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# Clinical Trials of a New Low Prime Hollow Fiber Membrane Oxygenator

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## Abstract

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A new membrane oxygenator has been introduced by Travenol Laboratories with continued development carried out by Sarns Inc. The polypropylene hollow fibers are wound in a pattern perpendicular to the blood flow path and serve as the conduit for the ventilating gas. The membrane surface area is 1.8 M<sup>2</sup>. The device contains an integral stainless steel bellows heat exchanger and a temperature probe well built into the blood outlet. The oxygenator is held by a wire frame holder that can be mounted in any direction on the heart lung machine. A selection of various size collapsible PVC venous reservoir bags is available to meet individual patient needs. The venous inlet connector of the bag contains a temperature probe port and a connector for the cardiotomy drain line as well as a recirculation line that attaches to the oxygenator.

Twenty consenting adult patients undergoing either CABG or valve replacement were perfused using this oxygenating system. The largest patient had a BSA of 2.3 M<sup>2</sup> while the smallest was 1.48 M<sup>2</sup>. The mean patient size was 1.92 M<sup>2</sup>. For patients 2.0 M<sup>2</sup> or larger, a one liter reservoir bag was employed requiring a total system prime of 2.0 liters. For the remaining patients, a 500 ml bag and 1.75 liters of prime were used. In all but one case, the prime consisted of 500 ml of HES and the balance, Lactated Ringers to which was added 500 units heparin per liter of total prime. The remaining case utilized four units of fresh frozen plasma as a substitute for the HES and for 500 ml of the Lactated Ringers.

The blood gas results were very consistent and showed a very strong correlation between FiO<sub>2</sub> setting, BSA, blood temperature and pO<sub>2</sub>. The PaCO<sub>2</sub> was easily controlled to achieve alpha-stat by venti-

lating the oxygenator at the optimal ventilation rate. Results include an average PaO<sub>2</sub> of 137 mmHg with a mean O<sub>2</sub> transfer of 104 ml per minute and a maximum transfer of 244 ml per minute. There were no gas exchange nor acid-base problems. The heat exchanger performance was satisfactory.

The mean elevation in plasma hemoglobin was 19 mg/dl. The average decrease in platelet count was 37% while the hemodilutional hematocrit decrease was 26%. These data indicate that the oxygenator's blood handling characteristics compare favorably to other membrane oxygenators.

## Introduction

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The earliest configuration of hollow fiber membrane oxygenator suggested in the literature was one utilizing silicone rubber capillary tubing reported by Bodell, et al in 1962.<sup>1</sup> Because of the compliance of the silicone rubber capillaries, the gas exchange characteristics changed as the pressure changed. For this reason, this early membrane lung was designed so that blood flowed on the outside of the capillaries while the gas flowed through them. With the advent of microporous polypropylene and the technology to produce this material in hollow fibers of small, controlled geometry, several manufacturers reversed the earlier design and produced hollow fiber membrane oxygenators that used the capillary lumen for the blood path and circulated the ventilating gas around the fibers.<sup>2,3</sup> This configuration produced smooth laminar flow through the oxygenator and resulted in devices capable of producing uniform results.

These devices, however, require membranes of large surface area in order to oxygenate the blood.<sup>4</sup> For this reason, several new oxygenators have been produced with the gas flowing through the hollow fibers while the blood flows around the fibers.<sup>5,6</sup> The new Hollow Fiber Membrane Oxygenator (HFMO) designed by Travenol Laboratories with further development by Sarns Inc. is of the latter design.

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The Medical University of South Carolina was one of five heart surgery centers chosen to perform the FDA required clinical trials on the HFMO. Included for evaluation were different volume reservoir bags as well as a wire frame holder that supports both the reservoir bag and the oxygenator. The purpose of this report is to discuss the operational characteristics of this HFMO system based upon data generated during the FDA trials.

## Materials and Methods

The HFMO system was used to provide extracorporeal circulation for 20 adult patients undergoing routine cardiac surgical procedures. All patients signed an informed consent document approved by the Institutional Review Board.

The oxygenator (Figure 1) is constructed of micro-porous polypropylene hollow fibers wound in 48 layers perpendicular to the direction of blood flow. The effective surface area of blood-membrane contact is 1.8 square meters. The oxygenator contains a unique integral heat exchanger mounted beneath the fiber bundle. The heat exchanger is made from a stainless steel bellows with internal baffles to ensure even distribution of the circulating water. Blood flows up between the folds of the bellows and heat exchange occurs across the 0.15 square meters of contact surface. Both the fiber bundle and the heat exchanger are housed within a clear acrylic case, making the entire blood path visible.

The collapsible PVC reservoir bags (Figure 2), available in either 500, 1000 or 2000 ml sizes, are identical in design and vary only in their volume capacity. The venous inlet connector contains a temperature probe port, a medication port, a venous sampling port and an inlet for cardiotomy reservoir drainage as well as a recirculation line that attaches to the oxygenator. The reservoir bag mounts on a wire frame holder directly above the oxygenator which is spindled on the holder by its endcaps. The holding assembly will mount on either side of, or in back of virtually any heart-lung machine.

Blood was pumped<sup>a</sup> from the reservoir bag via 3/8" PVC tubing into the heat exchange section of the oxygenator. The blood passes between the parallel vanes of the bellows where caloric exchange occurs then up into the oxygenating compartment. The blood flows perpendicular to the hollow fibers passing between and around them where gas exchange occurs. The oxygenator outlet manifold, which contains an arterial sample port and a temperature probe well, collects the oxygenated blood which then goes to the patient. An

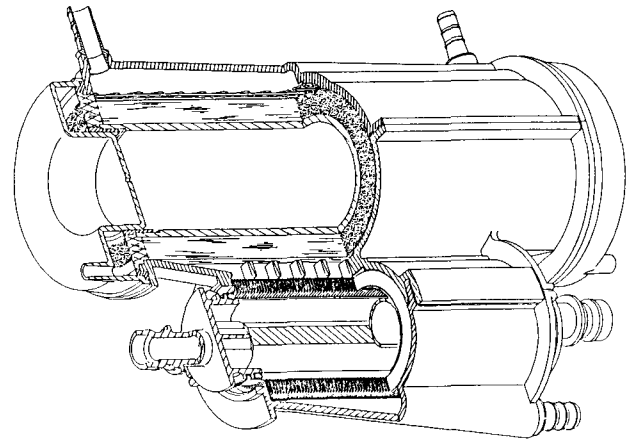


Figure 1

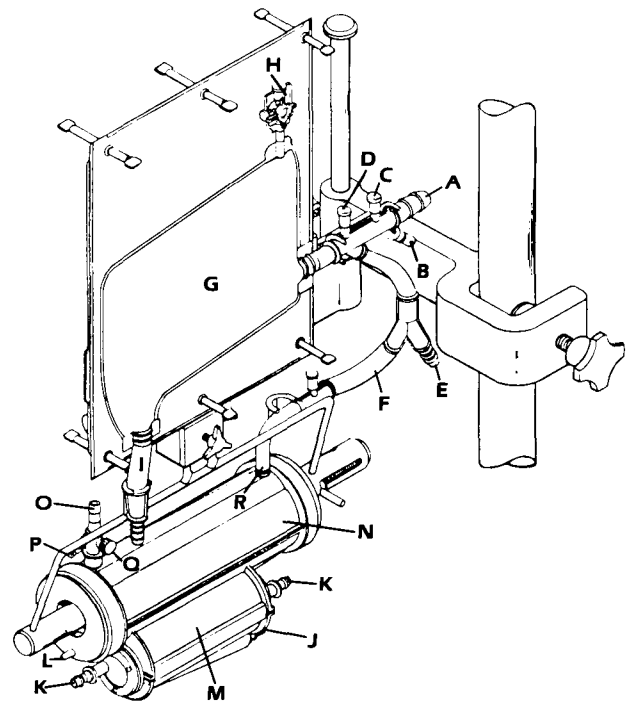


Figure 2: A = Venous Inlet, B = Ven Temperature Port, C = Venous Sampling Port, D = Administration Port, E = Cardiotomy Drain Port, F = Recirculation Line, G = Reservoir, H = Air Purge Port, I = Reservoir Outlet, J = Blood Inlet, K = Water Ports, L = Gas Port, M = Heat Exchanger, N = Oxygenator Fiber Bundle, O = Blood Outlet, P = Arterial Temperature Port, Q = Arterial Sampling Port, R = Recirculation Port

<sup>a</sup> Sarns Modular Pump, Sarns Inc., Ann Arbor, MI 48103

**Table 1**  
**Hematology and Blood Chemistry Schedule**

	Pre-Op	Pre-CPB	Post-CPB	PO Day-3	PO Day-7
Plasma Hgb		X	X	X	
Platelet Ct		X	X	X	
WBC		X	X	X	
BUN	X			X	X
Creatinine	X			X	X
LDH	X			X	X
SGOT	X			X	X
Alk Phosphatase	X			X	X
Total Bilirubin	X			X	X

arterial line filter<sup>b</sup> was used which was constantly purged via a valved purge line<sup>c</sup> into either a filtered<sup>d</sup> (valve replacement or aneurysm) or nonfiltered<sup>e</sup> (CABG) cardiomy reservoir. A purge line<sup>f</sup> was also connected from the reservoir bag's air purge port to a Leur Lock port on one of three suction lines to facilitate air removal from the bag reservoir.

For 13 of the patients whose body surface area (BSA) was less than two square meters, the 500 ml reservoir bag was used and the prime consisted of 1250 ml Lactated Ringers<sup>g</sup> and 500 ml Hespan<sup>h</sup> to which was added 1000 units of beef lung heparin. Seven patients had BSAs of two square meters or greater. For these patients, a 1000 ml reservoir bag was employed. For 6, the prime consisted of 1500 ml of Lactated Ringers and 500 ml of Hespan along with 1000 units of beef lung heparin. The final patient was undergoing a second mitral valve replacement and was on coumarin therapy until the time of operation. The prime contained four units of fresh frozen plasma (FFP), 1200 ml Lactated Ringers and 4300 units of beef lung heparin. One patient who also had been on coumarin therapy received two units of FFP while on bypass. Three patients each had two units of packed red cells added during bypass when their hematocrits fell below 25%.

Upon initiation of bypass, blood flow was adjusted to 2.2 liters per minute per square meter BSA. During moderate hypothermia (25–28°C), the flow index was reduced to 1.6 liters per minute and, to facilitate rewarming, the index was raised to 2.8.

During bypass, arterial and venous oxyhemoglobin

saturations were constantly monitored using the Bentley Oxy-Sat meter<sup>i</sup>. The PaO<sub>2</sub> and arterial saturation were controlled by varying the FiO<sub>2</sub> of the ventilating gas<sup>j</sup>. The ventilating gas flow was set at the estimated optimal ventilation rate<sup>6</sup> and maintained at that flow rate in order to achieve alpha-stat.<sup>7</sup> The exhaust gas CO<sub>2</sub> concentration was also continuously monitored<sup>k</sup> to assure that adequate amounts of CO<sub>2</sub> were being removed to achieve alpha-stat. Blood gas analysis<sup>l</sup> was performed at least every twenty minutes during bypass. The temperature corrected data were recorded while O<sub>2</sub> consumption and CO<sub>2</sub> production values were calculated using the uncorrected data.

The integral heat exchanger was evaluated by calculating the heat exchanger performance factor (PF) during both cooling and rewarming phases of bypass. These PFs were graphed versus the blood flow rates. The time required to rewarm each patient to a rectal temperature of 35°C was also noted.

The type and frequency of hematology and chemistry measurements are presented in Table 1. All patients were evaluated by their attending physician for signs of renal, metabolic, neoplastic, neurological, respiratory or vascular disease before and after surgery and the results compared.

Mean values and standard deviations for all values were calculated. Where appropriate, multiple regression analysis was performed to relate results to controlling functions. All analyses were performed on an IBM PC<sup>m</sup> computer using SYSTAT software<sup>n</sup>.

b Pall Biomedical Products Corporation, Glen Cove, NY 11542

c American Bentley, Irvine, CA 92714

d Model 5M 1471, Sarns Inc., Ann Arbor, MI 48103

e Model 5M 1470, Sarns Inc., Ann Arbor, MI 48103

f Double Male Connecting Line, American Bentley, Irvine, CA 92714

g Travenol Laboratories Inc., Deerfield, IL 60015

h American Critical Care, McGaw Park, IL 60085

i American Bentley, Irvine, CA 92714

j Sechrist Air-Oxygen Mixer, Sechrist Inc., Anaheim, CA 92806

k Foregger CO<sub>2</sub> Monitor, Northwest Oxygen Corp., Chamblee, GA 30341

l ABL-4 blood gas analyzer, Radiometer, Copenhagen, Denmark

m International Business Machines Corp., Boca Raton, FL 33432

n Systat, Inc., Evanston, IL 60202

## Results

Fourteen of the patients underwent coronary artery bypass grafting. Four patients had quadruple, six triple, two double, and one patient a single graft. One of the patients undergoing triple bypass had a concurrent left ventricular aneurysmectomy. Four patients had their aortic valves replaced while two underwent mitral valve replacement. One patient was undergoing reoperation.

Data describing the patients' size, bypass time, urine output, and hematology results are summarized in

Table 2. Note that the mean postbypass hematocrit is 74% of the prebypass level while the postbypass platelet count is depressed to 63% of the prebypass level. The mean elevation of plasma free hemoglobin was 18.8 mg/dl. Only one patient had a postbypass plasma hemoglobin concentration greater than 50 mg/dl. None of the other chemistry values (also summarized in Table 2) showed any significant changes attributable to the oxygenator.

Table 3 contains the summary of blood gas data. The maximum O<sub>2</sub> transfer measured during this study was 245 ml/min while the maximum CO<sub>2</sub> removal was

**Table 2**

	AGE	BSA	TIME	URINE	HCT 1	HCT 2
MINIMUM	36	1.48	45	12	.27	.21
MAXIMUM	83	2.30	132	1020	.43	.34
MEAN	54.2	1.92	98.7	253	.35	.26
SD	12.0	0.21	22.4	250	.039	.033
	PLT 1	PLT 2	WBC 1	WBC 2	PLHGB1	PLHGB2
MINIMUM	105	63	3.1	5.1	9.6	16.6
MAXIMUM	378	220	18.4	22.8	32.0	101.8
MEAN	194	122	6.9	9.8	18.3	37.1
SD	61	39	3.4	3.7	7.7	18.1
	LDH 1	LDH 2	BUN 1	BUN 2	CREAT1	CREAT2
MINIMUM	114	125	10	8.0	0.7	0.1
MAXIMUM	430	551	36	63	2.1	2.0
MEAN	227	299	17	18	1.1	1.0
SD	83	138	6.1	13	0.3	0.4

AGE = years, BSA = body surface area in square meters, TIME = bypass time in minutes, URINE = bypass urine production in cc, HCT 1 = prebypass hematocrit in %, HCT 2 = post bypass hematocrit in %, PLT 1 = prebypass platelet count in thousands/mm<sup>3</sup>, PLT 2 = postbypass platelet count in thousands/mm<sup>3</sup>, WBC 1 = pre bypass white cell count in thousands/mm<sup>3</sup>, WBC 2 = post bypass white cell count in thousands/mm<sup>3</sup>, PLHGB1 = prebypass plasma hemoglobin in mg/dl, PLHGB2 = postbypass plasma hemoglobin in mg/dl, LDH 1 = pre bypass lactic dehydrogenase in mU/ml, LDH 2 = post operative day 3 lactic dehydrogenase in mU/ml, BUN 1 = pre bypass blood urea nitrogen in mg/dl, BUN 2 = post operative day 3 blood urea nitrogen in mg/dl, CREAT1 = prebypass creatinine in mg/dl, CREAT2 = post bypass creatinine in mg/dl.

**Table 3**

	TEMP	PBAR	QBLOOD	QGAS	FIO2
NUMBER	105	105	105	105	105
MINIMUM	18.0	757	2360	2250	.25
MAXIMUM	39.0	780	5940	5200	.90
MEAN	31.5	768	3907	2936	.52
SD	5.0	6.5	886	376	.14
	HCT	PaO <sub>2</sub>	PaCO <sub>2</sub>	SAT(A)	SAT(V)
NUMBER	105	105	105	105	105
MINIMUM	16	48	21	95.0	50.3
MAXIMUM	34	410	49	99.9	94.6
MEAN	25.1	137	32	99.1	71.3
SD	7.5	63	7.5	2.5	10.2

TEMP = arterial blood temperature in degrees C., PBAR = barometric pressure in mmHg, QBLOOD = blood flow in ml/min, QGAS = gas flow in ml/min, FIO2 = fraction of oxygen in the ventilating gas, HCT = hematocrit in %, PaO<sub>2</sub> = arterial pO<sub>2</sub> in mmHg, PaCO<sub>2</sub> = arterial pCO<sub>2</sub> in mmHg, SAT(A) = arterial oxyhemoglobin saturation in %, SAT(V) = venous oxyhemoglobin saturation in %.

260 ml/min. There was an excellent correlation ( $r = .840$ ) between the  $\text{FiO}_2$  setting and the temperature, BSA and the  $\text{PaO}_2$ . The regression equation for this relationship is:

$$\text{FiO}_2 = .225 \cdot \text{BSA} + .017 \cdot \text{Temp}(\text{°C}) + .001 \cdot \text{PaO}_2 - .564. (p < .000)$$

There were no incidences of serious acid base disturbance. The mean pH (calculated from  $[\text{H}^+]$ ) at the end of bypass was 7.37 while the mean  $\text{PaCO}_2$  was 36.2 mmHg. Alpha-Stat was achieved simply by maintaining the optimal ventilation rate during hypothermic periods.

The heat exchanger performed well. During cooling, the mean performance factor was .477 with a standard deviation of .081. During rewarming, the performance factor mean value was .469 with a .115 standard deviation. When the performance factor was plotted against blood flow, the slope of the line was less than .001 indicating that performance was consistent over the blood flow range employed in this patient series. The average rewarm time was 24.4 minutes. The longest rewarm time was 40 minutes, while one patient was warmed in 10 minutes.

Only one patient in this series had any postoperative complication. That patient had to be returned to the operating room the evening of surgery for postoperative bleeding. The average surgical intensive care unit stay was just over one day while the average postoperative hospital stay was just under seven days. The attending physicians reported no changes in any patient's noncoronary disease status as a result of the perfusion.

## Discussion

The patient population for this study represented a typical sample of adult patients operated on at this institution. The BSA range was quite typical and thus the metabolic requirements. The performance of the HFMO during this study leads us to believe that it is an appropriate oxygenator for all adult patients.

The hematology results are similar to many other reports of membrane oxygenator performance. The slightly larger drop in platelet count (37%) when compared to the dilutional drop in hematocrit (25.9%) represents platelet consumption. The results from this study compare favorably to studies involving flat plate<sup>6,7</sup> and hollow fiber membrane oxygenator<sup>8,9</sup> design.

The trauma caused by the oxygenator system was minimal as indicated by the plasma hemoglobin and enzyme studies. The one elevated post operative plasma hemoglobin level occurred in a patient having a left internal mammary artery implant. Almost a liter of blood was returned to the system by the cardiomy suction system from the left pleural space just prior to the termination of bypass. We suspect that this blood

was damaged in a manner similar to blood allowed to pool in the pericardium.<sup>10</sup>

The control of blood gasses by this system was excellent. After the first several perfusions, the  $\text{FiO}_2$  needed to achieve good arterial  $\text{pO}_2$  was highly predictable. The regression equation developed can be used to calculate the proper  $\text{FiO}_2$  to achieve a desired  $\text{PaO}_2$  for a variety of patient sizes and a variety of operating temperatures.

The variability in the  $\text{PaCO}_2$  data is due to the fact that these patients were all perfused using the alpha-stat technique. This means that, during hypothermia, the  $\text{PaCO}_2$  is decreased to keep a constant  $\text{CO}_2$  content. It is noteworthy that the oxygenator was able to clear up to 260 ml/min of  $\text{CO}_2$ . This should suffice for the largest of patients.

Heat exchange was very efficient. The rewarm times were better than those reported for several of the newer membrane oxygenators.<sup>11,12</sup> The fact that there was no slope to the regression plot of performance factor and blood flow implies that, at least over the range of blood flows encountered in this study, the performance remains constant. The same lack of slope was found when the performance factor was plotted versus either water temperature or inlet blood temperature.

The priming volume of the HFMO was lower than other membrane systems.<sup>13,14</sup> Utilizing the 500 ml reservoir bag, the minimal priming volume for the system when used with our tubing set and accessories is 1500 ml as opposed to 2000 ml with the next lowest prime membrane oxygenator system. The 1500 ml priming volume is also lower than those reported for several of the newer membrane oxygenator systems. Although no pediatric size patients were included in this study, the low priming volume of the system indicates usage in children.

The oxygenator design incorporates the smallest amount of membrane material of any of the current devices, 1.8 square meters. This reduced surface for blood exposure may be of benefit. Clancy et al implicated microporous polypropylene in complement activation.<sup>14</sup> It would seem logical that the less surface area to which the blood is exposed, the less plasma protein derangement. Furthermore, the membrane material is the most expensive element in a membrane oxygenator. Hopefully, the small amount of membrane required by this design will result in a lower cost to the patient.

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### Questions from the Audience

*Question:* Do you have a rough figure for the priming volume?

*Answer:* The minimum priming volume we found with our system was 1500 milliliters. I compare that to 2000 for the next lowest priming membrane that we use. I went into the literature and looked at flat plate and hollow fiber, what's been reported from their testing, and this was lower than all those.

*Question:* What about if they give for the blood compartment and heat exchanger compartment singular?

*Answer:* I don't have that broken down into two. It's around 300 for the entire unit.

*Question—Tom Frazier:* Is there anything in particular that you did not like about the unit? What sort of pressure drop did you see across the unit?

*Answer:* During our clinical trials, we didn't measure the pressure drop. It was very minimal if you felt the line pressure. There was nothing we didn't like about it.

*Question—Ron Richards:* With the cardiotomy inlet coming into those small chambers at the bottom, when air gets into that lower chamber, did it clear very quickly? Does it strain into the bag and not the lower unit?

*Answer:* No, it then goes to the purge port on top of the collapsible bag and is vented out there. Circulation path was very good. I don't think we ever circulated any bubbles into the oxygenator.

*Question—Mary Williams:* When you use this new flow technique, with the blood going outside the bundles, if you noticed any channeling through this oxygenator, did you happen to cut them apart afterwards and look at them?

*Answer:* No we didn't. But as the slides showed, the tolerances between the fiber bundle and the shell itself are very, very close and very well controlled. If there were going to be straining, I think we would see it. The fact that we got such consistent oxygenator performance, pO<sub>2</sub>s, has made a high consistency from device to device.

*Question:* What is your experience with debubbling a full colloid prime?

*Answer:* The only colloid used was Hespan. We had no trouble debubbling or priming it. I started out gravity priming these things and continued, but I'm sure that you could pump prime and gravity prime, and however you want.