Low-Frequency Positive-Pressure Ventilation With Extracorporeal CO₂ Removal in Severe Acute Respiratory Failure

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Forty-three patients were entered in an uncontrolled study designed to evaluate extracorporeal membrane lung support in severe acute respiratory failure of parenchymal origin. Most of the metabolic carbon dioxide production was cleared through a low-flow venovenous bypass. To avoid lung injury from conventional mechanical ventilation, the lungs were kept "at rest" (three to five breaths per minute) at a low peak airway pressure of 35 to 45 cm H₂O (3.4 to 4.4 kPa). The entry criteria were based on gas exchange under standard ventilatory conditions (expected mortality rate, >90%). Lung function improved in thirty-one patients (72.8%), and 21 patients (48.8%) eventually survived. The mean time on bypass for the survivors was 5.4 ± 3.5 days. Improvement in lung function, when present, always occurred within 48 hours. Blood loss averaged 1800 ± 850 mL/day. No major technical accidents occurred in more than 8000 hours of perfusion. Extracorporeal carbon dioxide removal with low-frequency ventilation proved a safe technique, and we suggest it as a valuable tool and an alternative to treating severe acute respiratory failure by conventional means.

EXTRACORPOREAL assist with an artificial lung to support a patient with severe acute respiratory failure (ARF) of parenchymal origin was first reported by Hill et al. in 1972. Since then many teams have experimented with this therapeutic approach to "buy time" for lungs to heal. In 1976, Gille and Bagniewski reviewed the worldwide experience with extracorporeal support for ARF in 233 cases and reported an 85% mortality rate.

From 1974 to 1976, the National Heart, Lung, and Blood Institute supported a multicenter trial in severely ill patients with ARF to compare extracorporeal venous-arterial support plus conventional continuous positive-pressure ventilation (CPPV) with CPPV alone.

The entry criteria for the extracorporeal membrane oxygenation (ECMO) study were based on gas exchange during standard ventilatory conditions. The ECMO study selected an extremely ill patient population, with a mortality rate of 91.7% in the control (CPPV) group. There was no improvement in survival with ECMO. These poor results inhibited use of long-term extracorporeal support for ARF years to come.

In 1979, we began to assess clinically a method of extracorporeal support conceptually different from ECMO. The rationale of this technique was to prevent further damage to diseased lungs by reducing their motion (pulmonary rest), although three to five "sighs" were provided each minute to preserve the functional residual capacity (LFPPV [low-frequency positive-pressure ventilation]).

With this method, oxygen uptake and carbon dioxide (CO₂) removal were dissociated. Oxygenation was primarily accomplished through the motionless lungs (apneic oxygenation) while CO₂ was cleared through the artificial lung (ECCO₂R [extracorporeal CO₂ removal]).

The LFPPV-ECCO₂R was performed at an extracorporeal blood flow of 20% to 30% of cardiac output in a venovenous bypass mode. The aim of this article is to report the clinical results obtained by LFPPV-ECCO₂R in 43 patients with ARF who met gas-exchange criteria similar to those used in the ECMO study.

PATIENTS AND METHODS

Our study group consisted of 43 patients (18 males and 25 females; mean age, 26 years; range, 2 to 56 years) with ARF of various etiologies (see below). All patients but one were referred to our institute from other intensive care units. The mean duration of mechanical ventilation before bypass was 9.0 ± 4.6 days, of which approximately half was spent in the referring hospital and half at our institute.

Attempts to optimize mechanical ventilation before bypass included ventilation with positive end-expiratory pressure (PEEP) (up to 25 cm H₂O [2.5 kPa]), inverted ratio ventilation, high-frequency jet ventilation, and a commonly employed regimen of medical treatment (sedation, muscle relaxants, control of body temperature, diuretics, vasoactive drugs, and antibiotics).

Entry Criteria

Informed consent was obtained from the closest relative. All consecutive patients meeting either of the following "ECMO criteria" were admitted:

- Serum lactate concentration >15 mmol/L
- Hypoxemia: a PaO₂/FiO₂ ratio <200 mm Hg
- Unsuccessful use of conventional mechanical ventilation with a success rate of <70% for at least 48 hours
- Hemodynamic instability: mean arterial pressure <50 mm Hg

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Summary of the document:

To the study and underwent LFPPV-ECCO₂R. The ECMO study included a total static lung compliance lower than 30 mL (centimeters of water) (0.306 L/kPa), not required in the ECMO study. Total static lung compliance was measured during paralysis, and anesthesia by determination of the volume-pressure curve of total respiratory system. Although total static lung compliance does not represent the true lung compliance, it was chosen as an index of both lung elasticity and “opening pressure” of the respiratory system. Total static lung compliance was not measured when an air leak was present (13 cases).

Exclusion Criteria

As in the ECMO study, we excluded patients with a pulmonary capillary wedge pressure greater than 25 mm Hg (3.3 kPa), patients with chronic systemic disease, including irreversible central nervous system (CNS) injury, and patients with severe chronic pulmonary disease, terminal cancer, and major burns.

Unlike the ECMO study, the duration of the pulmonary insult or the age of the patient was not considered reasons for exclusion. Of 43 patients, four had been treated with CPPV for more than 21 days and three were younger than 12 years.

Evaluation of Other ‘Organ System Failures’

According to the “additional data collection” in the ECMO study, six major risk factors were identified: liver dysfunction (ie, bilirubin level >2 mg/dL [34 μmol/L] and/or serum transaminase values three times normal), renal dysfunction (creatinine level >2 mg/dL [177 μmol/L]), CNS dysfunction (ie, coma), coagulation disorders (with or without actual bleeding), host defense failure (ie, sepsis diagnosed by positive blood cultures), and cardiovascular failure (ie, vasoactive drugs were required to support systemic perfusion). No attempts were made to quantify the degree of organ failure, and they were noted as present or absent.

Extracorporeal CO₂ Removal

This technique has been fully described elsewhere and only briefly summarized here. The ECMO system was always performed using venovenous bypass. In the first 14 cases, a femoral-jugular bypass was employed. We later developed a double-lumen catheter system where bypass was performed with a single cannulation through the femoral vein (ten cases). In the last 15 perfusions, we used a saphenous-saphenous vein access route. Due to individual vascular access problems, other routes were used in four cases. The saphenous-saphenous access was technically the simplest and did not require drainage of the distal vein.

Vascular Access

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Extracorporeal Circuit

The blood circuit was assembled using silicone rubber tubing with polyethylene connectors. Suitable side ports were provided for sampling, monitoring, and connection to a hemodialyzer or ultrafilter, if required. Two membrane lungs (9 m² total membrane surface area for adult patients) were used in series. The priming volume of the blood circuit, including the membrane lungs, was approximately 1.8 L. The membrane lungs were ventilated separately with a humidified mixture (usually 15 L/min each) of room air and oxygen. Subatmospheric pressure was maintained in the gas circuit. Blood and gas circuits were enclosed in a thermostated compact system. Monitoring included oxygen saturation of the drained venous blood, blood pressure drop across the membrane lung, extracorporeal blood flow, gas flow rates, and system temperature.

Low-Frequency Positive-Pressure Ventilation

The patient’s lungs were inflated, with PEEP ranging from 15 to 25 cm H₂O (1.5 to 2.5 kPa). The lungs were ventilated three to five times per minute, with peak airway pressure limited to 35 to 45 cm H₂O (3.4 to 4.4 kPa) (representative expiratory time, 10 to 18 s). Under these conditions, mean airway pressure approximated PEEP. The tidal volume was greatly influenced by total static lung compliance. To provide for oxygen consumption during the long end-expiratory pause, we directed a continuous flow of oxygen (1 to 2 L/min) into the trachea through a small catheter advanced through a side port in the tracheal tube connector. Excess oxygen was vented through the PEEP valve. Despite the continuous oxygen flow, the alveolar oxygen pressure was governed primarily by the FIO₂ setting on the ventilator. In essence, LFPPV-ECCO₂R provided for apneic oxygenation to which mandatory “sighs” were superimposed.

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Clinical Management

The patients were paralyzed (pancuronium bromide given intravenously) and anesthetized (alfaxalone-alphadalone and/or midazolam and/or barbiturates and/or fentanyl given intravenously) throughout the bypass procedure. The LFPPV-ECCO₂R was performed using the following guidelines.

Connection to Bypass.—The catheters were inserted after a dose of intravenous heparin, 100 U/kg in a single bolus. The heparinized lactated Ringer’s prime solution in the perfusion circuit was replaced with warmed whole blood and the perfusion was begun. The blood temperature in the circuit was kept at 37°C before connection to bypass to avoid sudden cooling. Extracorporeal blood flow was progressively raised from 200 to 300 mL/min to the selected maintenance flow of 20% to 30% of cardiac output over about 20 minutes.

Initially the FiO₂ of the ventilator and the one of the membrane lungs were kept at the prebypass levels. The ventilation of the natural lungs was decreased to maintain the arterial CO₂ pressure in the normal range, to compensate for increase in CO₂ removal by the membrane lungs. While ventilation of the lungs was decreased, PEEP was raised to maintain the mean airway pressure at prebypass level, to prevent sudden pulmonary edema. When the respiratory rate was below five breaths per minute, we began a continuous slow flow of humidified 100% oxygen into the trachea through a small atracheator, as discussed earlier.

Maintenance

After the initial equilibration period, our goal was to provide for adequate gas exchange at the lowest FiO₂ and airway pressure tolerated. When oxygenation improved, we decreased the FiO₂ in the ventilator and in the membrane lungs. When PaO₂ was greater than 80 mm Hg (10.7 kPa) at an FiO₂ of 0.4, and the FiO₂ of the membrane lungs was 0.21, we lowered PEEP progressively.

The extracorporeal system thermostat was adjusted aiming at a normal patient body temperature. Core temperatures between 36.5°C and 37.5°C were considered satisfactory.

During routine perfusion, gas exchange and hemodynamic measurements were obtained every hour. Volume-pressure curve and coagulation testing were done once or twice a day. Routine blood chemistry and chest roentgenograms were performed once a day or whenever indicated based on clinical status. The general patient’s care was unchanged from the care of the severely ill patients with ARF not on bypass. The main difference was the continuous heparinization required to maintain the activated clotting time at twice the normal value.

Weaning and Disconnection From Bypass.—When PaO₂ consistently remained above 80 mm Hg (10.7 kPa) on an FiO₂ of 0.40 and when the total static lung compliance rose to over 30 mL (centimeters of water) / (0.986 L/kPa) with some clearing evident on chest roentgenograms, we began to wean the patient off bypass. Muscle relaxation was first suspended, and the patient was allowed to breathe spontaneously with continuous positive airway pressure. The ECO₂R was progressively decreased by reducing the gas flow to the membrane lungs.

The patient’s support system was disconnected when the patient was able to maintain adequate gas exchange with continuous positive airway pressure at an FiO₂ of 0.4 and a PEEP of 10 to 15 cm H₂O (0.1 to 1.5 kPa), or at low-frequency intermittent mandatory ventilation for at least six hours, without any gas exchange in the membrane lungs.

Staff Requirement

Our nurse-patient ratio was 1:1. A physician or technician with expertise in the extracorporeal apparatus was always present. Hematologists and surgeons were always available for consultation. The daily cost of patient care on bypass was approximately twice the daily cost of a severely ill patient receiving standard intensive care with mechanical ventilation.

Statistical Analysis

Data are expressed as mean±SD. Comparisons between groups of patients were performed by the t test for unpaired data.

RESULTS

A total of 43 patients underwent LFPPV-ECCO₂R between January 1980 and January 1985. Five patients qualified for study by the fast entry criteria and 38 by the slow entry criteria. Twenty-one patients (48.8%) survived.
Table 1.—Respiratory Parameters* Before Bypass

<table>
<thead>
<tr>
<th>Group</th>
<th>V̇E, mL/kg/min</th>
<th>FICO₂</th>
<th>PEEP, cm H₂O (kPa)</th>
<th>Pao₂, mm Hg (kPa)</th>
<th>Paco₂, mm Hg (kPa)</th>
<th>Right to Left Shunt</th>
<th>Cṁex, mL/cm² H₂O (L/kPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survivors (n=21)</td>
<td>233.91±73.51</td>
<td>0.72±0.18</td>
<td>11.74±2.96</td>
<td>51.82±15.24</td>
<td>44.15±9.32</td>
<td>0.51±0.12</td>
<td>25.53±9.76</td>
</tr>
<tr>
<td>Nonsurvivors (n=22)</td>
<td>247.10±74.33</td>
<td>0.85±0.12</td>
<td>12.91±4.50</td>
<td>52.61±11.85</td>
<td>53.49±12.40</td>
<td>0.54±0.12</td>
<td>24.36±1.94</td>
</tr>
</tbody>
</table>

*Respiratory parameters include the following: V̇E, minute ventilation; FICO₂, inspired oxygen fraction; PEEP, positive end-expiratory pressure; Pao₂, arterial oxygen pressure; Paco₂, arterial carbon dioxide pressure; and Cṁex, total systemic lung compliance.

Table 2.—Hemodynamic Parameters* Before Bypass

<table>
<thead>
<tr>
<th>Group</th>
<th>CI, L/min/m²</th>
<th>PAP, mm Hg (kPa)</th>
<th>PCWP, mm Hg (kPa)</th>
<th>PVR, Dyne s/cm²</th>
<th>SVR, Dyne s/cm²</th>
<th>CVP, mm Hg (kPa)</th>
<th>BP, mm Hg (kPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survivors (n=21)</td>
<td>4.12±1.21</td>
<td>30.90±11.17</td>
<td>8.40±5.25</td>
<td>305.95±200.66</td>
<td>7.59±5.79</td>
<td>1080.53±406.85</td>
<td>85.29±17.25</td>
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<tr>
<td>Nonsurvivors (n=22)</td>
<td>4.58±1.13</td>
<td>30.86±9.14</td>
<td>11.33±5.03</td>
<td>239.98±119.19</td>
<td>8.05±4.61</td>
<td>875.86±337.70</td>
<td>82.27±20.38</td>
</tr>
</tbody>
</table>

*Hemodynamic parameters include the following: CI, cardiac index; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; SVR, central venous pressure; CVP, systemic vascular resistance; and BP, mean arterial pressure.

Table 3.—Organ Failures Before Bypass

<table>
<thead>
<tr>
<th>Patients</th>
<th>CNS*</th>
<th>Host Defense</th>
<th>Kidney Dysfunction</th>
<th>Cardiovascular</th>
<th>Coagulation Disorders</th>
<th>Liver Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survivors (n=21)</td>
<td>2</td>
<td>6</td>
<td>3</td>
<td>10</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Nonsurvivors (n=22)</td>
<td>7</td>
<td>8</td>
<td>4</td>
<td>10</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Mortality</td>
<td>78</td>
<td>67.1</td>
<td>57</td>
<td>50</td>
<td>50</td>
<td>41.2</td>
</tr>
</tbody>
</table>

*CNS indicates central nervous system.

and were eventually discharged. The etiology of ARF and the survival rates are shown in Fig 2. Survivors were obtained from all groups of ARF. The lowest survival rate was in patients with post-traumatic ARF (22%). The age distribution of the patients and related mortality ratio are shown in Fig 3.

The severity of ARF immediately before bypass was comparable in survivors and nonsurvivors (Tables 1 and 2), with the exception of a significantly lower FICO₂ and arterial CO₂ pressure in survivors.

The duration of pulmonary insult, although not statistically different, was somewhat shorter in survivors (7.86±11.7 days) than in nonsurvivors (11.9±11.6 days). However, two of four patients with more than 21 days of CPPV before bypass eventually survived.

The numbers of individual failing or dysfunctioning organ systems before bypass are listed in Table 3 and Fig 4, respectively. The highest mortality was associated with CNS failure (78%) and the lowest mortality was associated with liver dysfunction (41%).

No patient survived with five or more organ failures (including the lungs). However, survival was 67% in 12 patients with four organ system failures, including patients in whom both the artificial lung and the artificial kidney were used simultaneously (seven patients, two survivors).

Survivors required 5.40±3.50 days of bypass while nonsurvivors were on bypass a mean of 10.64±6.58 days (P<.01).

Improved lung function, if any, was always seen within 48 hours after beginning of bypass. During the first six hours of the procedure, cardiac index and mean pulmonary artery pressure decreased significantly (P<.05) toward normal values, both in survivors and nonsurvivors (Fig 5).

Significant differences in Pao₂ and right to left shunt between survivors and nonsurvivors were measured after 12 and six hours of bypass, respectively (Fig 6). There were no significant differences in central and systemic hemodynamics between these two groups (Fig 5).

Irrespective of ultimate survival, 31 (72.8%) of 43 patients had improved lung function during bypass (improved Pao₂, right to left shunt, total static lung compliance, and chest x-ray films).

Irrespective of ultimate survival, the only differences found in the respiratory and hemodynamic parameters before bypass between patients who had improved lung function and those who did not was a significantly lower arterial CO₂ pressure (45.7±9.5 mm Hg [61±13 kPa] vs 57.1±13.7 mm Hg [7.6±1.8 kPa], P<.01) and FICO₂ (0.76±0.17 vs 0.87±0.11, P<.05).

Complications

No major accidents occurred in more than 8000 hours of extracorporeal perfusion. The average number of organ failures was not higher during bypass than in the prebypass period. In particular, the incidence of sepsis did not increase during bypass. One bypass lasting 32 days was performed without complications and was electively terminated after a lung biopsy had revealed total interstitial and intra-alveolar fibrosis. The only bypass-related adverse finding was bleeding. An average of 1800±850 mL/d of whole blood was transfused (including 200 to 300 mL/d removed for blood tests). In three cases, intrapulmonary bleeding was the
terminal event. Minor bleeding, often requiring a surgical revision every two to three days, occurred at the cannula- tition sites. Major bleeding occurred from chest tubes, or during pulmonary surgery while on bypass (usually to treat a bronchopleural fistula; three patients, one survivor).

On six occasions, the membrane lungs were replaced due to either a reduced efficiency in gas exchange and/or the presence of disseminated intravascular coagulation. Otherwise, one set of membrane lungs lasted the entire procedure.

COMMENT

Survival from ARF depends on the severity of lung injury, the nature of the underlying disease, and the number of associated failing organs. The impaired gas exchange is only part of the problem. When the underlying disease does not respond to drug therapy, surgery, or an early favorable natural evolution, survival is unlikely whatever the mode of respiratory support.

In this study we report on the effectiveness of LFPPV-ECCO2R in 43 patients with severe ARF of parenchymal origin, selected primarily by the criteria of the previous ECMO study. The ECMO study produced an overall mortality rate of 91% in 1977, with 48 patients treated with CPPV and 42 patients treated with venous-arterial bypass and CPPV.

When similar criteria were used in another population of patients with ARF treated conventionally, the mortality rate was reported as 93%. In 1985, a review of 72 patients meeting ECMO criteria on admission or during their course in the intensive care unit, but not on ECMO, showed a mortality of 91.7% (W. Zapol, MD, written communication, June 5, 1985). In our 43 patients with severe ARF evaluated by the same criteria and treated with LFPPV-ECCO2R, the mortality rate was 51.2%. We recognize that we lack an indigenous control population; however, after our first novel and successful clinical applications of LFPPV-ECCO2R, we decided we could not ethically organize a randomization in moribund patients. First, we wished to explore the clinical outcome and obtain experience with this therapy. Moreover, bypass therapy was never offered as an alternative treatment, but always as a last resort, after CPPV and other nonconventional forms of treatment, such as inverted-ratio ventilation or high-frequency jet ventilation, had failed to improve gas exchange.

Since the expected mortality rate for patients meeting ECMO entry criteria was consistently greater than 90%, why did LFPPV-ECCO2R result in a lower mortality? If the impairment of gas exchange was similar, then the observed difference may have been due to a different patient population or may have been due to an improved lung therapy with LFPPV-ECCO2R.

The mean age of our patients was lower than in the ECMO study, but we found no relationship between age and mortality (Fig 3). Differences in ARF patient population may never be completely ruled out. However, the etiologies seen in our patients were similar to those reported in the ECMO trial. Pneumonia in both studies was the major cause of ARF (23 in our study—14 viral and nine bacterial). We report a slightly higher incidence of post-traumatic ARF (nine vs two) while pulmonary embolism, sepsis, and shock were almost equally represented. The number of "organ failures" may have had an important effect on mortality as shown in the "additional data collection" of the ECMO study. That study found a major correlation between mortality and the number of failing organs. In our patients, 38 of 43 had one or more additional "organ failure," highly indicative of a severely ill patient population (Fig 4).

Hence, the improvement in survival obtained by LFPPV-ECCO2R compared with CPPV-ECMO may lie in the technique itself. Both the bypass mode and the respiratory treatments were, in fact, different.

The choice of the venous route instead of the venous-arterial route may play a role. During venous
bypass, pulmonary hemodynamics remain unaffected, while during venous-arterial bypass (as in ECMO) there may be significant pulmonary hyperperfusion. It has been suggested that reducing lung perfusion during ARF may lead to pulmonary thrombosis, and it is important to recall that the terminal respiratory units are nourished primarily by pulmonary blood flow and not by the peripheral blood flow. Moreover, Kolobow et al. induced pulmonary infarction in healthy sheep after six hours of total venous-arterial bypass with the heart in ventricular fibrillation. They suggested that elevated focal lung tissue pH caused by the ventilation of nonperfused alveoli was the direct cause of pulmonary infarction. These factors may also possibly lead to the possibility of lung repair during venous-arterial bypass. As to the respiratory treatment, neither LFPPV nor CPPV cures the injured lungs. The most we can expect from the “best” respiratory treatment is to support gas exchange without further damage to the lungs. We believe it possible that CPPV damages the lungs more than LFPPV does. In severe ARF, high FiO2 and PEEP are required for oxygenation, while high peak pressure and minute ventilation are mandatory for CO2 removal. Experimental evidence demonstrates that high FiO2 peak pressures, and a high minute ventilation are noxious to the lung. To maintain gas exchange during severe ARF with CPPV, these noxious factors are directed to the healthiest gas exchange regions of the injured lungs. With LFPPV, the lungs are able to rest, thereby avoiding high peak pressures and large minute ventilation, allowing for a more “gentle treatment” of the lung. From this reason we believe that LFPPV, with a low total static lung compliance as an indication for bypass, the reduced mortality rate in our patients may then reflect a reduced lung damage from LFPPV compared with CPPV.

Irrespective of survival, the acute response to bypass therapy deserves comment. Thirty-one of 45 patients experienced consistent improvement in their lung function. Uniformly, any improvement occurred within 48 hours after beginning bypass. This may have important practical consequences allowing the withdrawal of bypass if no response is observed within two or three days. These patients who did not experience improvement of their lung function had a significantly higher arterial CO2 pressure in the prebypass period. This may reflect a more advanced lung disease. However, the duration of pulmonary injury was not different between patients who experi-

enced improved lung function and patients who did not. Increased arterial CO2 pressure may indicate a more severe injury to the pulmonary micro-circulation. This point needs to be clarified.

We believe LFPPV-ECCO2R to be a safe technique, with a relatively good outcome in otherwise almost hopeless acute respiratory failure. However, the lack of a properly improvement in a significant number of our patients suggests that lung damage had advanced to a stage beyond which recovery may no longer be possible. Hence, the continued adherence to ECMO criteria may need to be reevaluated. Now is the time to conduct a randomized study to confirm the effectiveness of LFPPV-ECCO2R.

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