ declined. In spite of these differences in performance, both membrane lungs were capable of eliminating CO₂ in quantities sufficient for complete ventilatory support during apneic oxygenation over the 5–8 hour duration of these studies. The mean pCO₂ and pH of all 14 pigs was held to 36.9 mmHg and 7.41 respectively.

Figures 4 and 5 identify the linear regression analysis of the oxygen transfer capability of each membrane lung at various blood inlet oxygen saturations and gas inlet oxygen concentrations (F_iO₂). At an inlet oxygen saturation of 70%, for example, and F_iO₂ of 0.209 and 1.0, the M-2000 $\dot{V}O_2$ was 27.2 and 43.1 ml/min respectively. For the Capiox II 33 under the same conditions, the $\dot{V}O_2$ was 18.2 and 45.6 ml/min.

Table 1 identifies the mean blood path pressure drop and gas inlet pressure for each membrane lung. The gas inlet pressure varied little with gas flow for either lung over the gas flow rates used for this study. At no time were blood path pressures ever exceeded by the gas path pressure.

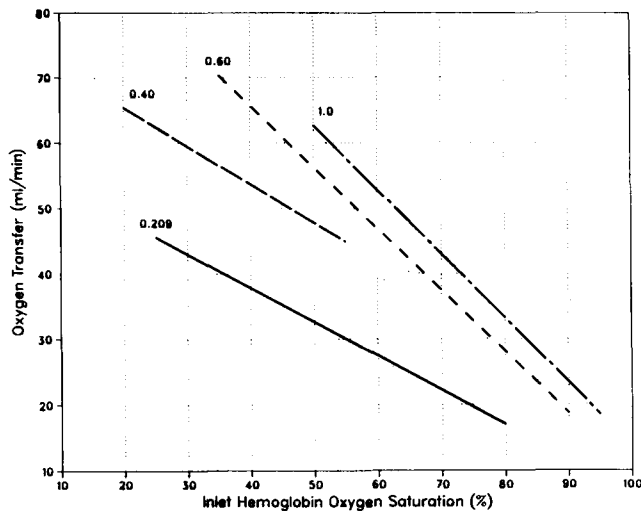


Figure 4: Linear regression data for oxygen transfer as a function of inlet hemoglobin saturation and gas inlet oxygen fraction for the M-2000

0.209: $m = -52.0, b = 58.6, r = -0.83, p < 0.01$
 0.40: $m = -58.6, b = 77.1, r = -0.59, p < 0.05$
 0.60: $m = -94.0, b = 103.3, r = -0.92, p < 0.01$
 1.0: $m = -98.1, b = 111.7, r = -0.97, p < 0.01$

Discussion

The primary determinate of the success of a membrane lung in this study was its ability to remove CO₂ in quantities sufficient to keep paCO₂ within normal limits at low extracorporeal blood flow. Low bypass flow is an important advantage of ECCO₂R, allowing it to be performed through smaller peripheral canulae with minimal roller pump trauma, thus facilitating its long term application. Low gas flow was sought to avoid pressurizing the gas path over the blood path. Both the M-2000 and the Capiox II 33 were clearly capable of maintaining arterial pCO₂ within normal limits in this pig model with and without endotoxin induced respiratory distress. The contrast

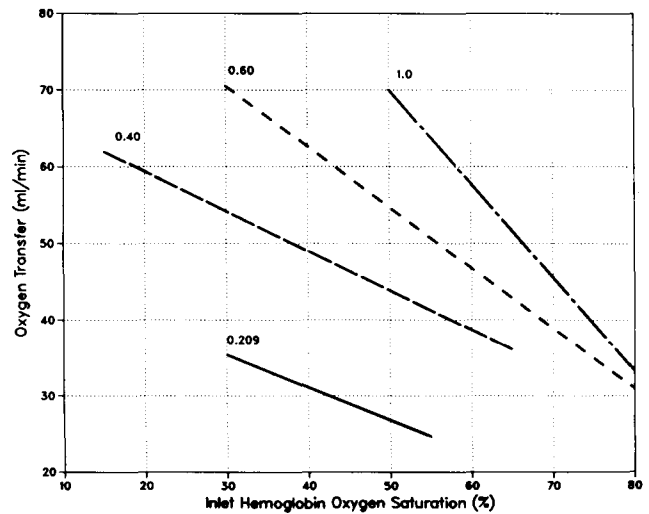


Figure 5: Linear regression data for oxygen transfer as a function of inlet hemoglobin saturation and gas inlet oxygen fraction for the Capiox II 33.

0.209: $m = -43.0, b = 48.3, r = -0.83, p < 0.05$
 0.40: $m = -51.8, b = 69.8, r = -0.95, p < 0.01$
 0.60: $m = -79.3, b = 94.4, r = -0.98, p < 0.01$
 1.0: $m = -122.5, b = 131.3, r = -0.96, p < 0.01$

Table 1
Comparison of the blood path pressure drop and gas inlet pressure for the microporous membrane lungs

Membrane Lung	Pressure Drop (mmHg)	Gas Inlet Pressure (mmHg)
Capiox II 33	42.2 (7.5)	3.2 (3.9)
M-2000	20.7 (9.2)	3.3 (2.6)

Values are means \pm (S.D.) for 47 data collections for the Capiox II 33 and 71 data collections for the M-2000.

in CO₂ elimination capabilities between the lungs is most likely due to the fact that the membrane surface areas of the two devices were different. The gas inlet pressure remained negligible over the range of gas flow rates used (3–10 L/min) and, in spite of the low blood path pressures, posed no threat to the transmembrane pressure gradient.

Although the membrane lung used for ECCO₂R will have as its major role CO₂ elimination, it also must augment the process of oxygenation. For passive apneic oxygenation, the bulk flow of oxygen into the alveolar space occurs as oxygen is consumed by the pulmonary blood flow.^{5,7} If the membrane lung can be used to establish the partial pressure of nitrogen in the venous blood, this will equilibrate with the alveolar gas thereby affecting the alveolar-arterial oxygen gradient. It is not necessary for the membrane lung to support the entire oxygenation process. It is only desired that it be capable of manipulating and maintaining the alveolar oxygen content by controlling the alveolar nitrogen. Both of the microporous membrane lungs used for this study were capable of this process. For the pigs not receiving endotoxin, as the F_iO₂ was raised from 0.209 to 0.60 the resulting paO₂ was increased from a mean value of 72.7 mmHg to 227.7 mmHg. From an F_iO₂ of 0.60 to 1.0 the mean paO₂ increased further to 420.6 mmHg.

In conclusion, it is apparent that these microporous membrane lungs are capable of performing as CO₂ eliminators using low-flow extracorporeal bypass. Arterial pCO₂ can effectively be held to normal limits in this pig model regardless of the degree of respiratory distress. The physical dynamics are such that, over the range of gas flow rates used, gas inlet pressure remained insignificant. The lungs were additionally capable of augmenting the process of apneic oxygenation by manipulating and maintaining the level of alveolar nitrogen concentration. Although our studies did not utilize the membrane lungs for extended periods of time, we did not observe any deterioration in function over the 5–8 hour duration of these experiments.

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