

## Clinical Trials of an Intravenous Oxygenator in Patients with Adult Respiratory Distress Syndrome

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In patients with severe adult respiratory distress syndrome, mechanical ventilation may not be able to ensure gas exchange sufficient to sustain life. We report the use of an intravenous oxygenator (IVOX) in five patients who were suffering from severe adult respiratory distress syndrome as a result of aspiration, fat embolism, or pneumonia. IVOX was used in an attempt to provide supplemental transfer of CO<sub>2</sub> and O<sub>2</sub> and thereby reduce O<sub>2</sub> toxicity and barotrauma. All patients were tracheally intubated, sedated, and chemically paralyzed and had a PaO<sub>2</sub> < 60 mmHg when the lungs were ventilated with an FI<sub>O<sub>2</sub></sub> = 1.0 and a positive end expiratory pressure of ≥ 5 cmH<sub>2</sub>O. The right common femoral vein was located surgically, and the patient was systemically anticoagulated with heparin. A hollow introducer tube was inserted into the right common femoral vein, and the furled IVOX was passed into the inferior vena cava and advanced until the tip was in the lower portion of the superior vena cava. IVOX use ranged from 2 h to 4 days. In this group of patients, IVOX gas exchange ranged from 21 to 87 ml × min<sup>-1</sup> of CO<sub>2</sub> and from 28 to 85 ml × min<sup>-1</sup> of O<sub>2</sub>. One of the five patients survived and was discharged from the hospital. The IVOX transferred up to 28% of metabolic gas-exchange requirements. One patient with a small vena cava showed signs of caval obstruction. Three other patients demonstrated signs of a septic syndrome after the device was inserted. In the patient who survived, the IVOX did not appear to play a significant role in his outcome. Clinical considerations and factors limiting the use of the IVOX are presented. Because of gas-exchange limitations, design alterations to the IVOX may be required. (Key words: Lungs, adult respiratory distress syndrome: membrane lung.)

PATIENTS WITH IMPAIRED exchange of O<sub>2</sub> or CO<sub>2</sub> are commonly treated with increased positive end expiratory

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pressure (PEEP) and increased FI<sub>O<sub>2</sub></sub> to improve oxygenation and with increased minute ventilation for respiratory acidosis. If gas exchange of patients with adult respiratory distress syndrome (ARDS) fails to improve adequately with these conventional modalities, the only alternative therapy has been extracorporeal membrane oxygenation (ECMO).<sup>1-5</sup> Current adult ECMO perfusion uses primarily venovenous perfusion. One or two Sci-Med Spiral Coil Membrane Lung(s) (Sci-Med Life Systems, Inc., Minneapolis, MN) with a 3.5-m<sup>2</sup> surface area per lung are used for gas exchange, and either a roller pump or centrifugal pump for blood propulsion. A randomized trial of ECMO and maximal ventilatory therapy in the late 1970s revealed an equally poor prognosis for treatment with ECMO (primarily venoarterial perfusion) or with standard mechanical ventilation.<sup>5</sup> Despite this result, some centers have continued to offer ECMO to selected patients.

More recently survival rates of 47-50% have been reported using ECMO.<sup>3,6,7</sup> While these results are more encouraging, these studies were flawed by lack of control patients. Therefore, the actual effect of ECMO on patient outcome was uncertain. In a recent randomized study,<sup>¶</sup> a common method of ECMO, extracorporeal CO<sub>2</sub> removal, combined with inverse ratio ventilation was compared with conventional positive pressure ventilation. The result was statistically indistinguishable, with survival rates of approximately 40% for both groups. Not considered here is the costly, labor-intensive<sup>4</sup> nature of ECMO and its invasiveness (the insertion of two large cannulae into the central circulation and exposing the blood to several square meters of prosthetic surface). The cannulae classically have been inserted by surgical cutdown, but recently a percutaneous insertion has been described.<sup>8</sup>

All of these factors have provided impetus for developing alternative O<sub>2</sub> and CO<sub>2</sub> exchange methods for patients with severe respiratory failure. Alternative modes of ventilation such as high frequency ventilation,<sup>9</sup> pressure control with reverse ratio ventilation,<sup>10</sup> or combinations of modes<sup>11</sup> have been described but not fully evaluated for use in severe ARDS. The shortcomings of ECMO have led to the development of a miniaturized membrane lung for intracaval O<sub>2</sub> and CO<sub>2</sub> exchange, termed an intra-

¶ Morris AH: Protocols, ECCCO2R, and the evaluation of new ARDS therapy. Japanese Journal of Intensive Care Medicine 16:61-63, 1992

venous oxygenator (IVOX). We report the use of an IVOX in five patients who were suffering from severe ARDS.

### Methods and Materials

The IVOX (fig. 1) was designed and manufactured by CardioPulmonics, Inc. (Salt Lake City, UT) and was originally described by Mortensen.<sup>12</sup> The development and protocol for clinical use of the IVOX have been described previously.<sup>13,14</sup> Animal studies<sup>15</sup> have demonstrated the safety of the device and up to  $81 \text{ ml} \times \text{min}^{-1}$  of  $\text{O}_2$  transfer and  $67 \text{ ml} \times \text{min}^{-1}$  of  $\text{CO}_2$  transfer across the membrane. The use of IVOX in three patients has been reported with one survivor with  $\text{CO}_2$  exchange of  $24\text{--}74 \text{ ml} \times \text{min}^{-1}$ .<sup>16</sup>

The IVOX is a cigar-shaped bundle of 600–1,000 hollow fibers, depending on which size device is employed. The microporous, polypropylene fibers have an outside diameter of  $200 \mu\text{M}$ , a wall thickness of  $23 \mu\text{M}$ , a length of 46–61 cm, and pores  $0.2\text{--}0.3 \mu\text{M}$  long by  $0.4 \mu\text{M}$  wide. The fibers are coated with silicone (highly cross-linked dimethyl-siloxane)  $0.5\text{--}1.5 \mu\text{M}$  in thickness. Four sizes of the device are available for clinical trials. The sizes range from 7 to 10 mm (table 1) based upon the diameter of the manifold. This is determined largely by the number of fibers in the device, thus the larger the device, the greater the number of fibers and, hence, surface area of the device. The surface area of the 7–10-mm diameter devices range from  $0.21$  to  $0.52 \text{ m}^2$ .

The introducer used for IVOX insertion into the right common femoral vein is in the shape of a hollow, trun-

FIG. 1. The intravenous oxygenator (*left*) and a schematic diagram (*right*). To clarify gas flow pathways, the schematic diagram shows a single microporous fiber, inlet and outlet manifold, and inlet and outlet conduits. The schematic diagram is not drawn to scale.

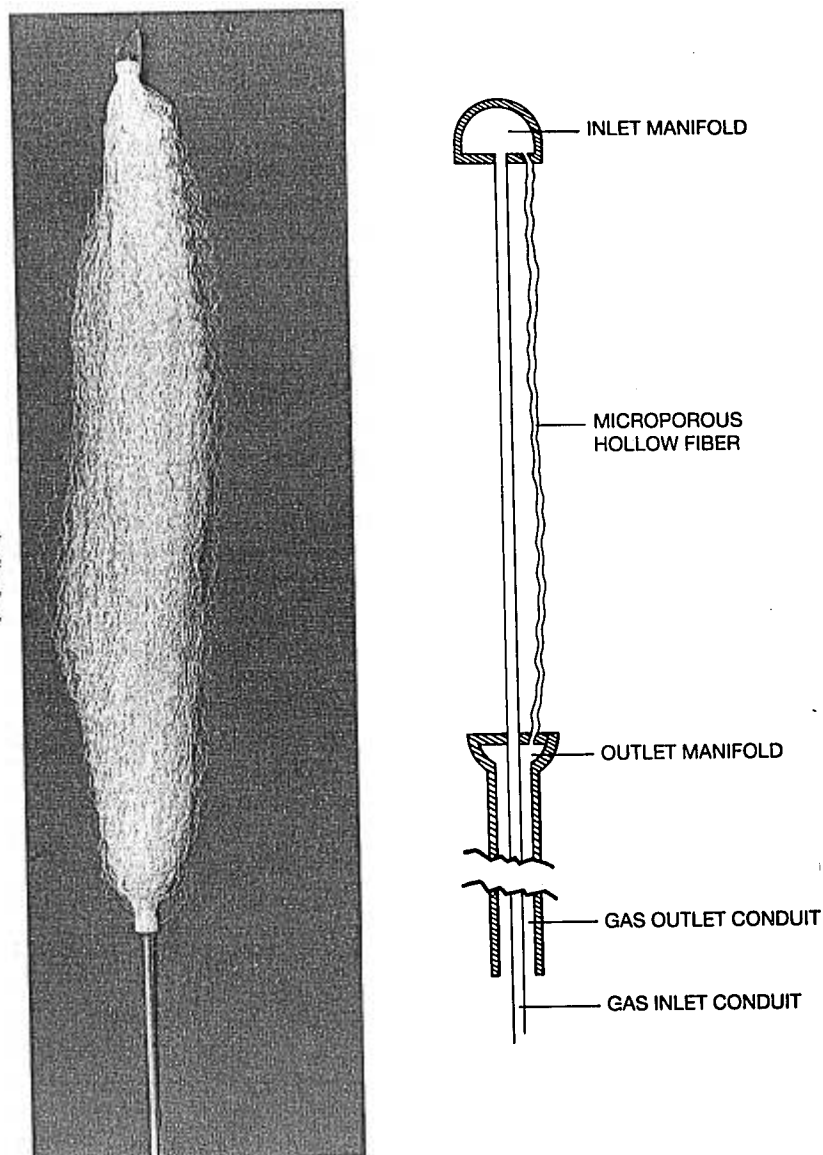


TABLE 1. Dimensions of Intravenous Oxygenator (IVOX) Devices

IVOX Size	Furled Diameter (mm)	Approximate Furled Circumference (mm)	Number of Fibers	Surface Area (m <sup>2</sup> )	Gas Flow Rate (ml · min <sup>-1</sup> )	Individual Fiber Length (cm)	Total Fiber Length (m)	Approximate Introducer Circumference (mm)
7	11.1	35	589	0.21	1300	46	272	38
8	12.0	38	703	0.32	1600	59	414	41
9	13.5	42	894	0.41	1900	59	531	45
10	15.0	47	1107	0.52	2700	61	673	50

Hollow fiber diameter 200  $\mu$ m; hollow fiber wall thickness 23  $\mu$ m; and silicone membrane thickness 0.5–1.5  $\mu$ m.

cated ram's horn. Introducers ranged in circumference from 38 to 50 mm at the narrower end. For insertion of the introducer, a 10-cm incision was made over the right common femoral vein, the vessel was dissected free, and ligatures were placed proximally and distally to control bleeding while the venotomy was performed. A guide wire was inserted through the introducer into the vena cava, and the IVOX was then slid over the guide wire such that the cephalad tip of the device was located in the inferior portion of the superior vena cava as determined by fluoroscopy or serial chest x-rays.

A flow of 1–2 L  $\times$  min<sup>-1</sup> of 95% O<sub>2</sub> and 5% He passed through the central supply tube and into the hollow fibers. The gases were supplied to the inlet manifold of the hollow fibers at atmospheric pressure and were drawn through the fibers by a subatmospheric pressure (approximately 300 mmHg absolute pressure) in the exhaust tubing. The exhaust gases were collected in the manifold at the other end of the device and then exited to the atmosphere. This represented a gas flow resistance of 230 mmHg  $\times$  min  $\times$  l<sup>-1</sup>. The subatmospheric pressure is used to avoid the problem of positive gas pressure forcing gas bubbles through any broken IVOX fibers into the vena cava. O<sub>2</sub> and CO<sub>2</sub> exchange, similar to that in extracorporeal oxygenators, occurred by diffusion across the membrane driven by the partial pressure gradients of O<sub>2</sub> and CO<sub>2</sub>.

Our use of the IVOX was part of phase 1 of a study approved by the Food and Drug Administration (FDA) to assess the safety of the device and met the approval of our Institutional Review Board. Patients entering into this trial were tracheally intubated, sedated, and chemically paralyzed. Patients qualified for the study by meeting blood gas entry criteria similar to those of the national ECMO study.<sup>5</sup> They had severe ARDS with a pulmonary shunt of  $\geq 30\%$  with a PEEP of  $\geq 5$  cm. This shunt roughly corresponded to a PaO<sub>2</sub> < 60 mmHg while breathing 100% O<sub>2</sub>. The common femoral vein, internal jugular vein, and the vena cava were evaluated by venography and/or ultrasonography to determine whether the diameter of these vessels was adequate to insert and unfurl the IVOX device.

The patients ranged in age from 19 to 40 yr (table 2).

In addition to the diagnosis of ARDS, precipitating or concurrent diagnoses are shown here. The patients were afebrile, had no positive blood, sputum, or urine cultures for more than 48 h, and had no acute elevations in leukocyte count at the time the IVOX was implanted. When appropriate, they had received antibiotics to treat infections before insertion. Patients 2, 4, and 5 also had large air leaks through bronchopleural fistulas. The amount of PEEP varied between patients, but up to 20 cmH<sub>2</sub>O PEEP was used. Pulmonary shunt fractions varied from 32% to 62% throughout the group.

The patients were given anesthetic doses of fentanyl intravenously before the insertion of the IVOX. Sedation was maintained by continuous infusion of midazolam, which was titrated to control blood pressure in each patient's normal range, and muscle relaxation was maintained with vecuronium bromide. The patients were given a bolus of 400 units/kg heparin *via* the pulmonary artery catheter. Anticoagulation was maintained throughout the time the device was *in situ* by continuous infusion of heparin to maintain an activated clotting time at approximately 250 s (normal range, 90–120 s). The activated clotting time was measured hourly once stable.

During the time the IVOX was implanted, two primary issues were addressed. First, in accordance with the pri-

TABLE 2. Clinical and Laboratory Demography

Patient	Age/Sex	Diagnosis	Murray Score*	Pre-IVOX Pulmonary Shunt Fraction (%)
1	34/F	Pneumococcal pneumonia	4/4	48–62
2	19/M	Femur fracture, fat embolism	4/4	53–58
3	21/M	Chest trauma, pneumonectomy, aspiration pneumonia	4/4	32–40
4	27/F	Aspiration pneumonia	4/4	42–52
5	40/M	Gunshot wound to right chest, lobectomies	4/4	39–55

\* From Murray *et al.*: Am Rev Respir Dis 138:720–723, 1988. The score is based on the average of scores of chest x-ray, PaO<sub>2</sub>/FIO<sub>2</sub> ratio, PEEP, and pulmonary compliance, with 4/4 indicating the most severe adult respiratory distress syndrome.

TABLE 3. Simultaneous Measurements of O<sub>2</sub> and CO<sub>2</sub> Transfer across Intravenous Oxygenator (IVOX) and Natural Lung

Patient Number	IVOX Size	Patient Weight (kg)	$\dot{V}_{O_2}$ (lung)*	$\dot{V}_{CO_2}$ (lung)*	$\dot{V}_{O_2}$ (IVOX)†	$\dot{V}_{CO_2}$ (IVOX)†	% $\dot{V}_{O_2}$ by IVOX	% $\dot{V}_{CO_2}$ by IVOX
1	7	52	142	133	13/61.9	14/66.7	8.3	9.5
2	7	78	335	323	29/138.1	31/147.6	8.0	8.4
3	7	61	363	318	31/147.6	28/133.3	7.9	8.1
4	8	61	215	206	84/262.5	82/256.3	28.1	28.5
5	9	126	242	310	65/158.5	62/151.2	21.1	16.7

\* Gas exchange expressed in milliliters per minute at 21.1° C and 760 mmHg.

† Gas exchange expressed in milliliters per minute and in milliliters

per minute per square meter of IVOX surface at 21.1° C and 760 mmHg.

mary goal of phase 1 of the FDA trial, the safety of the IVOX insertion, chronic implantation, and removal was addressed. This was determined by assessment of vital signs, cardiovascular parameters (cardiac output, central venous pressure, pulmonary artery pressure, pulmonary artery capillary wedge pressure), and mixed venous and arterial blood gas analysis. Continuous pulmonary artery hemoglobin O<sub>2</sub> saturation by oximetric pulmonary artery catheter and coagulation parameters (activated clotting time, platelet count, PT, aPTT) also were measured.

Second, the amount of IVOX and natural lung gas exchange was determined simultaneously. A computer<sup>17</sup> was used to control sampling by a mass spectrometer (MGA-1100, Perkin-Elmer, Pomona, CA) of the gases entering and exiting the IVOX and to control the measurement of outlet gas flow rate by a thermoconductivity flow meter (Sierra SideTrak mass flow controller, Sierra Instruments, Carmel Valley, CA). Mass spectrometer sampling occurred every 5 min for a duration of 60 s at a flow rate of 240 ml × min<sup>-1</sup> and had no effect on IVOX inlet or outlet gas flow rates because of the sampling locations. A gas mixture of 5% He and 95% O<sub>2</sub> from a common tank was used as the inlet gas for both the IVOX and the mechanical ventilator. This was done to eliminate He transfer across the IVOX membrane (a potential source of error in the equations below). The He provided an inert, relatively insoluble gas with little transfer across the membrane and was used to determine the ratio of inlet to outlet total gas flow rate, *i.e.*, a Haldane correction. By mass balance, we were able to determine O<sub>2</sub> and CO<sub>2</sub> transfer across the IVOX membrane:

$$\dot{V}_{O_2} = \dot{V}_i \times (F_{iO_2} - F_{iHe} \times F_{eO_2}/F_{eHe}) \quad (1)$$

$$\dot{V}_{CO_2} = \dot{V}_i \times F_{eCO_2} \times F_{iHe}/F_{eHe} \quad (2)$$

where  $\dot{V}_{O_2}$  and  $\dot{V}_{CO_2}$  are the O<sub>2</sub> and CO<sub>2</sub> gas transfer, respectively,  $\dot{V}_i$  is the inlet total gas flow rate, F is the gas fraction, i represents inlet, and e is exit. The computer determined in real time the O<sub>2</sub> and CO<sub>2</sub> exchange to provide continuous display of gas exchange. The gas-exchange apparatus and program was validated by the stoichiometric analysis of combustion of absolute ethanol.<sup>18</sup>

## Results

The results of the use of the IVOX and the patient outcomes are summarized in tables 3 and 4. A #7 size IVOX was used for patient 1 for 20 h, but gas exchange was low ( $\dot{V}_{O_2} = 13 \text{ ml} \times \text{min}^{-1}$  and  $\dot{V}_{CO_2} = 14 \text{ ml} \times \text{min}^{-1}$ ), and FI<sub>O<sub>2</sub></sub>, PEEP, and respiratory minute volume could not be decreased. The implantation of the smallest IVOX was accompanied initially by a decrease in systemic arterial blood pressure and cardiac output, which responded to blood administration. During this time, the patient had continued deterioration of oxygenation. Blood cultures taken after insertion of the IVOX showed no growth. Bacterial culture of the IVOX surface obtained at the time of autopsy produced no bacterial growth. The most significant finding during the autopsy was her unexpectedly small inferior vena cava, into which a dilator no larger than 10 mm in diameter could be passed. Before insertion, this patient underwent ultrasonography of her right common femoral and internal jugular veins. It had been assumed that, if these vessels were adequate for placement of the device, the inferior vena cava would be large enough for its unfurling. We believe that this patient's 10-mm diameter inferior vena cava was too small to allow unfurling of the IVOX and may have caused some venous obstruction. Because of this finding, all of our subsequent patients had their inferior vena cava diameter evaluated by ultrasound or venography before IVOX implantation.

Patient 2 received 2 h of treatment with a #7-sized IVOX, after which ECMO was used because of insufficient IVOX gas exchange ( $\dot{V}_{O_2} = 29 \text{ ml} \times \text{min}^{-1}$  and  $\dot{V}_{CO_2} = 31 \text{ ml} \times \text{min}^{-1}$ ). FI<sub>O<sub>2</sub></sub>, PEEP, and respiratory minute volume could not be decreased while the IVOX was being used. The patient had excellent gas exchange with ECMO for 8 days. ECMO O<sub>2</sub> and CO<sub>2</sub> transfer were approximately 300 ml × min<sup>-1</sup>. He had stable hemodynamics until the eighth day of ECMO, but he died after an intractable septic syndrome developed.<sup>19</sup> All blood cultures showed no bacterial growth.

Patient 3 sustained chest trauma requiring a right pneumonectomy with subsequent ARDS. Because of peak inspiratory pressures of 60–70 cmH<sub>2</sub>O and concern of

TABLE 4. Cardiovascular Parameters before and after Insertion of IVOX

Patient Number	Heart Rate (beats/min)	Systemic Blood Pressure (mmHg)	Cardiac Output (l/min)	Systemic Vascular Resistance (dyn · cm · s <sup>-5</sup> )	Pulmonary Artery Pressure (mmHg)	Pulmonary Vascular Resistance (dyn · cm · s <sup>-5</sup> )	Central Venous Pressure (mmHg)	Pulmonary Capillary Wedge Pressure (mmHg)
1 Pre-IVOX	115	85/52	3.39	1156	42/25	306	14	18
1 Post-IVOX	113	136/72	4.77	889	34/24	NA*	15	NA*
2 Pre-IVOX	100	149/95	8.52	1406	54/28	NA*	14	NA*
2 Post-IVOX	102	NA†	NA†	NA†	NA†	NA†	NA†	NA†
3 Pre-IVOX	142	143/89	9.6	742	68/35	225	16	19
3 Post-IVOX	135	151/100	8.5	998	59/27	254	10	12
4 Pre-IVOX	117	103/63	4.22	1099	50/23	379	18	16
4 Post-IVOX	104	127/69	6.50	800	43/29	222	22	16
5 Pre-IVOX	113	130/65	10.3	528	81/43	NA*	20	NA*
5 Post-IVOX	125	130/65	7.6	579	77/43	NA*	13	NA*

IVOX = intravenous oxygenator; NA = not available.

\* Pulmonary artery catheter could not be positioned to obtain wedge pressures.

† Because of difficulty with insertion of the IVOX and low gas exchange, the IVOX was removed and extracorporeal membrane oxygenation was begun before the patient had stable hemodynamic and gas exchange parameters.

disruption of the bronchial stump and poor gas exchange, the patient was treated with a #7-sized IVOX. IVOX fibers broken at the time of insertion allowed blood to leak into the IVOX with a persistent decrease in IVOX gas exchange (initially  $\dot{V}O_2 = 31 \text{ ml} \times \text{min}^{-1}$  and  $\dot{V}CO_2 = 28 \text{ ml} \times \text{min}^{-1}$ ). We elected to discontinue the IVOX after 20 h because of low gas exchange. Again, at no time could the  $FI_{O_2}$ , PEEP, and respiratory minute volume be decreased. Blood and IVOX surface cultures showed no growth. The patient's pulmonary status subsequently improved, and he was separated from mechanical ventilation and discharged from the hospital. He is fully recovered and has returned to normal activities.

In patient 4, an aspiration pneumonia and ARDS developed with large bronchopleural fistulas (inspired min-

ute volume of  $19.4 \text{ L} \times \text{min}^{-1}$  and expired minute volume of  $11.0 \text{ L} \times \text{min}^{-1}$ ) and subsequently was treated for 4 days with a #8-sized IVOX.  $\dot{V}O_2$  and  $\dot{V}CO_2$  by IVOX were  $84 \text{ ml} \times \text{min}^{-1}$  and  $82 \text{ ml} \times \text{min}^{-1}$ , respectively (28.1% of total  $O_2$  exchange and 28.5% of total  $CO_2$  exchange). During this time, the tidal volume decreased from 350 ml to 150 ml with a constant respiratory rate, the positive inspiratory pressure decreased from 33 to 22 cmH<sub>2</sub>O, the  $Paco_2$  increased from 94 to 101 mmHg, and pH decreased from 7.34 to 7.28. The  $FI_{O_2}$  decreased from 1.0 to 0.80, and the PEEP decreased from 6 to 4 cmH<sub>2</sub>O, with arterial hemoglobin  $O_2$  saturations decreasing from 89% to 82%. A septic syndrome developed, and the IVOX was removed in the course of treating her apparent septicemia. However, the patient continued to have pro-

TABLE 5. Hematologic Studies before IVOX Insertion and Removal

Patient Number	Prothrombin Time (s) (nl = 10-13)	Partial Thromboplastin Time (s) (nl = 26-37)	Fibrinogen (mg · dl <sup>-1</sup> ) (nl = 150-400)	Platelet Count (10 <sup>3</sup> /mm <sup>3</sup> ) (nl = 140-340)	Fibrin Split Products (μg · ml <sup>-1</sup> ) (nl < 10)	Plasma Free Hemoglobin (mg · dl <sup>-1</sup> ) (nl < 10)
1 Preinsertion	13.4	38	459	22	80	156
1 Preremoval	20.1	>120	220	34	40	14
2 Preinsertion	15.1	33	227	93	320	NVH
2 Preremoval	NA	NA	NA	85	NA	NA
3 Preinsertion	10.8	29	497	396	20	8
3 Preremoval	15.5	>120	449	338	40	NA
4 Preinsertion	12.3	57	630	157	20	8
4 Preremoval	12.8	71	467	133	60	8
5 Preinsertion	11.7	22	424	210	40	3
5 Preremoval	16.8	>120	480	140	40	14

Values were obtained within 4 h of initiating IVOX, and last was value obtained before its discontinuance.

IVOX = intravenous oxygenator; NA = not available; NVH = "no visible hemolysis" reported from the clinical laboratory.

gressive hypotension and died despite maximal medical support. Again blood and IVOX surface cultures were negative.

In patient 5, a #9-sized IVOX was inserted for 48 h, and  $\dot{V}O_2$  and  $\dot{V}CO_2$  by IVOX were  $65 \text{ ml} \times \text{min}^{-1}$  and  $62 \text{ ml} \times \text{min}^{-1}$ , respectively. During this time, the tidal volume decreased from 1,700 to 1,300 ml with a constant respiratory rate, the positive inspiratory pressure decreased from 71 to 65  $\text{cmH}_2\text{O}$ , and the  $\text{PaCO}_2$  increased from 47 to 50 mmHg, with pH decreasing from 7.31 to 7.29. The  $\text{FI}_{O_2}$  decreased from 1.0 to 0.90, and the PEEP decreased from 18 to 14  $\text{cmH}_2\text{O}$ , with arterial hemoglobin  $O_2$  saturation decreasing from 81% to 75%. A septic syndrome developed during this time, and the patient subsequently died. IVOX surface and blood cultures showed no growth.

At autopsy, all of the patients who died because of sepsis were found to have multiple lung abscesses. The IVOX devices in patients 1, 4, and 5 were examined *in situ* at autopsy for deposition of clot. The posterior aspect of the vena cava was opened longitudinally and the IVOX gently washed with water. No clot was seen on the fibers' exchange surfaces, but some, less than 1 mm long, adhered to the inferior manifold. Examination of the patients' injured lungs showed no evidence of acute thromboembolism. In patients 2 and 3, the IVOX was furled tightly before removal while the patients were alive. Upon removal the devices were free of clot. At autopsy, patient 2 showed no signs of acute thromboembolism. All devices were intact at the time of removal. There were no significant trends noted in coagulation tests (table 5).

### Discussion

In theory, use of the IVOX as a life-support device in patients with severe ARDS may supplement and reduce the mechanical ventilation required for patient gas exchange. Adequate IVOX gas exchange is required to decrease the high inspiratory pressures, PEEP, and  $\text{FI}_{O_2}$  to reduce lung injury caused by barotrauma and  $O_2$  toxicity.<sup>20</sup> The current prototypes provided a maximum of one-third of basal gas exchange and must be thought of as limited lung assist devices. Only in patients 4 and 5 could small changes in ventilator settings be made. In contrast, during venovenous ECMO,  $\text{FI}_{O_2}$  usually can be reduced to 0.21 and respiratory minute volume usually can be reduced to one-third or one-half of the pre-ECMO value.<sup>3</sup> A more efficient intravascular device than the current IVOX will be needed to significantly reduce the risk of  $O_2$  toxicity and barotrauma in patients with ARDS.

Accurate determination of the contribution of IVOX to total gas exchange required a method to simultaneously measure  $O_2$  and  $CO_2$  exchange across the device and the natural lung. Blood phase measurements of IVOX gas exchange based on mass balance were impossible since

venous blood streams of highly varying hemoglobin  $O_2$  saturation and flow rate empty into the inferior vena cava.<sup>21</sup> In contrast, gas phase measurements were obtained readily. Gas phase measurements of  $CO_2$  transfer from membrane lungs were obtained simply as the product of the exiting  $CO_2$  concentration and total exhaust gas flow rate.<sup>22</sup> Gas phase measurements of  $O_2$  transfer across membrane lungs were based upon classic pulmonary physiology techniques. In humans, steady state pulmonary  $O_2$  transfer has been determined by collecting the expired minute volume and measuring the concentrations of  $O_2$  and nitrogen in inspired and expired gases. The inspired minute volume was calculated from the product of the ratio of concentrations of the expired nitrogen to inspired nitrogen with the expired minute volume assuming no net transfer of nitrogen across the lung.<sup>23</sup> This ratio of the expired nitrogen to inspired nitrogen is referred to as the Haldane correction.  $O_2$  transfer rate was calculated as the difference of the product of inspired minute volume and  $O_2$  concentration with the product of expired minute volume and  $O_2$  concentration.

In IVOX, a low concentration (5%) of He in the inlet gas was used for the Haldane correction, and mass transfer calculations were made while maintaining a high  $O_2$  driving gradient for diffusion. The Haldane correction is accurately calculated in this case because the net transfer of He across the IVOX membrane was minimized by: 1) the low silicone permeability of the IVOX membrane to He (approximately one-half that of  $O_2$ ),<sup>24</sup> 2) the low solubility of He in the blood ( $8.7 \text{ ml He} \times \text{atm He}^{-1} \times \text{L blood}^{-1}$ ),<sup>24</sup> and 3) the use of a 5% He/95%  $O_2$  gas mixture from the same supply tank for both the ventilator and IVOX for 30 min before making measurements, thus reducing the He driving gradient across the membrane by equilibrating the partial pressure of He in the gas and blood phases.

Accuracy in gas-exchange measurements of natural lungs having a large bronchopleural fistula was achieved by connecting the output of the chest tubes directly into a gas-tight, high-flow pump that emptied into a meteorologic balloon that simultaneously collected the expired respiratory gas. Since the accuracy of our system has been verified by absolute ethanol combustion, we believe that the low  $O_2$  and  $CO_2$  transfer measurements we observed are correct.

$O_2$  exchange across the IVOX is limited primarily by its location in the venous circulation. The IVOX appears to exchange most  $O_2$  with inferior vena cava blood. The short distance that the device extends into the superior vena cava in all likelihood does not allow sufficient surface

\*\* Galletti PM, Snider MT, Silbert-Aiden D: Gas permeability of plastic membranes for artificial lungs. Medical Research Engineering 5:20-23, 1966

area for significant gas exchange to occur, with the blood returning *via* the superior vena cava. Moreover, the blood returning from the coronary sinus into the right atrium is never exposed to the IVOX. Since more than 80% of the surface area of the IVOX lies within the inferior vena cava, the  $PO_2$  and blood flow of the inferior vena cava are probably the primary determinants of  $O_2$  exchange. If the IVOX were capable of increasing hemoglobin  $O_2$  saturation in the caval blood to 100%, then a theoretical maximum  $O_2$  exchange can be calculated as the product of the blood flow with an average percent deoxygenated hemoglobin in the inferior vena cava (before instituting IVOX gas exchange) and the blood  $O_2$  carrying capacity. For example, an inferior vena cava flow of  $3\text{ L} \times \text{min}^{-1}$  (approximately one-half the cardiac output), an  $O_2$  carrying capacity of 15 ml  $O_2$  per 100 ml blood, and an inferior vena cava hemoglobin  $O_2$  saturation of 50% (as might be present in these severely hypoxic patients), the maximum possible  $O_2$  exchange would be  $225\text{ ml} \times \text{min}^{-1}$ . The lower IVOX gas exchange observed in this study suggests that either the IVOX has less efficient  $O_2$  exchange or the inferior vena cava blood flow was lower than expected in severe ARDS. For example, decreased splanchnic blood flow in patients with sepsis may reduce IVOX gas exchange.

$CO_2$  exchange across the IVOX is probably primarily limited by its driving gradient (venous  $PCO_2$  minus IVOX gas phase  $PCO_2$ ). The only method for increasing this gradient is to reduce alveolar ventilation and permit the mixed venous  $PCO_2$  to increase a permissive hypercarbia. We permitted the  $Pa_{CO_2}$  to reach 80–100 mmHg in patients 4 and 5 by decreasing tidal volume. This decreased peak airway pressures and barotrauma while obtaining the maximum possible  $CO_2$  driving gradient across the IVOX. In these patients, the administration of sodium bicarbonate was used to maintain the arterial pH between 7.25 and 7.4. The extent to which this maneuver can be employed without sequelae is unknown.

Redesign of an intravenous membrane lung might result in increased gas-exchange properties. There is a diminishing return from increasing IVOX size, *i.e.*, the number of fibers, residing within the vena cava. As the vena cava becomes progressively occluded with fibers and resistance to blood flow within the vena cava is increased, extra-caval collaterals, *e.g.*, azygos and hemiazygos veins, probably receive increasing amounts of the venous return. Unfortunately, no topographic data exist that defines local gas exchange along the surface of the IVOX. Vaslef *et al.*<sup>25</sup> have described an alternative to Mortensen's design for an intravascular oxygenator. In their design, short lengths of microporous fibers are grouped in looped segments along a catheter. Other intravenacaval devices have been patented, but no studies have been published showing their feasibility or gas-exchange capabilities. Finally, better gas exchange might be expected if the gas-exchange

surface of the intravascular lung is extended into the right atrium, right ventricle, and pulmonary artery, where the entire venous return including the coronary sinus flow could be contacted.<sup>26</sup> No device other than IVOX has begun clinical trials.

Medical management during IVOX continues to evolve as experience is gained with the device and reflects the small amount of gas exchange as well as the large surface area of prosthetic material. Reduction of  $O_2$  consumption and  $CO_2$  production requires muscle relaxation after adequate sedation and mild hypothermia (to as low as  $35^\circ\text{C}$ ). Fluid management is more difficult. Management of severe ARDS patients usually includes diuresis to decrease the transmural pulmonary capillary hydrostatic pressure as approximated by the pulmonary capillary wedge pressure to reduce lung water and improve natural lung function. This is limited by maintenance of adequate organ perfusion, and there most likely needs to be a balance between the hydration to improve IVOX function and the dehydration to decrease interstitial fluid. Erythrocyte transfusion may be useful in maintaining intravascular volume.

Infection continues to be a major concern when prosthetic devices with large areas of plastic are exposed to the bloodstream. The presence of an infection can be difficult to diagnosis in the patient with a mildly increased temperature, cardiac output, and leukocyte count. The effect of the intravascular prosthetic surface on eradication of septicemia is a concern. Intravascular prosthetic surfaces have been shown to enhance the circulatory effects of sepsis in animals.<sup>27</sup> Standard therapy in the presence of an infection is to remove the intravascular catheters and replace them when needed. If the IVOX has relieved severe hypoxemia, its removal may be accompanied by a recurrence of hypoxemia. An intractable septic syndrome developed in three of our five patients during use of the IVOX, with lung abscesses found at autopsy. The role of the IVOX in the course of these infections is uncertain and may have been contributory. This may be less of a problem if the IVOX is used in patients with less severe lung injury than that in the patients reported here. Perhaps the use of covalently bound molecules on the surface to act as antiseptics or inhibit bacterial adhesion may be required.<sup>28</sup> Although we investigated our patients for infections before inserting the IVOX, undetected infection may have become apparent only after insertion of the IVOX.

Appropriate patient selection is imperative for use of this device. The diameters of the access vessels and the vena cava at various levels must be measured by ultrasound or venography to determine the largest size device that might be implanted. This anatomic limitation of vessel size must be balanced against the patient's  $O_2$  and  $CO_2$  exchange requirements. As our first patient demonstrated, there may be significant anatomic limitations of

the vena cava and access vessels limiting the size of IVOX device that can be placed. Thus patients with large gas-exchange requirements and small vessels would not benefit from IVOX implantation. Current prototypes of IVOX with their limited gas exchange must be considered as lung assist devices. In this early phase of IVOX testing, only patients who were near death from severe hypoxia despite maximum medical and mechanical ventilation therapy were studied. In the future, when the risk of the use of IVOX is better defined, the use of IVOX in patients earlier in their clinical course may prevent some of the effects of the  $O_2$  toxicity and barotrauma to which our patients were subjected. This will be addressed in phase 2 of FDA-approved testing. Currently, we would consider the use of the IVOX only in patients with: 1) an intrapulmonary shunt fraction less than 35% (Patients with higher shunt fractions would only be considered for ECMO.) and greater than 25% (Lower shunt levels would not warrant the use of such invasive therapy.) requiring  $FI_{O_2} \geq 0.80$  and PEEP  $\geq 15$  cmH $_2$ O, 2) negative blood cultures for a minimum of 48 h, and 3) a common femoral vein greater than 12 mm and inferior vena cava greater than 15 mm in diameter to allow insertion of a size 9 or 10 IVOX.

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