Intravenous Cava-Membrane Oxygenation and Carbon Dioxide Removal in Severe Acute Respiratory Failure*

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Study objective: To characterize the physiologic response to, and safety of, intravenous cava-membrane oxygenation and carbon dioxide removal.

Design: Interventional before-after study.

Setting: University teaching hospital ICU.

Patients: Twenty-two patients with severe acute respiratory distress syndrome (ARDS).

Interventions: Implantation of a hollow-fiber membrane oxygenator (IVOX; CardioPulmonies; Salt Lake City, Utah) into the superior and inferior venae cavae by venotomy of the right femoral or right internal jugular vein for a duration of up to 20 days.

Measurements: Hemodynamic measurements using pulmonary artery and systemic arterial catheters, ventilator settings (FIo2, minute ventilation, peak inspiratory pressure, and positive end-expiratory pressure), arterial and mixed venous blood gases (pH, Pco2, Po2, and measured saturation), and clinical laboratory determinations (CBC, fibrinogen, plasma hemoglobin, complement C3 and C5) were obtained. Calculations of PaO2/FIo2 ratio and PaCO2-VE product were used to assess gas exchange efficacy. Microbiologic cultures were obtained from the device and wound following implantation. Survival to ICU discharge and hospital discharge were recorded.

Results: Implantation was successful in 20 of 22 patients. Gas exchange rates averaged 50.4 ± 15.8 mL·min⁻¹ for carbon dioxide and 71.1 ± 20.2 mL·min⁻¹ for oxygen. A reduction in FIO₂ from 0.78 ± 0.16 to 0.63 ± 0.21 and in VE from 177 ± 94 mL·kg⁻¹·min⁻¹ to 127 ± 58 mL·kg⁻¹·min⁻¹ was possible within 4 h post-implantation. By 12 h, FIO₂ was reduced to 0.57 ± 0.18. Indices of gas exchange improved significantly after implantation, with PaO₂/FIo₂ ratio increasing from 79 ± 20 to 112 ± 47 and PaCO₂-VE product decreasing from 7.6 ± 4.2 to 4.9 ± 2.5 within 4 h. A significant reduction in peak inspiratory pressure was achieved (45 ± 10 to 38 ± 9 cm H₂O). Major complications were blood loss during implantation requiring transfusion in 11 patients, a retroperitoneal bleed in 1 patient, and femoral deep venous thrombosis in 4 patients, but there were no long-term sequelae or IVOX-related deaths. The ICU and hospital survival were 10/20 (50%) and 8/20 (40%), respectively.

Conclusions: Intravenous cava-membrane oxygenation and carbon dioxide removal can provide partial respiratory support during severe respiratory failure and permit reductions in the level of mechanical ventilator support, with an acceptable safety profile.

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Key words: carbon dioxide; oxygen; oxygenators, membrane; positive-pressure respiration; respiration, artificial; respiratory distress syndrome, adult; respiratory insufficiency; venae cavae; ventilators, mechanical

Patients with the acute respiratory distress syndrome (ARDS), first described in 1967,1 have a significant mortality.2 Advances in critical care medicine over the past two decades have, until recently, had little apparent impact on this mortality rate.3,4 Two large-scale prospective studies of mortality have been reported. A collaborative study conducted in conjunction with the 1975-1977 National Institutes of Health (NIH) extracorporeal membrane oxygenation (ECMO) trial in adults demonstrated a 66% mortality in patients with acute hypoxic respiratory failure.5 Patients with severe ARDS meeting the ECMO entry criteria and enrolled in the conventional therapy group of the ECMO trial had a 92% mortality rate.6 A second, more recent prospective survey of survival in patients with hypoxic respiratory failure, using entry criteria similar to the NIH collaborative trial, indicated a mortality rate of 45%, and 67% if hypoxemia was documented on at least one occasion.7 The only recent prospective trial of survival in patients with severe ARDS meeting the same criteria

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Table 1—Physical Characteristics of IVOX

<table>
<thead>
<tr>
<th>Device Size</th>
<th>Surface Area, cm²</th>
<th>No. of Fibers</th>
<th>Fiber Length, cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>2,100</td>
<td>589</td>
<td>40</td>
</tr>
<tr>
<td>8</td>
<td>3,200</td>
<td>703</td>
<td>43</td>
</tr>
<tr>
<td>9</td>
<td>4,100</td>
<td>894</td>
<td>47</td>
</tr>
<tr>
<td>10</td>
<td>5,200</td>
<td>1,107</td>
<td>50</td>
</tr>
</tbody>
</table>

as the 1975 NIH trial was reported by Morris et al in 1994. The control group in this study comparing pressure-controlled inverse ratio ventilation (PC-IRV) with PC-IRV and extracorporeal carbon dioxide removal, according to a rigidly controlled protocol, had a mortality of 58%, suggesting that carefully applied ventilator and patient management may reduce mortality. Nevertheless, mortality in patients with severe ARDS remains high, and efforts to further reduce it remain the subject of both laboratory and clinical research.

Basic pathophysiologic changes in ARDS include intrapulmonary shunting and elevated dead-space resulting in impaired exchange of oxygen and carbon dioxide. Hypoxemia and hypercarbia can become pronounced, and are treated with mechanical ventilation and positive airway pressure with increased inspired oxygen fraction (FiO₂), minute ventilation (Ve), and positive end-expiratory pressure (PEEP). Excessive pressures can develop in the distal airways and alveoli. Since there is marked inhomogeneity in ventilation, more compliant areas of the lung undergo overdistention and increase the risk of injury. Attempts to deliver tidal volumes necessary for CO₂ removal in this setting can worsen the injury. Evidence has been accumulating for 30 years that the intensity of mechanical ventilatory support, in particular the levels of airway pressure and lung volume, required in ARDS to maintain adequate blood gas tensions can create and potentiate injury to the parenchyma through this overdistention of distal airways and alveoli.

Volume-induced pulmonary trauma is difficult to identify and assess, since in its early stages, the clinical, radiographic, and histologic picture is usually similar to the underlying disease process of ARDS. The development of clinically identifiable barotrauma (interstitial air, mediastinal and subcutaneous emphysema, and pneumothoraces) signals a much later stage when alveolar injury is already established.

Restricting the application of pressure and volume are current goals in mechanical ventilation, but cannot always be adequately achieved without extrapulmonary augmentation of gas exchange. Extra corporeal techniques, such as CO₂ removal combined with low-frequency positive pressure ventilation and venovenous extracorporeal membrane oxygenation, aimed at reducing pulmonary injury are becoming established, but they require substantial resources and are associated with a small but defined risk. Survival rates of approximately 50% and better in adults with severe ARDS, however, have been reported in these clinical series.

An intracorporeal membrane oxygenator has the potential to provide extrapulmonary gas exchange without all of the risk associated with extracorporeal systems and with fewer resources. The provision of intracorporeal, extrapulmonary gas exchange should permit significant reductions in the intensity of mechanical ventilation. To test this hypothesis, we conducted a clinical trial of intracavala caval gas exchange with a hollow-fiber membrane oxygenator (IVOX; CardiO Pulmonics; Salt Lake City) in patients with severe ARDS. The goals of the clinical trial were: (1) to assess the ability of the intracorporeal device to allow reductions in inspired oxygen fraction, delivered lung volume, and applied airway pressure, and (2) to assess complications and other aspects of device utilization related to patient safety.

METHODS AND MATERIALS

This investigation was a prospective evaluation of the clinical safety and efficacy of intracavala caval membrane gas exchange. The criteria for selection of patients and data collection protocol were prospectively defined by the device sponsor under an FDA-approved investigational device exemption. The study was approved by the Institutional Review Board for Human Research of Louisiana State University Medical Center, and informed consent was obtained from the patient or legally authorized representative.

Patients

We enrolled 22 patients between September 1990 and December 1993 with severe ARDS and failure of mechanical ventilation to support gas exchange at a modest level of intensity. Entry criteria included FiO₂ = 0.50 resulting in PaO₂ < 80 mm Hg with at least one of the following: (1) PEEP ≥ 10 cm H₂O; (2) peak inspiratory pressure ≥ 45 cm H₂O; or (3) mean airway pressure ≥ 30 cm H₂O. Alternatively, hypercapnia with a PaCO₂ ≥ 45 mm Hg and a minute volume > 150 mL·min⁻¹·kg⁻¹ qualified for enrollment if hypoxemia was not present. Patients were excluded if they had uncontrolled bacteremia or fungemia, circulatory insufficiency or cardiogenic shock, venous thrombosis or obstruction in an entry vein or the vena cava, or a contraindication to systemic heparinization.

Device Description

The intravascular oxygenator (IVOX) is an elongated hollow-fiber oxygenator mounted on a dual-lumen support catheter. The fibers, 200 μm in diameter, are fabricated from microporous polypropylene and coated with siloxane to eliminate the gas-blood interface. All blood-contacting surfaces are heparin bonded to reduce thrombogenesis. The fibers of each device number from approximately 590 to 1,100 and are 40 to 50 cm in length, depending on the device size (Table 1). The device is implanted via surgical venotomy of the right common femoral or right internal jugular vein, and advanced under fluoroscopic guidance.
Table 2—Clinical Characteristics of Patients

<table>
<thead>
<tr>
<th>Patient No./Age, yr/Sex</th>
<th>ARDS Etiology</th>
<th>Lung Injury Score*</th>
<th>Prior ARF Duration, d</th>
<th>IVOX Device Size</th>
<th>Implant Site†</th>
<th>Duration of Implant, d</th>
<th>ICU Survival</th>
<th>Hospital Survival</th>
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<td>1/21/M</td>
<td>Viral pneumonia</td>
<td>3.29</td>
<td>1</td>
<td>10 RCF</td>
<td>RCF</td>
<td>6</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2/55/F</td>
<td>Urinary tract sepsis</td>
<td>3.29</td>
<td>6</td>
<td>10 RCF</td>
<td>RCF</td>
<td>19</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>3/67/M</td>
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<td>3.86</td>
<td>12</td>
<td>— RCF</td>
<td>RCF</td>
<td>—</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>4/33/F</td>
<td>Bacterial pneumonia</td>
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<td>13</td>
<td>9 RCF</td>
<td>—</td>
<td>12</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>5/67/F</td>
<td>Peritonitis, sepsis</td>
<td>3.14</td>
<td>3</td>
<td>10 RJ</td>
<td>5 RCF</td>
<td>—</td>
<td>No</td>
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<tr>
<td>6/44/F</td>
<td>Septic shock</td>
<td>3.71</td>
<td>10</td>
<td>8 RCF</td>
<td>11 RCF</td>
<td>—</td>
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<tr>
<td>7/35/F</td>
<td>Bacterial pneumonia</td>
<td>3.40</td>
<td>21</td>
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<td>—</td>
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<tr>
<td>8/23/F</td>
<td>Aspiration pneumonitis</td>
<td>3.71</td>
<td>1</td>
<td>10 RCF</td>
<td>RCF</td>
<td>1</td>
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<td>No</td>
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<tr>
<td>9/72/F</td>
<td>Pneumonia, unknown</td>
<td>3.57</td>
<td>11</td>
<td>10 RCF</td>
<td>RCF</td>
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<tr>
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<td>Postpartum ARDS</td>
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<td>6</td>
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<td>11/22/F</td>
<td>Postpartum ARDS</td>
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<td>10</td>
<td>— RCF</td>
<td>RCF</td>
<td>—</td>
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<td>12/41/M</td>
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<td>3.43</td>
<td>9</td>
<td>9 RCF</td>
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<td>—</td>
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<tr>
<td>13/22/F</td>
<td>Aspiration pneumonitis</td>
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<td>1</td>
<td>8 RJ</td>
<td>6 RCF</td>
<td>—</td>
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<tr>
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<td>7</td>
<td>10 RJ</td>
<td>RCF</td>
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<td>10</td>
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<td>16/35/M</td>
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<td>6</td>
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<td>3</td>
<td>8 RCF</td>
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<td>3</td>
<td>9 RJ</td>
<td>20 RCF</td>
<td>—</td>
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<td>No</td>
</tr>
<tr>
<td>20/45/M</td>
<td>Bacterial pneumonia</td>
<td>3.43</td>
<td>1</td>
<td>9 RCF</td>
<td>18 RCF</td>
<td>—</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>21/55/F</td>
<td>Viral pneumonia</td>
<td>3.43</td>
<td>11</td>
<td>8 RJ</td>
<td>8 RCF</td>
<td>—</td>
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<td>22/40/F</td>
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<td>3.57</td>
<td>11</td>
<td>8 RCF</td>
<td>15 RCF</td>
<td>—</td>
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<td>Yes</td>
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</table>

*Lung injury severity score.19
†Duration of mechanical ventilation for acute respiratory failure (ARF) prior to IVOX implantation.
‡Implant site: RCF=right common femoral vein; RIJ=right internal jugular vein.

into position in the venae cavae. Once in place, the gas exchange bundle extends from the inferior vena cava to the superior vena cava, traversing the right atrium. The support catheter contains gas supply and exhaust conduits. A gas controller supplies oxygen via negative pressure on the exhaust line, to maintain a negative intraluminal gas pressure. Gas exchange takes place between the intraluminal gas phase and the extraluminal blood phase by diffusion across the siloxane membrane.

Measurements

Each patient underwent left femoral arterial and left internal jugular or subclavian vein pulmonary arterial catheterization prior to implantation. Mean systemic arterial pressure (MAP), mean pulmonary artery pressure (MPAP), mean right atrial pressure (RAP), and pulmonary artery wedge pressure (PAWP) were obtained with disposable precalibrated pressure transducers (Abbott Laboratories; Chicago) and a clinical physiologic monitoring system (Spacelabs Inc; Redmond, Wash). Intrathoracic vascular pressures were measured at end-expiration. Prior to measurements, a zero point calibration was performed, referenced to the midaxillary level in the supine position. Cardiac output was measured using standard thermodilution methods with 10-mL indicator boluses. The mean of three to five consecutive consistent measurements (<15% difference) was calculated and indexed to body surface area (cardiac index, CI). Systemic and pulmonary vascular resistances were calculated using standard formulas, indexed to body surface area, and expressed as dyne·cm·sec⁻¹·m².

Arterial and pulmonary artery blood were sampled for pH, PCO₂, PO₂, and hemoglobin saturation with the patient receiving stable ventilator settings. Gas tension and pH measurements were performed with standard laboratory blood-gas electrodes (model ABL 350, Radiometer Inc, Copenhagen, Denmark). Total hemoglobin, oxyhemoglobin, carboxyhemoglobin, and methemoglobin concentrations were measured with multiple wavelength spectrophotometry (model ASM-3, Radiometer Inc, Copenhagen, Denmark). Whole blood activated coagulation time (ACT) was measured with a commercial device (Hemocheck model 801; International Technidyne Corp; Edison, NJ). Standard clinical laboratory determinations included complete blood cell count, coagulation profile, blood chemistry, complement levels, and plasma hemoglobin.

Carbon dioxide transfer by IVOX was measured as the product of the exhaust gas flow and exhaust gas fractional CO₂ concentration determined by mass spectrometry. Oxygen transfer was measured as the difference between pulmonary artery oxygen transport measured with the device turned on and off. This measurement provides approximate results for oxygen transfer since it assumes that the patient remains in steady state during the interval between measurements.

Assessment of the severity of pulmonary impairment at baseline was made with the lung injury score of Murray et al10 for patients with ARDS, which incorporates calculations of PaO₂/FIO₂ ratio, physiologic shunt, and pulmonary compliance through the use of standard equations. The PaO₂/FIO₂ ratio was used as a measure of the efficacy of O₂ exchange. In an analogous fashion, the PCO₂–V̇E product was calculated as a measure of the efficacy of CO₂ exchange. Differences between baseline and postimplantation values reflect the contribution of IVOX to gas exchange.

All physiologic and laboratory measurements were made just prior to IVOX implantation (baseline), immediately postimplantation, at 4, 12, and 24 h postimplantation, and daily thereafter. An additional set of hemodynamic measurements was obtained at 1 h postimplantation. Data collected during the initial 48 h after implantation are more likely to represent the acute physiologic effects of device intervention and less likely to represent disease state changes; therefore, hemodynamic and respiratory variables are reported for this time period only. Remaining laboratory and clinical data obtained for the assessment of safety and outcome are
reported for the duration of implantation. Survival to device explantation, ICU discharge, and to hospital discharge were recorded.

Device Implantation

Implantation was performed under local anesthesia and intravenous sedation with midazolam (2 to 5 mg) and fentanyl (50 to 250 µg). The right internal jugular and common femoral vein were assessed with Doppler ultrasound for size and patency. The larger of the two veins was surgically isolated, a venotomy was made, and an introducer sheath was placed. Heparin, 3 mg·kg⁻¹, was administered intravenously to achieve an ACT greater than 400 s. After furling to its minimum diameter, the device was inserted through the introducer sheath, and unfurled. The introducer was removed, and the venotomy was closed around the gas conduit tubing. Heparin infusion was initiated when the ACT decreased to 250 s, and titrated to maintain an ACT approximately 200 s for the duration of implantation. Vancomycin was administered intravenously for microbial prophylaxis for the duration of implantation, unless the patient was previously receiving antibiotics with a spectrum including Gram-positive cocci.

Mechanical Ventilation Protocol

Prior to implantation, patients were ventilated with a ventilator (Servo model 900C; Siemens Elema; Solna, Sweden). The modes of ventilation were volume-limited controlled ventilation with a constant inspiratory flow (n=3) and pressure-limited controlled ventilation with a decelerating flow pattern and inspiratory fraction >0.5 (n=19). All patients were maintained on a regimen of stable ventilator settings for at least 6 h prior to implantation. The FIO₂ was adjusted to maintain an arterial saturation of 90 to 92% by pulse oximetry prior to baseline measurement.

Following implantation, the FIO₂ and VE were systematically reduced beginning 30 to 60 min postimplantation. The FIO₂ was reduced to maintain arterial saturation at baseline values (90 to 92%) by pulse oximetry. Inspiratory pressure and tidal volume were reduced to maintain an approximately constant PaCO₂ as determined by intermittent sampling of arterial blood. The mode of ventilation was not altered during the 48-h physiologic evaluation period.

Device Explantation

Explantation in survivors was performed under local anesthesia and sedation, comparable to implantation. Two patients had mechanical ventilation discontinued and were extubated prior to explantation. The remaining survivors were breathing spontaneously with pressure support ventilation. Following administration of sedation and infiltration anesthesia, the skin incision was opened and the vein isolated. Proximal and distal ligatures were placed, and the venotomy was opened and gently dilated. The device was furled and withdrawn. The venotomy was repaired in all but one patient with an internal jugular approach, in which case the vein was ligated. The wound was irrigated and closed in layers. Prophylactic antibiotic therapy was discontinued after two subsequent doses.

Following explantation, the device was cultured by both swabbing the fibers and sampling of sterile saline solution used to wash the device. The device was then examined for the presence of thrombi, fractured fibers, and degree of fiber agglutination.

Necropsy

Permission for necropsy was obtained in eight of the nonsurvivors. The access site was explored for evidence of venous injury and hematoma. The visceral organs with the device in the great vessels were removed en bloc. The venae cavae and posterior wall of the right atrium were opened by a posterior longitudinal incision to expose the device in situ. The position of the device was noted, and the vascular endothelium was examined for evidence of injury. The right side of the heart and pulmonary vasculature were examined for presence of thrombi. Samples were obtained for standard histologic examination.

Statistical Analysis

Hemodynamic and laboratory values are expressed as mean±SD. Blood loss and transfusion volumes are reported as median and range. The effects of intervention are reported as the mean difference between baseline and postimplantation values. Comparisons of continuous variables between baseline and postimplantation values were made with repeated measures analysis of variance (ANOVA). A t test of Dunnett's for multiple comparisons against a control was used in significant ANOVA models to test for differences from baseline. Comparisons of two groups were made with the t test for unpaired variables. Comparison of frequencies was made with Fisher's exact test. A p value less than 0.05 was chosen as significant (α error), and all tests of significance were two-tailed. Calculations were performed with specific software (SAS, Statistical Analysis System V6.08; SAS Institute; Cary, NC).

Results

Of the 22 patients enrolled in the study, we could not complete implantation in one patient due to abnormal venous anatomy, and a second patient died of hypoxemia before implantation could be completed. Data on IVOX performance and efficacy were available on the remaining 20 patients. Characteristics of all patients are given in Table 2.

Device Gas Exchange

All devices transferred gas as evidenced by measurements of CO₂ exchange in the 20 subjects completing implantation. The mean CO₂ transfer rate for all device sizes during the first 48 h was 50.4±15.8 mL min⁻¹ (range, 22.8 to 95.0 mL min⁻¹). Oxygen transfer measurements in 12 patients during the first 48 h was 71.1±20.2 mL min⁻¹ (range, 20.1 to 111.9 mL min⁻¹). Transfer rates for each device size are given in Table 3.

Effects on Mechanical Ventilatory Support

The FIO₂ was significantly reduced from a baseline of 0.78±0.16 to 0.63±0.21 by 4 h postimplantation and to 0.57±0.18 by 12 h postimplantation (Fig 1, top[A]). The FIO₂ remained significantly lower for the remainder of the 48-h study period. This reduction was achieved despite a rise in PaO₂, although this rise did

<table>
<thead>
<tr>
<th>Device Size</th>
<th>CO₂ Transfer, mL·min⁻¹</th>
<th>O₂ Transfer, mL·min⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>37.0±12.9</td>
<td>64.5±5.5</td>
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<tr>
<td>8</td>
<td>46.1±14.2</td>
<td>59.9±16.7</td>
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<td>9</td>
<td>51.3±12.3</td>
<td>91.4±4.2</td>
</tr>
<tr>
<td>10</td>
<td>64.3±14.8</td>
<td>76.3±22.7</td>
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</table>
not reach significance since our goal was to maintain a stable SaO2 of 90 to 92%.

Minute ventilation was reduced significantly by 4 h postimplantation from 177 ± 94 to 127 ± 58 mL·kg·min⁻¹, and remained low for the 48-h study period (Fig 1, center [B]). This reduction in V̇E was a result of decreases in tidal volume and respiratory rate. The PCO2 remained relatively constant despite the reduction in V̇E over the evaluation period. The device permitted a reduction in peak inspiratory pressure from 46 cm H2O to 42 and 38 cm H2O by 4 and 12 h postimplantation, respectively (Fig 1, bottom [C]).

**Effects on Efficacy of Gas Exchange**

Significant increases in PaO2/FIO2 ratio were noted, with values increasing from 79 at baseline to 113 by 4 h postimplantation. This increase was sustained for the duration of the 48-h observation period (Fig 2, top [A]). Significant decreases in PCO2-V̇E product from 7.7 to 4.9 L·kg⁻¹·min⁻¹·mm Hg were noted by 4 h postimplantation (Fig 2, bottom [B]). This decrease was also sustained for the duration of the 48-h study period.

**Hemodynamic Effects**

Pulmonary artery wedge pressure and cardiac output decreased transiently from 16.2 ± 4.4 mm Hg and 3.7 ± 0.9 L·min⁻¹·M² to 14.4 ± 3.2 mm Hg and 3.0 ± 0.8 L·min⁻¹·M² at 1 h, most likely due to blood loss associated with implantation. Both indices were restored by 4 h postimplantation with correction of volume loss in those patients requiring it (Fig 3). There was no significant change in mean systemic arterial pressure, heart rate, pulmonary artery pressure, or RAP.

All hemodynamic indices remained stable for 4 h postimplantation through the remainder of the 48-h observation period.

**Hematologic Effects**

A reduction in platelet count was encountered during the study (Fig 4, top [A]). Levels decreased following implantation from a baseline of 164 ± 109×10³ to 103 ± 37×10³ cells·µL⁻¹ within 24 h postimplantation, and remained low over the next 7 days. Fibrinogen levels decreased significantly following implantation, from 404 ± 161 to 256 ± 78 mg·dL⁻¹, but returned to baseline values by 12 h postimplantation, and remained stable (Fig 4, center [B]).

Mean plasma hemoglobin values remained stable over 7 days. Values remained entirely within the normal range (<20 mg·dL⁻¹) in 11 patients. Seven patients had isolated elevations to between 20 and 30 mg·dL⁻¹, and isolated increases to 36 and 36.4
mg·dL⁻¹ were seen following blood transfusions in two of these patients.

A significant reduction in complement C3 from 71 ± 29 mg·dL⁻¹ to 49 ± 21 mg·dL⁻¹ occurred by 1 h postimplantation, but returned to previous levels by 72 h postimplantation. This decrease suggests transient activation of C3 to C3a, which may have been related to device implantation. No changes in complement C5 were noted.

Complications

Median blood loss during implantation was 420 mL (range, 150 to 1,000 mL). This resulted in transient hypotension of clinical significance in five of the first nine patients. The next 11 patients received a colloid infusion of 500 mL just prior to implantation, and only one hypotensive episode was subsequently encountered. The median transfusion volume subsequent to implantation was 0 mL·d⁻¹ (range, 0 to 1,750 mL·d⁻¹; mean, 203 ± 324 mL·d⁻¹). One patient (patient 15) developed continued bleeding from the implantation incision requiring surgical exploration and ligation of a bleeding vessel; no subsequent bleeding occurred. A second patient (patient 22) developed a wound hematoma with partial dehiscence following explantation. The hematoma was evacuated and the wound healed without further complication.

A clinically identifiable retroperitoneal hemorrhage occurred in one patient. A spontaneous hemorrhage developed at day 17 in patient 2, and was believed to be related to anticoagulation. Treatment with IVOX and heparin was discontinued, blood was administered, and no surgical intervention was required. Explantation had been planned for the following day, so little loss of benefit resulted, and the patient survived.

Deep venous thrombosis documented by duplex Doppler ultrasound examination occurred following explantation in four patients receiving femoral implantations. Three were treated with heparin, and one was treated with a 24-h course of streptokinase, followed by heparin. Recannulation occurred in all
patients; this was confirmed by repeated ultrasound examination. None of the four patients had clinical evidence of pulmonary embolism. The one patient receiving streptokinase had a negative pulmonary ventilation-perfusion radionuclide scan, and the remaining patients were not studied.

There were no instances of wound, device, or blood-borne infection in any patient. Four patients had sepsis prior to device implantation, of whom two had bacteremia treated with antibiotics prior to implantation, with negative blood cultures by the time the device was implanted.

Examination of the device following explantation in survivors and nonsurvivors revealed slight agglutination of some of the fibers due to platelet-fibrin deposition, but was limited to less than 5% of the gas exchange surface. Small thrombi were identified within the interior of the fiber bundle at the junction of the proximal and distal manifolds in all devices, but were tightly adherent and not considered significant. No thrombus formation was found on the gas exchange surface of any of the devices.

Necropsy Findings

Necropsy was performed on eight patients. The causes of death included peritonitis and diffuse alveolar damage in one patient, severe pneumonia with diffuse alveolar damage in two patients, near drowning with ARDS in one patient, and diffuse alveolar damage (ARDS) in the remaining four patients. The causes of death indicated by necropsy were consistent with the clinically indicated causes of death in all cases. There were no findings to suggest IVOX contributed to death in any patient. The only unexpected finding was a pelvic retroperitoneal hematoma (in the patient requiring wound exploration) of approximately 150 mL in size.

Survival

Ten patients survived the course of ARDS and were transferred from the ICU. Two of these patients died subsequent to ICU care, and eight were discharged from the hospital alive. This represents a short-term survival of 50% and discharge survival of 40% of patients who completed device implantation.

There was no statistical difference between survivors and nonsurvivors with respect to age, prior duration of respiratory failure, lung injury score, cardiac index, PaO2/FIO2, lung compliance, or intrapulmonary shunt (Table 4). There was a higher incidence of multiple organ dysfunction at study entry in nonsurvivors as compared with survivors (5/10 vs 1/10), but the difference did not reach statistical significance (p=0.14).

Discussion

The application of airway pressure therapy is currently the accepted means to support impaired gas exchange in respiratory failure. Patients with severe respiratory failure who require elevated levels of inspired oxygen and minute ventilation continue to have a high mortality. Since airway pressure therapy does not reverse the underlying pathophysiologic condition, improved outcome must await more definitive therapy. There is ample evidence, however, that the application of excessive airway pressure not only can result in classic barotrauma syndromes (pneumomediastinum, pneumatoceles, pneumothorax), but may enhance or propagate the underlying parenchymal injury in respiratory failure.9-14,21 The hypothesis that reducing airway pressures in respiratory failure may lead to decreased pulmonary injury has led to the clinical application of techniques to limit alveolar overdistention. Hickling et al,22 in an uncontrolled trial, reported a lower mortality in patients with ARDS through the use of low-volume pressure-limited ventilation and permissive hypercapnia. Morris et al15 reported a 42% survival in a group of patients treated with pressure-controlled inverse ratio ventilation using a rigidly controlled management protocol in patients whose entry criteria have previously been associated with up to 90% mortality. Extracorporeal support of gas exchange, including extracorporeal CO2 removal and venovenous ECMO can permit substantial reductions in requirements for ventilatory support. By transferring gas exchange function to the extracorporeal circuit, more substantial reductions in ventilator support (lung rest) are possible. Recent series of venovenous extracorporeal and CO2 removal report survival rates of 50% and higher.16-18

Extracorporeal techniques, however, are resource

| Table 4—Characteristics of Survivors and Nonsurvivors at Entry Into Study |
|-----------------|-----------------|----------------|
|                  | Survivors       | Nonsurvivors   | p Value |
| Age, yr          | 43.0±14.5       | 38.5±19.5      | 0.56    |
| Prior duration of acute respiratory failure, d | 5.9±4.4 | 6.9±6.3 | 0.68 |
| Lung injury score19 | 3.42±.23 | 3.45±.19 | 0.68 |
| Cardiac index, L·min⁻¹·M⁻² | 4.1±.95 | 3.5±.83 | 0.14 |
| PaO2/FIO2 ratio | 84±16 | 75±27 | 0.98 |
| Static compliance, mL·cm H2O⁻¹ | 23.5±7.1 | 27.1±10.7 | 0.39 |
| Intrapulmonary shunt, % | 42.9±11.1 | 48.1±10.0 | 0.28 |
intensive and introduce an additional set of risks and complications, including equipment failure, activation of complement, hemolysis, thrombocytopenia, and bleeding. Intracorporeal membrane oxygenation and CO₂ removal have the potential to provide gas exchange support with a lesser risk than extracorporeal systems.

The feasibility of intracorporeal support has been demonstrated previously in animal models and in selected cases of human ARDS. We report a clinical trial in 22 patients with a consistent protocol aimed at reducing the level of airway pressure support and inspired oxygen fraction.

In our patients with ARDS who completed implantation, intravascular membrane oxygenation and CO₂ removal were able to support gas exchange and permit a reduction in the level of airway pressure support. In each patient, we were able to achieve a reduction in FiO₂ or increase in PaO₂, a reduction in V̇E or peak inspiratory pressure, or both. The degree of benefit, however, was of smaller magnitude than seen with extracorporeal techniques. Maximal gas exchange via this intracorporeal device was estimated at 30 to 35% of total gas exchange requirements, while extracorporeal techniques can achieve as much as 80% or greater support.

Except for the initial hemodynamic instability in some patients associated with acute blood loss, hemodynamic tolerance was excellent. There was no evidence of hemodynamic compromise in any patient. Atrial and pulmonary capillary wedge pressure remained stable for the initial phase of implantation, as did cardiac output. Hemodynamic variables worsened in patients who went on to develop multiple organ dysfunction, but there was no evidence of obstruction to implicate IVOX as the cause.

There were no episodes of sepsisemia associated with use of IVOX. The potential for microbiologic colonization would appear to be great based on the large surface area of the device (up to 0.52 m²). However, no patient developed bacteremia or fungemia, and all cultures of the devices following explantation were negative despite implantation periods of up to 20 days. The use of prophylactic antibiotics likely contributed to the lack of incidence of infection, but the safety of the device with regard to infectious complications appears quite good.

We encountered minimal morbidity and no mortality directly associated with application of IVOX. The principal morbidities encountered were blood loss at the time of implantation, bleeding complications of anticoagulation, and deep venous thrombosis. The only hematologic effect noted was a decrease in platelet count. It could not be determined if the reduction in platelet count was related to IVOX or due to heparin-induced thrombocytopenia, hemodilution, or decreased production typically associated with the critical illness in these patients. Postmortem and postexplantation examination of the device revealed small isolated areas of platelet-fibrin thrombi, but the contribution of this to the decreases in platelet count is likely small. Improvement in insertion techniques can potentially reduce or eliminate morbidity due to blood loss during implantation. Perfection of device coating can potentially eliminate the need for anticoagulation and its attendant complications. We have not been able to evaluate methods to reduce deep venous thrombosis because of the small number of patients.

Survival in our patient group was comparable to other reported series of severe respiratory failure employing extracorporeal support. At entry into the study, survivors and nonsurvivors were comparable with respect to duration of respiratory failure, hemodynamic function, and several measures of severity of pulmonary injury. None of these variables was therefore predictive of survival. There was a higher incidence of multiple organ dysfunction at time of study entry in nonsurvivors, but our series was too small to determine if multiple organ dysfunction was statistically associated with outcome.

The contribution of gas exchange by IVOX to total patient requirements was restricted and represents the major limitation of the device in its present form. Despite this restriction, gas exchange levels are comparable to low-flow extracorporeal venovenous support. This preliminary and uncontrolled trial, although confirming the feasibility and relative safety of partial intracorporeal support of gas exchange, is subject to the limitations of a small, single-center trial and needs to be supported by larger, prospective comparative trials. Enhancements to the performance of the existing device could expand the role of intracorporeal support of severe respiratory failure.

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