Report on the Clinical Trials of the Plexus Membrane Blood Oxygenator


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Abstract

Twenty adult patients gave informed consent to clinical cardiopulmonary bypass (CPB) trials with a new adult hollow fiber membrane oxygenator. Clinical CPB trials averaged 88 ± 25 min (mean ± 1 SD) for these patients that weighed 78 ± 13 Kg and had BSA's = 1.9 ± 0.2 m^2. Blood flow averaged 4.0 ± 0.8 L/min, and hypothermia was employed at 26.5 ± 2.4°C. FiO_2's = 0.59 ± 0.15, and gas to blood flow ratios = 0.64 ± 0.18 were required to maintain the PaO_2 > 100 mmHg and to accomplish alpha-stat. The oxygenator exhibited a pressure drop of 50-60 mmHg at 5.09 l/min and a heat exchanger performance factor over .55 during most of CPB.

Multiple regression analysis of the clinical database demonstrated that the FiO_2 required to achieve a desired PaO_2 was dependent on the blood flow, gas flow, and SvO_2 (r^2 = 0.83, standard error = 0.09). The gas flow required to accomplish alpha-stat was dependent on patient age, weight, blood flow, arterial blood temperature, and desired PaCO_2 (r^2 = 0.71, standard error = 0.6).

The Plexus blood oxygenator is safe for adult cardiopulmonary bypass and its clinical performance is statistically predictable.

Introduction

Microporous hollow fiber membrane oxygenators have been determined to be extremely efficient at gas exchange (1) while causing minimal trauma to blood (2). Recently, attention has been directed toward other features that these types of oxygenators can provide to increase their effectiveness. Larger gas exchange surface area combined with lower prime volume (1, 2), preservation of membrane integrity during long cases (1), and simplicity of assembly, prime and operation (3, 4, 5) all enhance the safety of the efficient gas transfer capabilities of the hollow fiber membrane oxygenator.

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Blood is pumped from the venous reservoir into the venous inlet at the bottom of the oxygenator and flows over the anodized aluminum heat exchanger. The blood path is around the outside of the fibers while the gas flows inside the fibers. Gas exchange occurs, and the blood then flows down through the center of the hollow fiber bundle and out through the arterial outlet which is also located at the bottom of the oxygenator.

Twenty clinical trials of the Shiley Plexus Membrane Oxygenator were performed at the Medical University of South Carolina. The purpose of these trials was to evaluate the performance of the oxygenator quantitatively. To this end ventilation rate and FiO₂ predictor equations were developed from patient and bypass variables for this oxygenator.

Materials and Methods

Each case utilized a roller pump (a), a tubing pack (b) containing an arterial line filter (c) which was continuously purged into a filtered cardiotomy reservoir (d), and a 1000 ml reservoir bag (e). In 18 of the cases, the bypass circuit was primed with 500 ml of 6% hetastarch, 1200 ml lactated Ringer’s solution, and 1000 u beef lung heparin. Two units of packed red blood cells were added to the prime in the other two cases to keep the post-dilutional hematocrit greater than 20%. Estimated optimal ventilation rate (6) was used to predict initial on-bypass gas flow.

Prebypass laboratory measurements included a hematology panel, plasma free hemoglobin, coagulation times, chemistry and enzyme studies. The hematology and plasma free hemoglobin measurements were repeated at 15 minutes on bypass, the end of bypass, 24 hours and 72 hours post-bypass. The coagulation, chemistry and enzyme studies were repeated at 24 hours and 72 hours post-bypass. Blood gas analysis (f) was performed at 15 minutes, 30 minutes, and every 30 minutes thereafter on bypass. Arterial and venous hemoglobin saturations were monitored using the Bentley OxySAT meter (b). The sweep gas rate was set at the estimated optimal ventilation rate (6) and adjusted to achieve alpha-stat. Expired gas % CO₂ was monitored using a CO₂ analyzer (g). Oxygenated crystalloid cardioplegia (Ringer’s solution with CO₂, systemic vascular resistance (SVR), hematocrit (HCT), saturation of venous oxyhemoglobin (SvO₂), arterial and venous blood temperatures (TABLD, TVBLD), arterial bicarbonate levels (AHCO₃), arterial and venous partial pressures of oxygen and carbon dioxide (PaO₂, Pvo₂, PaCO₂, and Pvo₂), and oxygen transfer (VO₂).

Results

A theoretical (preliminary) and a clinical multiple linear regression analysis to predict the ventilation rate necessary to achieve alpha-stat using from one to eight variables was performed. The software selected BSA, TABLD, AHCO₃, PaCO₂, and Pvo₂ as the best subset of independent variables, and developed the following theoretical equation:

\[ \text{Gas Flow} = 1.60(\text{BSA}) + 0.235(\text{BLDQ}) + 0.0404(\text{HCT}) + 0.099(\text{TABLD}) - 0.133(\text{AHCO₃}) - 0.104(\text{PaCO₂}) + 0.059(\text{Pvo₂}) - 0.043(\text{FiO₂}) - 1.36 \]

The correlation coefficient \( r^2 \) is 0.78, \( p < 0.0001 \), standard error = 0.56. For the clinical equation, the possible predictor variables were reduced to age, WT, BSA, BLDQ, HCT, SvO₂, TABLD, and PaCO₂. The best subset of predictor variables contained WT, BLDQ, TABLD, and PaCO₂ in the following equation.

\[ \text{Gas Flow} = 0.022(\text{WT}) + 0.32(\text{BLDQ}) + 0.12(\text{TABLD}) - 0.077(\text{desired PaCO₂}) - 1.92. \quad r^2 = 0.71, \quad p < 0.0001, \quad \text{standard error} = 0.63 \]

A similar analysis of the FiO₂ data was performed. The theoretical FiO₂ equation showed that of the possible predictor variables listed in the methods, GF, TABLD, PaO₂, PaCO₂, age, and VO₂ were significant in the following equation:

\[ \% \text{FiO₂} = 3.79(\text{GF}) - 0.69(\text{TABLD}) + 0.107(\text{PaO₂}) + 1.01(\text{PaCO₂}) - 0.278(\text{AGE}) + 0.043(\text{VO₂}) + 35.6, \quad r^2 = 0.86, \quad p < 0.0001, \quad \text{standard error of 0.080} \]

The possible variables for the clinical FiO₂ predictor equation were reduced to WT, BSA, BLDQ, GF, SVR, HCT, SvO₂, TABLD, PaO₂, and age. The variables found to have the most significant relationship with FiO₂ were BLDQ, GF, SvO₂, TABLD, PaO₂, and age. An \( r^2 \) of 0.83, \( p < 0.0001 \) with a standard error of 0.087 was achieved with the following clinical equation:

<table>
<thead>
<tr>
<th>Table 1. Consenting patient population statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>Weight (Kg)</td>
</tr>
<tr>
<td>BSA (m²)</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
</tr>
<tr>
<td>CPB Hematocrit</td>
</tr>
<tr>
<td>Low Temp (°C)</td>
</tr>
</tbody>
</table>

b. Baxter Bentley, Irvine, CA 92714.
c. Pall Biomedical Products Corporation, Glen Cove, NY 11542.
d. C.R. Bard, Inc., Billerica, MA 01821.
e. Sarns Inc./3M, Ann Arbor, MI 48103.
f. Radiometer, Copenhagen, Denmark.
g. Puritan-Bennett Corp., Los Angeles, CA 90066.
h. Electromedics, Englewood, CO 80112.
i. BMDP Statistical Software, Inc., Los Angeles, CA 90025.
\( \% \text{FiO}_2 = 4.82(\text{BLDQ}) + 2.54(\text{GF}) - 0.237(\text{SvO}_2) + 1.07 \times (\text{desired PaO}_2) + 31.3 \).

Selected mean laboratory values with standard errors are shown in Table 2.

**TABLE 2: Selected Mean Laboratory Values and Standard Errors**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PPB</th>
<th>PLT</th>
<th>LDH</th>
<th>CeMB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre CPB</td>
<td>12.8 ± 1.0</td>
<td>227 ± 10.6</td>
<td>82.9 ± 7.0</td>
<td>1.42 ± 1.0</td>
</tr>
<tr>
<td>15 min on CPB</td>
<td>21.3 ± 1.5</td>
<td>135 ± 8.4</td>
<td>182.9 ± 17.1</td>
<td>19.5 ± 4.8</td>
</tr>
<tr>
<td>End CPB</td>
<td>46.3 ± 6.5</td>
<td>140 ± 9.0</td>
<td>144.0 ± 12.0</td>
<td>1.0 ± 1.6</td>
</tr>
<tr>
<td>24 hr post-op</td>
<td>19.0 ± 2.1</td>
<td>189 ± 12.8</td>
<td>182.9 ± 17.1</td>
<td>19.5 ± 4.8</td>
</tr>
<tr>
<td>72 hr post-op</td>
<td>19.0 ± 2.1</td>
<td>189 ± 12.8</td>
<td>182.9 ± 17.1</td>
<td>19.5 ± 4.8</td>
</tr>
</tbody>
</table>

The observed pressure drop across the oxygenator was 50-60 mmHg at a blood flow rate of 5 L/min. Heat exchanger performance was good with an overall mean performance factor of 0.55. At an arterial blood temperature of 37°C, the FiO\(_2\) was maintained at 0.6 - 0.8 (Figure 2) which kept the PaO\(_2\) between 100 and 300 for most patients (Figure 3). The gas to blood flow ratio was between 0.4 and 0.8 respectively for hypothermia and normothermia for most patients (Figure 4). Figure 5 shows close adherence to alpha-stat. As TABLD increased VO\(_2\) also increased, from between 50-150 ml/min at hypothermia to between 50-250 ml/min at normothermia (Figure 6) as did VCO\(_2\) (Figure 7). Discussion

**FIGURE 2:**

**SHILEY PLEXUS OXYGENATOR TRIALS**

FiO\(_2\) vs Art Bld Temp oC

**FIGURE 3:**

**SHILEY PLEXUS OXYGENATOR TRIALS**

PaO\(_2\) mmHg vs FiO\(_2\)

**FIGURE 4:**

**SHILEY PLEXUS OXYGENATOR TRIALS**

G:BQR vs Temp oC

**FIGURE 5:**

**SHILEY PLEXUS OXYGENATOR TRIALS**

PaCO\(_2\) mmHg vs Art Bld Temp oC

**FIGURE 6:**

**SHILEY PLEXUS OXYGENATOR TRIALS**

VO\(_2\) vs Art Bld Temp oC

Upon initiation of bypass, the FiO\(_2\) and ventilation rate are often approximated according to the perfusionist's own empiric

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knowledge of what may be required based on the patient's age, size and disease state. Subsequent adjustments are made using blood gas analysis. Mathematical models to predict oxygenator performance have been used successfully since 1981 (7). Regression equations to estimate ventilation rate and \( \text{FiO}_2 \) based on actual patient data describe the performance of the oxygenator and may permit tighter control of blood gas values.

The statistical software package used to analyze the data allows the input of all independent variables that may have an effect on the dependent variables \( \text{FiO}_2 \) and ventilation rate. The program then uses the Mallow's method (8) to select the independent variables that have a significant effect on the dependent variables. Subsets of variables were selected using Mallow's technique. This creates a theoretical equation. The programmer then eliminates from the theoretical equation those variables which may be inaccessible to the perfusionist while on bypass and repeats the analysis. If several independent variables are highly correlated with one another, some may be eliminated by the software in favor of one variable. The software adds and removes variables from the equation looking for the best variable subset. A variable is removed from the equation if its elimination does not significantly decrease the correlation. In this way a clinically useful equation is derived and simplified.

From the ventilation rate theoretical equation, the programmer eliminated bicarbonate level and \( \text{PvCO}_2 \) since these are not easily accessible while on bypass. Weight and BSA were very well correlated with each other, so BSA was eliminated as a variable since the correlation would not be significantly reduced by its removal. BSA and hematocrit correlated well with blood flow, so both were eliminated in favor of blood flow. TABLD and desired \( \text{PaCO}_2 \) were also significant predictor variables in the clinical equation. This clinical ventilation rate equation may be updated to take into account the fact that flows and temperatures change on bypass, whereas the estimated optimal ventilation rate assumes a constant respiratory quotient of 0.8 for every temperature and flow rate (6). More precise regulation of \( \text{PaCO}_2 \) should be possible using this equation for the Plexus oxygenator.

In the case of the \( \text{FiO}_2 \) equation, \( \text{VO}_2 \) and \( \text{PaCO}_2 \) were eliminated from the theoretical equation by the programmer. Age, weight, TABLD, \( \text{VO}_2 \), and BLDQ were highly correlated with each other; therefore, the program used blood flow as the best predictor variable and eliminated the others. Gas flow, \( \text{SvO}_2 \), and \( \text{PaO}_2 \) also remained in the clinical equation because of their significant contribution to the correlation.

Classical membrane oxygenator performance graphs teach that \( \text{VO}_2 \) and \( \text{CO}_2 \) transfer (\( \text{VCO}_2 \)) are independent of each other, in other words, that the required minimal \( \text{FiO}_2 \) is independent of the ventilation rate. But, although its effect is small, \( \text{VCO}_2 \) and especially \( \text{PaCO}_2 \) do affect the \( \text{FiO}_2 \) requirement, as can be seen in the Bohr effect on the oxyhemoglobin curve. The correlation of \( \text{PaCO}_2 \) on the required \( \text{FiO}_2 \) for this oxygenator is small but significant (p < 0.002). The theoretical \( \text{FiO}_2 \) equation shows that every mmHg increase in \( \text{PaCO}_2 \) at the same gas flow requires a one percent increase in \( \text{FiO}_2 \) to maintain oxygen transfer. However, the relationship between gas flow and \( \text{FiO}_2 \) are probably not causal; the two variables are highly correlated because they are both adjusted in the same direction during cooling and warming.

Design characteristics and laboratory values were also observed during this study. An \( \text{FiO}_2 \) of 0.8 is sufficient to support most patients at normothermia. Only slight changes in gas to blood flow ratio are required during warming. Oxygen and carbon dioxide transfer changes are predictable over a range of temperatures. Laboratory values were typical and compared favorably with those of other oxygenator studies (2). The design of this oxygenator is practical with the venous and arterial outlets at the bottom of the unit, causing blood to flow up over the heat exchanger and down through the center of the fiber bundle and allowing the oxygenator to act as a trap for gross air. The gas exchange characteristics and low prime volume of this oxygenator make it useful for a wide range of patient sizes.

References