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Validation of a Model for Flow-Dependent Carbon Dioxide Exchange in Artificial Lungs

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Abstract: The exchange rate of CO_2 in artificial lungs depends on the sweep gas flow rate. Control of the amount of CO_2 removed by an artificial lung requires quantitative knowledge of the flow dependence. A simple model of the dependence of CO_2 exchange on sweep gas flow rate in artificial lungs has been previously presented (1). For a given partial pressure of CO_2 in the blood phase, sweep gas flow rate, and CO_2 exchange rate, the model indicates how close the CO_2 exchange rate is to the maximum level attainable by the artificial lung. The focus of this study was to validate the model experimentally by testing 2 commercial artificial lungs in an in vitro test loop. The CO_2 exchange rate for each artificial lung was measured over a range of sweep gas flow rates. Linear regression was used to fit the data to the model and estimate the maximum possible CO_2 exchange rate and the average water-side P_{CO_2} ($\bar{P}_{CO_2}^{w}$). The difference between the measured and regressed values of $\bar{P}_{CO_2}^{w}$ was used as an indicator of the ability of the model to quantitatively predict the dependence of CO_2 exchange on gas flow rate. This difference was less than 5% for each experiment, indicating that the model can be used to guide control of CO_2 exchange rates in artificial lungs. **Key Words:** Cardiopulmonary bypass—Extracorporeal carbon dioxide removal—Extracorporeal membrane oxygenation.

In the natural lung, oxygen enters the bloodstream by diffusion from inspired air across the epithelium of the alveolar sacs and the endothelium of the pulmonary capillaries. Carbon dioxide diffuses in the opposite direction. Artificial lungs or oxygenators are devices that replicate these processes using synthetic polymer membranes to separate the patient's blood from a supply of pure oxygen (the sweep gas). The sweep gas, which may also contain anesthetic, flows through individual hollow fiber membranes and absorbs CO_2 diffusing from the blood. The exchange rate of CO_2 in artificial lungs depends directly on the flow rate of the sweep gas. Decreasing the sweep gas flow rate allows CO_2 to accumulate in the fiber lumens, raising the gas-side partial pressure of CO_2 (P_{CO_2}) and reducing the driving gradient for CO_2 exchange. During cardiopulmonary bypass and extracorporeal life support, reduction of the sweep gas flow rate is used to prevent hypocapnia and respiratory alkalosis (2). Arterial P_{CO_2} is controlled by adjusting the sweep gas flow rate, typically between 5 and 10 L/min (3), and adding up to 5% CO_2 to the sweep gas (2,4). Currently, the flow dependence of CO_2 exchange is understood only at a qualitative level. Quantitative knowledge of the flow dependence would allow better clinical control of CO_2 exchange and could lead to a feedback control system that would maintain a constant arterial P_{CO_2} by continuously adjusting the sweep gas flow rate.

A simple model of the dependence of CO_2 exchange on the sweep gas flow rate in artificial lungs has been previously presented (1). The model requires no knowledge of the device-specific mass transfer characteristics, nor does it require detailed mathematical modeling or computer simulation. For a given partial pressure of CO_2 in the blood phase, sweep gas flow rate, and CO_2 exchange rate, the model indicates how close the CO_2 exchange rate is to the maximum level attainable by the artificial lung. Essentially, the model shows that the ratio of

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the sweep gas flow rate to the CO_2 exchange rate determines the flow dependence of the CO_2 exchange. If the sweep gas flow rate is much greater than the CO_2 exchange rate, the CO_2 entering the fiber lumens is removed quickly enough to prevent elevation of the gas-side P_{CO_2}.

The model is independent of device-specific mass transfer characteristics by expressing the level of CO_2 exchange as a percentage of the maximum level obtainable by the artificial lung:

$$\frac{\dot{V}_{CO_2}}{\dot{V}_{CO_2}^{\max}} = 1 - \frac{P_O}{2\,\overline{P}_{co_2}^{\,b}} \frac{1}{Q_{gas}/\dot{V}_{CO_2}} \qquad (1)$$

where $\dot{V}_{CO_2}$ is the rate of CO_2 exchange; $\dot{V}_{CO_2}^{max}$ is the maximum rate of CO_2 exchange, that is, that for zero gas-side P_{CO_2}; P_o is the total gas pressure at the fiber bundle outlet; $\overline{P}_{CO_2}^{\,b}$ is the average blood-side CO_2 tension; and Q_{gas} is the sweep gas flow rate. The model predicts that the CO_2 exchange rate is within 85% of the maximum level if the sweep gas flow rate is greater than 50 times the exchange rate. For gas flow rates less than 40 times the exchange rate, CO_2 removal is highly flow-dependent, and CO_2 exchange is less than one half maximal if the gas flow rate is less than 20 times the exchange rate.

The focus of this study was to validate the model experimentally by testing 2 commercial blood oxygenators, the Optima (Cobe Cardiovascular, Inc., Lakewood, CO, U.S.A.) and the Maxima (Medtronic, Anaheim, CA, U.S.A.) in an in vitro test loop. Both oxygenators employ hollow fiber membranes for gas exchange. However, they differ in membrane surface area and blood flow path geometry and thus have different mass transfer characteristics. The CO_2 exchange rate for each artificial lung was measured over a range of sweep gas flow rates. As predicted by the model, experimental levels of CO_2 exchange were relatively insensitive to gas flow rate for flow rates greater than 50 times the nominal exchange rate. Linear regression was used to fit the data to the model and estimate the maximum possible CO_2 exchange rate and the average water-side P_{CO_2} ($\overline{P}_{CO_2}^{\,w}$). The difference between the measured and regressed values of $\overline{P}_{CO_2}^{\,w}$ was used as an indicator of the ability of the model to quantitatively predict the dependence of CO_2 exchange on the gas flow rate. This difference was less than 5% for each experiment. Thus, the data agree with the model in both the flow-dependent and flow-independent operating regions, regardless of device-specific mass transfer characteristics, and can be used to guide control of CO_2 exchange rates in artificial lungs.

METHODS

In vitro experiments

The CO_2 exchange rate over a range of gas flow rates was measured for 2 commercial blood oxygenators, the Cobe Optima and the Medtronic Maxima. Both oxygenators employ hollow fiber membranes for gas exchange. However, they differ in membrane surface area and blood flow path geometry and thus have different mass transfer characteristics. For example, at a blood flow rate of 3 L/min and a sweep gas flow rate of 3 L/min, the Optima achieves a CO_2 exchange rate of approximately 200 ml/min (Cobe Optima Instructions for Use, Cobe Cardiovascular, Inc.). Under the same conditions, the Maxima achieves a lower CO_2 exchange rate of approximately 175 ml/min (Medtronic Maxima Product Literature, Medtronic).

The test oxygenator was placed in a water-filled circulatory loop shown in Fig. 1. Because the model is independent of device-specific mass transfer characteristics, it can be validated in any test fluid. Hence, water was chosen for convenience and ease of experimentation. Water was driven through the loop by a centrifugal pump at a flow rate of either 4 or 6 L/min, and the water temperature was maintained at 37°C using a temperature bath connected to the reservoir.

Before reaching the test oxygenator, the water passed through a Shiley Plexus blood oxygenator (Irvine, CA) with a sweep gas mixture of CO_2 and N_2. This set the water-side P_{CO_2} ($P_{CO_2}^{\,w}$) at the inlet of the test oxygenator to approximately 90 mm Hg. The $P_{CO_2}^{\,w}$ at the outlet of the test oxygenator ranged from 15 mm Hg at the highest gas flow rates to 87 mm Hg at the lowest, causing the average $P_{CO_2}^{\,w}$ to vary from 50 to 86 mm Hg. Typically, the overall average $P_{CO_2}^{\,w}$ for a given experiment was between 60 and 70 mm Hg. Large changes in $P_{CO_2}^{\,w}$ from the inlet to the outlet of the oxygenator occurred because the pH was between 5.5 and 6, caus-

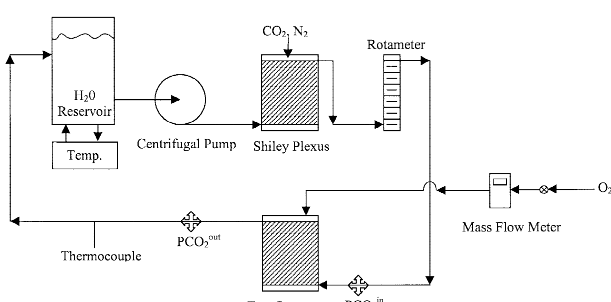

FIG. 1. The schematic drawing shows the in vitro circulatory loop used to test the flow-dependent CO_2 exchange of the Optima and Maxima commercial artificial lungs.

ing 56–80% of the total CO_2 content to be carried in the dissolved state. During in vivo use (pH = 7.4), only about 5% of the CO_2 content is carried in the dissolved state, and the bulk of the remainder exists as bicarbonate (6). Thus, when CO_2 is removed from blood at normal pH, the PCO_2^b changes only slightly. The inlet and average PCO_2^w levels used in these experiments, though higher than physiological, were necessary to keep the outlet PCO_2^w large enough to be accurately measured. Water-side PCO_2 was measured before and after the test oxygenator using an ABL 330 blood gas analyzer (Radiometer America, Westlake, OH, U.S.A.).

Pure oxygen was driven through the sweep gas pathway of the test oxygenator at flow rates measured using a Top Trak mass flow meter (Sierra Instruments, Inc., Monterey, CA, U.S.A.). The oxygen flow rate was randomly varied from 0 to 10 L/min^{RTP}, and the CO_2 exchange rate was measured at each gas flow rate.

Data analysis

The rate of CO_2 exchange was calculated assuming that it was fully accounted for by the change in concentration of dissolved CO_2 from the inlet to the outlet of the test oxygenator:

$$\dot{V}CO_2 = S \cdot Q \cdot (PCO_2^{\text{in}} - PCO_2^{\text{out}}) \qquad (2)$$

where $\dot{V}CO_2$ is the rate of CO_2 exchange; PCO_2^{in} and PCO_2^{out} are the inlet and outlet partial pressures of CO_2; Q is the water flow rate; and S is the solubility of CO_2 in water at 37°C (7.57 e-3 ml^{STP}/cm^3/mm Hg) (5). Changes in bicarbonate concentration were assumed negligible because the dehydration reaction by which bicarbonate is converted to dissolved CO_2 and water proceeds very slowly in the absence of carbonic anhydrase (6) (the presence of carbonic anhydrase accelerates this reaction 13,000 times). Additionally, at the operating pH of 5.5 to 6, most of the total CO_2 content was carried in the dissolved state.

As discussed earlier, the inlet PCO_2 was held constant throughout each experiment. Variation of the $\dot{V}CO_2$ with gas flow rate caused variation of the outlet PCO_2 and average PCO_2. The model is used most easily if the average water-side PCO_2 is constant. To allow the data to be fit to the model, the $\dot{V}CO_2$ at each gas flow rate was normalized by the ratio of the average PCO_2 for the entire experiment ($\bar{P}CO_2^w$) to the average PCO_2 at the current gas flow rate ($\bar{P}CO_2^{w,current}$):

$$\dot{V}CO_2^{\text{norm}} = \dot{V}CO_2 \cdot \frac{\bar{P}CO_2^{\text{w}}}{PCO_2^{\text{w,current}}} \qquad (3)$$

The normalized $\dot{V}CO_2$ at each gas flow rate is the $\dot{V}CO_2$ at that flow rate that would have been measured had the average PCO_2 been equal to $\bar{P}CO_2^w$. This allows the entire data set from 1 experiment to be analyzed as if the average PCO_2 had been constant at $\bar{P}CO_2^w$.

According to the model, the CO_2 exchange rate ($\dot{V}CO_2$) should be linearly proportional to the ratio of the CO_2 exchange rate to the sweep gas flow rate ($\dot{V}CO_2/Q_{gas}$), with y-intercept equal to the maximum CO_2 exchange rate attainable by the oxygenator ($\dot{V}CO_2^{max}$) and slope equal to $\dot{V}CO_2^{max} \cdot (P_O - P_{H20,vap})/(2 \cdot \bar{P}CO_2^w)$ (Eq. 1). To account for the transfer of water vapor into the sweep gas pathway, the model has been modified by replacing P_O with ($P_O - P_{H20,vap}$), where $P_{H20,vap}$ is the vapor pressure of water at 37°C (47 mm Hg) (5). The data from each experiment were plotted in this manner, and linear regression was performed to determine $\dot{V}CO_2^{max}$ and $\bar{P}CO_2^w$. The difference between the measured and regressed values of $\bar{P}CO_2^w$ was used as an indicator of the ability of the model to quantitatively predict the dependence of CO_2 exchange on gas flow rate.

RESULTS AND DISCUSSION

The dependence of CO_2 exchange on the sweep gas flow rate for the Optima at a water flow rate of 4 L/min is shown in Fig. 2. The figure shows both the measured $\dot{V}CO_2$ and the normalized $\dot{V}CO_2$ over the range of sweep gas flow rates used. As expected,

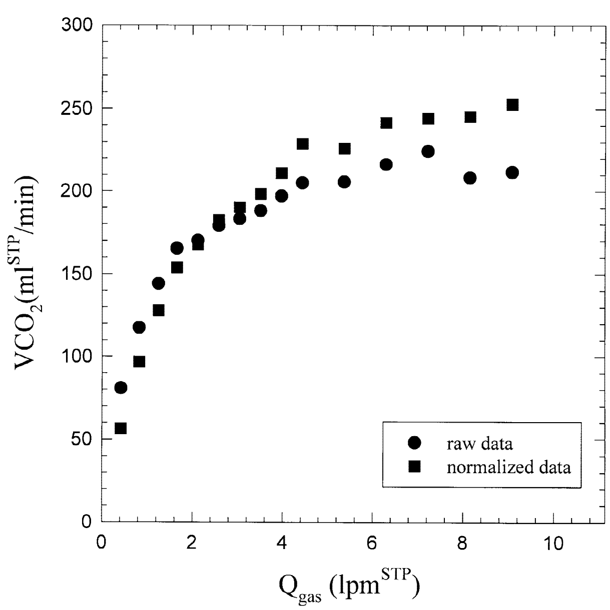

FIG. 2. The CO_2 exchange rate as a function of the gas flow rate for the Optima at a water-side flow rate of 4 L/min is shown.

CO_2 exchange is highly dependent on the sweep gas flow rate at low gas flow rates, but becomes relatively constant once the gas flow rate is sufficiently high. Increasing the gas flow rate from 1 to 4 L/min-^{STP} raises the normalized $\dot{V}CO_2$ from approximately 55 ml^{STP}/min to approximately 210 ml^{STP}/min, whereas increasing the gas flow rate further from 4 to 9.3 L/min^{STP} only raises the normalized $\dot{V}CO_2$ to 250 ml^{STP}/min. Normalization decreases the $\dot{V}CO_2$ at low gas flow rates and raises it at high gas flow rates because $\overline{P}CO_2^{w,current}$ is greater than the average water-side PCO_2 over the entire experiment ($\overline{P}CO_2^{w}$) at low gas flow rates and less than $\overline{P}CO_2^{w}$ at high gas flow rates.

The Optima and the Maxima were tested at water-side flow rates of 4 and 6 L/min, respectively. Figure 3a and b shows the Optima and Maxima experimental data expressed as the ratio of the normalized $\dot{V}CO_2$ to $\dot{V}CO_2^{max}$ (determined by linear regression) as a function of $Q_{gas}/\dot{V}CO_2$. Also shown is the dependence of $\dot{V}CO_2/\dot{V}CO_2^{max}$ on $Q_{gas}/\dot{V}CO_2$ predicted by the model at the measured average PCO_2 ($\overline{P}CO_2^{w,meas}$) and the regressed average PCO_2 ($\overline{P}CO_2^{w,reg}$). The measured values of $\overline{P}CO_2^{w}$ were 60.2 mm Hg for the Optima experiment and 69.5 mm Hg for the Maxima experiment. Linear regression of the normalized data yielded regressed values of $\overline{P}CO_2^{w}$ of 62.8 mm Hg and 67.3 mm Hg and regressed values of $\dot{V}CO_2^{max}$ of 304.9 ml^{STP}/min and 440.2 ml^{STP}/min for the Optima and Maxima, respectively. Each regression had an r^2 of 0.99. The percent differences between the measured and regressed values of $\overline{P}CO_2^{w}$ were 4.3% and 3.2% for the Optima and Maxima, respectively. Thus, the model was successful in predicting the measured values of $\overline{P}CO_2^{w}$ from 2 data sets, collected using different test oxygenators at different water flow rates, to within 5%. Its performance appeared to be unhindered by the large changes in PCO_2^{w} that occurred across the oxygenators. We expect that the model would perform at least as well if the experiments were performed in blood because the PCO_2^{b} would remain relatively constant throughout the experiment.

The utility of the model is two-fold. First, the ability of the model to predict the onset of flow-independent CO_2 exchange allows it to be used to determine the minimum sweep gas flow rate at which a given oxygenator should be operated if the goal is to provide the maximum possible rate of CO_2 exchange. Hence, oxygenators intended to support the entire adult resting CO_2 removal rate (200 ml^{STP}/min) (2) should be operated at a minimum sweep gas flow rate of 10 L/min to insure performance within 86% of maximal, assuming that 200 ml^{STP}/min is near the maximum level of CO_2 exchange that the oxygenator can achieve.

Second, the ability of the model to predict CO_2 exchange in the flow-dependent operating region, as shown by the closeness of the regressed and measured values of $\overline{P}CO_2^{w}$, indicates that it can also be used to guide quantitative control of CO_2 exchange in artificial lungs by manipulation of the sweep gas flow rate. Most commercial blood oxygenators can achieve removal rates of at least 200 ml^{STP}/min. The Optima displays a CO_2 removal rate of 350 ml^{STP}/min at a blood flow rate of 5 L/min and a gas flow rate of 10 L/min (Cobe Optima Instructions for Use, Cobe Cardiovascular, Inc.). As noted earlier, reduction of the sweep gas flow rate is a strategy used clinically during cardiopulmonary bypass to prevent hypocapnia. The model could be used to provide a quantitative estimate of the appropriate sweep gas flow rate. For example, when providing 200 ml^{STP}/min of CO_2 exchange, at a blood flow rate of 5 L/min, the Optima is operating at 57% of its maximum CO_2 exchange rate. Assuming an average

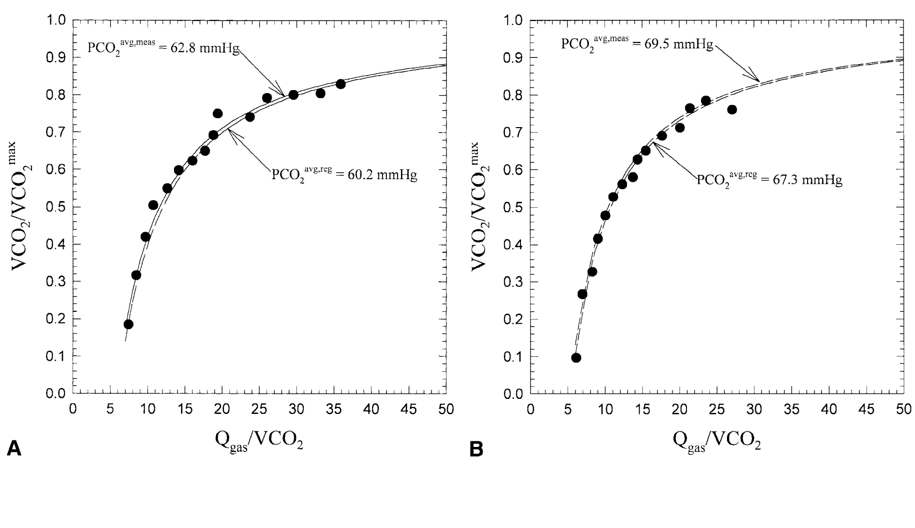

FIG. 3. The CO_2 exchange rate expressed as the percentage of the maximum rate for **(A)** the Optima at Q_{water} = 4 L/min and **(B)** the Maxima at Q_{water} = 6 L/min is shown. Also shown is the variation of $\dot{V}CO_2$ predicted by the model for the regressed and measured values of $\overline{P}CO_2^{w}$.

blood-side P_{CO_2} of 40 mm Hg, the model predicts a sweep gas flow rate of 3.8 L/min^{STP}. The perfusionist could use this value rather than reducing the gas flow rate by trial and error.

Additionally, the model could be implemented within a feedback control system that would continually adjust the gas flow rate to maintain a desired arterial P_{CO_2}.

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