Ex Vivo Testing of the Intravenous Membrane Oxygenator

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***Intravenous oxygenation represents a potential respiratory support* modality for patients with acute respiratory failure or with acute exacerbations of chronic respiratory conditions. Our group has been developing an intravenous oxygenator, the IMO, which uses a constrained fiber bundle and a rapidly pulsating balloon within the fiber bundle. Balloon pulsation drives blood flow past the fibers at greater relative velocities than would otherwise exist within the host vessel, and gas exchange rates are enhanced. The purpose of this study was twofold: (1) to characterize the gas exchange performance of the current IMO in an extracorporeal mock vena cava vessel under conditions of known fixed vessel geometry and controlled blood flow rates; and (2) to compare the IMO gas exchange performance to that reported for the clinically tested IVOX device within a comparable *ex vivo* set-up. The *ex vivo* flow loop consisted of a 1 inch ID tube as a mock vena cava that was perfused directly from an anesthetized calf at blood flow rates ranging from 1 to 4½ L/min. O_2 and CO_2 exchange rates were measured for balloon pulsation rates, which ranged from 0 to 180 bpm. Balloon pulsation significantly increased gas exchange, by 200–300% at the lowest blood flow rate and 50–100% at the highest blood flow rate. Balloon pulsation eliminated much if not all of the dependence of the gas exchange rate on blood flow rate as seen in passive oxygenators. This suggests that in clinical application the IMO may exhibit less gas transfer variability due to differences in cardiac output. Over the entire flow rate range studied, the CO_2 and O_2 gas exchange rates of the IMO at maximal balloon pulsation varied from approximately 250 to 350 ml/min/m^2. At maximum balloon pulsation the IMO exchanged CO_2 and O_2 at rates from 50–500% greater, depending upon the blood flow rate, than the exchange rates reported for the IVOX device in *ex vivo* tests. *ASAIO Journal* 2000; 46:261–267.**

Despite clear improvements in respiratory support therapies, acute respiratory distress syndrome (ARDS) remains a major cause of morbidity and mortality in severely ill patients.[1] ARDS pathology involves a rapidly progressive deterioration in the gas exchange function of the lung, which results from increased fluid accumulation in interstitial and alveolar spaces, secondary to an increased pulmonary endothelial and epithelial permeability.[2] The ARDS associated fatality rate in the United States remains near 50% of the 150,000 cases each year,[3] despite the use of supportive strategies such as mechanical ventilation and extracorporeal membrane oxygenation (ECMO). A potentially attractive new support measure for ARDS and other acute respiratory failures, including acute exacerbations of chronic lung failure, is intravenous oxygenation.[4–6] The underlying idea is to supplement basal O_2 supply and CO_2 removal by using a bundle of hollow fiber membranes placed directly within the vena cava by insertion through the femoral vein. Gas supply and removal lines run outside the body and provide a sweep gas flow of 100% O_2 through the fibers. Thus, O_2 diffuses into, and CO_2 diffuses out of, blood before blood flows to the natural lungs. Even in acute respiratory failure the lungs maintain some gas transfer capability[2]; therefore, intravenous oxygenation acts principally as lung assist rather than lung replacement therapy.

Our group has been actively developing an intravenous oxygenator, the IMO (*I*ntravenous *M*embrane *O*xygenator), for respiratory support of the failing lung.[4,7,8] The current IMO device uses a constrained fiber bundle made by wrapping hollow fiber fabric around a concentrically located polyurethane balloon. The constrained fiber bundle is intentionally smaller than vessel lumen size, which allows for shunt flow of blood past the device to reduce flow resistance.[8] Rapidly pulsating the central balloon with helium gas augments gas transfer by converting the shunt flow into cross-flow of blood directly past the fiber membranes. This balloon generated convection creates greater relative blood flow velocities past the fibers than would otherwise exist and, when combined with the efficiencies of gas transfer in cross-flow, produces improved levels of gas exchange. Current development efforts on the IMO are targeting O_2 and CO_2 gas exchange levels *in situ* of 240–260 ml/min/m^2 fiber membrane, so that a 0.5 m^2 device could provide approximately 50% of the basal metabolic requirements for O_2 supply and CO_2 removal in an average sized adult. The IVOX device, the only intravenous oxygenator to undergo human clinical trials, accomplished gas exchange rates up to 25–30% of metabolic requirements in ARDS patients,[9] and demonstrated that many of the hurdles surrounding intravenous respiratory support are surmountable. Nevertheless, clinical studies of the IVOX indicated that increased gas exchange capacity may be key to clinically effective intravenous respiratory support. Our gas exchange target for the IMO translates into intravenous oxygenators with approximately twice the gas exchange capacity of the clinically

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Submitted for consideration June 1999; accepted for publication in revised form October 1999.

This work was supported by the U.S. Army Medical Research, Development, Acquisition, and Logistics command under prior Contract No. DAMD17-94-C-4,052 and current Grant No. DAMD17-98-1-8,638. The views, opinions, and/or findings contained in this report are those of the authors and should not be construed as an official Department of the Army position, policy, or decision unless so designated by other documentation. The generous support of the McGowan Foundation and the McGowan Center for Artificial Organ Development is also appreciated.

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tested IVOX device, while maintaining comparable membrane area and insertion size.

Recent improvements in the IMO design have resulted in oxygenator prototypes with gas exchange levels at or above our current design target.[5] These assessments have largely been based on laboratory bench testing in simplified water perfusion systems, and analyses by which exchange in blood can be estimated from that in water.[10] The purpose of this study was to assess the gas exchange performance of the IMO in blood flowing through an extracorporeal (*ex vivo*) bypass circuit containing a 'mock' vena cava (MVC) vessel. The MVC approximates the lumenal size of the adult human vena cava. *Ex vivo* testing of the IMO allows us to evaluate gas exchange characteristics within a known fixed vessel geometry, using set and controllable blood flow rates, and with physico-chemically normal blood. More importantly, our *ex vivo* MVC circuit and test protocols are comparable to those reported in past extracorporeal studies of the clinically tested IVOX device.[11, 12] Thus, direct comparisons can be made between the gas exchange capabilities of the IMO in blood with that of the clinically tested IVOX under known, controlled, and comparable conditions of geometry and flow.

Methods

Two IMO prototype devices were evaluated in separate tests using an extracorporeal bypass circuit perfused from calves (93 and 98 kg). Each calf was premedicated with atropine, 45 mg, followed by induction of anesthesia with Brevital, 10 mg/kg. Following intubation, the animal was placed on a volume-controlled ventilator (Penlon AM1000, Abingdon, UK) and ventilated with a 1:1 mixture of low-flow oxygen and room air mixed with isoflurane (1–2.5%). The animal was then placed in right lateral decubitus position, and the neck and thorax were shaved, prepared with Betadine and alcohol, and draped. The left cervical region was incised to expose the jugular and carotid vessels. A 14-gauge arterial catheter was placed in the left carotid artery and connected to a fluid filled pressure transducer (Baxter Health Care Corp, Irvine, CA). A pressure and electrocardiograph monitor (Hewlett Packard, Andover, MA) was used to monitor arterial pressure and electrocardiogram (ECG). Blood gas tensions were measured with a gas analyzer (505 ABL Radiometer, Copenhagen, Denmark) and hemoglobin content and O_2 saturation measured with a co-oximeter (482 Instrumentation Laboratory, Lexington, MA). Anticoagulation was monitored by measurement of activated clotting times (ACT; Hemachron Jr., International Teledyne Corp, Edison, NJ). Body temperature was maintained at 37–38° C by the use of a heating pad.

A left thoracotomy was performed in the fifth intercostal space, and after heparinization (3.0 mg/kg), the pulmonary artery was cannulated with a venous cannula (24F, DLP, Grand Rapids, MI). A constant drip of heparin (nominally 0.5 mg/kg/hour) was administered directly into the extracorporeal circuit so that ACT remained at or above 500 seconds. A venous cannula (34F, Research Medical, Inc., Midvale, UT) was then placed in the jugular vein, advanced to the right atrium, and secured with ligatures. The extracorporeal circuit (described later in this article) was primed with approximately 2 L of lactated Ringer's solution, and the cannulas were connected so that inflow came from the jugular cannula, and outflow went to the pulmonary artery cannula. In one animal the inflow cannula was located in the inferior vena cava, with the outflow cannula in the right atrium. With cannulae connected to the circuit, blood flow through the circuit was started, and the IMO devices were evaluated as described later in this article. At the end of the protocol the animals were deeply sedated and euthanized with an injection of potassium chloride. All procedures involving animals were conducted in compliance with state and federal laws, standards of the Department of Health and Human Services, and approved protocols established by the Institutional Animal Care and Use Committee.

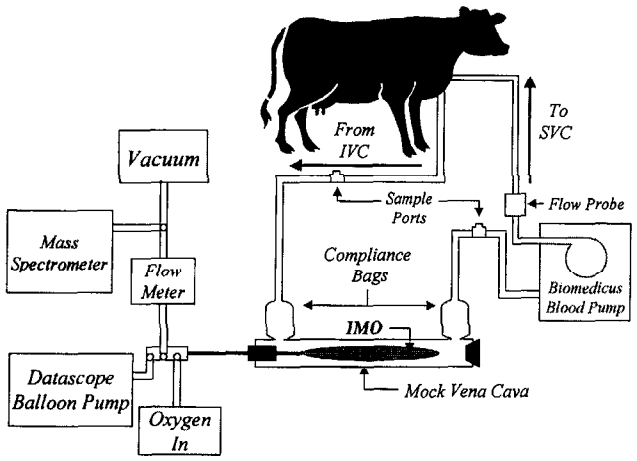

Figure 1. Schematic of the extracorporeal mock vena cava (MVC) test circuit.

The extracorporeal test circuit consisted of a mock vena cava test section (1 inch ID siliconized Tygon tubing, Cole Palmer, Vernon Hills, IL), 500 ml compliance bags on each end of the section (Neoprene breathing bags, Qosina, Edgewood, NY), and a Biomedicus blood pump (Medtronics Inc., Minneapolis, MN) **(Figure 1)**. Sampling ports were located on both the inflow line to the test section (½ inch ID Tygon tubing) and the outflow line back to the animal (3/8 inch ID Tygon tubing). Temperature was measured immediately before and after the compliance bags using separate thermistor style thermometers (Digi-Sense, Cole Palmer, Chicago, IL). The blood flow rate through the circuit was measured using an ultrasonic flowmeter and clamp-on flow probe (Transonic Systems Inc., Ithaca, NY) located on the outflow line after the pump. Before priming the circuit, the IMO prototype under test was placed in the center of the mock vena cava test section. The gas inflow port on the IMO was connected to a pure O_2 source, and the gas outflow port was connected to a vacuum to drive 100% O_2 sweep gas through the IMO at 3 L/min at subatmospheric pressure levels. The gas flow rate out of the IMO was measured with a gas mass flowmeter (Sierra Instruments, Monterey, CA) and the outflow gas composition (%O_2, %CO_2, %N_2) measured with a mass spectrometer (MGA 1,100, Marquette Medical Systems, Jupiter, FL). The balloon port on the IMO was connected to a helium intra-aortic balloon pump console (Datascope System 90, Fairfield, NJ).

After a 30- to 45-minute stabilization period at 2 L/min blood flow through the test section and 60 beats per minute (bpm) balloon pulsation, the gas transfer evaluation protocol

Table 1. Characteristics of IMO Devices Used in the *Ex Vivo* Studies

	IMO-S2	IMO-10	IVOX-7
Fiber type	Celgard 240 array (35fpi)	Celgard 240 array (35fpi)	KPF 190
No. fibers	980	750	589
Bundle length (cm)	25	30	30
Manifold size (mm)	12.7	11.0	7.0
Insertional size (mm)	14.2	12.5	12.6
Shaft diameter (mm)	7.6	5.0	5.4
Surface area (m^2)	0.23	0.21	0.21
Balloon size (ml)	34	41	
Bench $\dot{V}O_2$ (ml/min/m^2)	121 ± 1.8	119 ± 1.1	

IMO, intravenous membrane oxygenator.

began. Blood flow through the test section was varied from 1, 2, 3, to 4.5 L/min. At each blood flow, IMO balloon pulsation was varied from 0, 60, 120, 150, to 180 bpm. At each test condition of blood flow rate and balloon pulsation rate, blood samples were taken from the inflow and outflow sampling ports (2 sets about 10 minutes apart) for determination of respective inflow and outflow pO_2, pCO_2, pH, total hemoglobin (Hb), and % hemoglobin saturation (SO_2). With each set of blood-side samples, the gas flow rate and composition leaving the IMO was measured. The CO_2 exchange rate, $\dot{V}CO_2$, of the IMO was determined based on gas-side measurements using

$$\dot{V}CO_2 = Q_{gas}FCO_2^{out} \quad (1)$$

where Q_{gas} is the gas flow rate leaving the IMO, and FCO_2^{out} is the CO_2 fraction measured in the exiting gas. The O_2 exchange rate, VO_2, of the IMO was determined based on blood-side measurements using

$$\dot{V}O_2 = Q_{blood}[1.34C_{Hb}(SO_2^{out} - SO_2^{in}) + .003(pO_2^{out} - pO_2^{in})] \quad (2)$$

where Q_{blood} is the blood flow through the test section, SO_2 and pO_2 are the oxyhemoglobin saturation and O_2 tensions measured at the outlet (out) or inlet (in) as indicated, C_{Hb} is Hb concentration, and the O_2 capacity of Hb and physical solubility are 1.34 ml O_2/g Hb and .003 ml O_2/cm3/mm Hg, respectively.

Gas exchange evaluations were performed on two different IMO prototypes, an IMO-S2 series device and an IMO-10 series device. **Table 1** lists some of the important dimensions and features of these IMO devices, and compares select features to those of the clinically tested IVOX-7 device.[11] The IMO S2 and 10 devices have equivalent O_2 exchange capacities, as determined in our standard laboratory characterization test for gas exchange in water.[8]

Results

Values for the inlet CO_2 and O_2 gas tensions, hematocrit, total hemoglobin, and plasma free hemoglobin during the *ex vivo* tests are summarized in **Table 2**. Mean values for inlet pCO_2 and pO_2 were 46 ± 7.8 mm Hg and 17.9 ± 4.1 mm Hg, respectively, for the IMO-S2 test as compared to 53.8 ± 2.5 mm Hg and 23.7 ± 2.9 mm Hg, respectively for the IMO-10 test. The lower average pCO_2 in the IMO-S2 test can be attributed primarily to a period of 1½ hours when inlet pCO_2 dropped below 40 mm Hg despite appropriate ventilatory adjustments. The change in hematocrit shown in **Table 2** for both experiments reflects dilution from the Ringer's prime in the extracorporeal circuit. The hematocrit for the IMO-10 test stabilized by 100 minutes, whereas the calf in the IMO-S2 test required continued crystalloid infusion for blood loss, and hematocrit decreased further, reaching 18% by the end of the experiment. Total Hb varied from 10.2 to 7.0 g/dl and 11.7 to 8.5 g/dl during the IMO-S2 and IMO-10 tests, respectively. Plasma free hemoglobin reached levels of 21.4 and 11.8 mg/dl at the end of the IMO-S2 and IMO-10 tests, respectively.

The CO_2 and O_2 exchange rates measured for both IMO devices at a blood flow of 2 L/min through the mock vena cava are shown in **Figure 2**. For comparison purposes, all exchange rates are normalized to membrane surface area (*i.e.*, ml/min/m^2). The CO_2 exchange rate increased significantly with balloon pulsation rate for both IMO devices, as shown in **Figure 2A**. Peak CO_2 exchange rates were 340 and 311 ml/min/m^2 for IMO-S2 and IMO-10, respectively, which represent exchange

Table 2. Inlet Blood Gases, Hematocrits, and Hemoglobin Values

	IMO-S2 Test	IMO-10 Test
Inlet PCO_2 (range)	46 ± 7.8 mm Hg (34–62)	53.8 ± 2.5 mm Hg (49–64)
Inlet PO_2 (range)	17.9 ± 4.1 mm Hg (10–28)	23.7 ± 2.9 mm Hg (16–28)
Hematocrit (pre/post)[a]	34%/18%	33%/24%
Total Hb content	7.8 ± 1.1g/dl	9.1 ± 1.0 g/dl
Plasma free Hb (end)[b]	21.4 mg/dl	11.8 mg/dl

[a] 'Pre' value reflects hematocrit before connecting extracorporeal circuit; 'post' value reflects hematocrit at the end of the experiment.
[b] Reflects maximum plasma free hemoglobin at the end of the experiment.
IMO, intravenous membrane oxygenator.

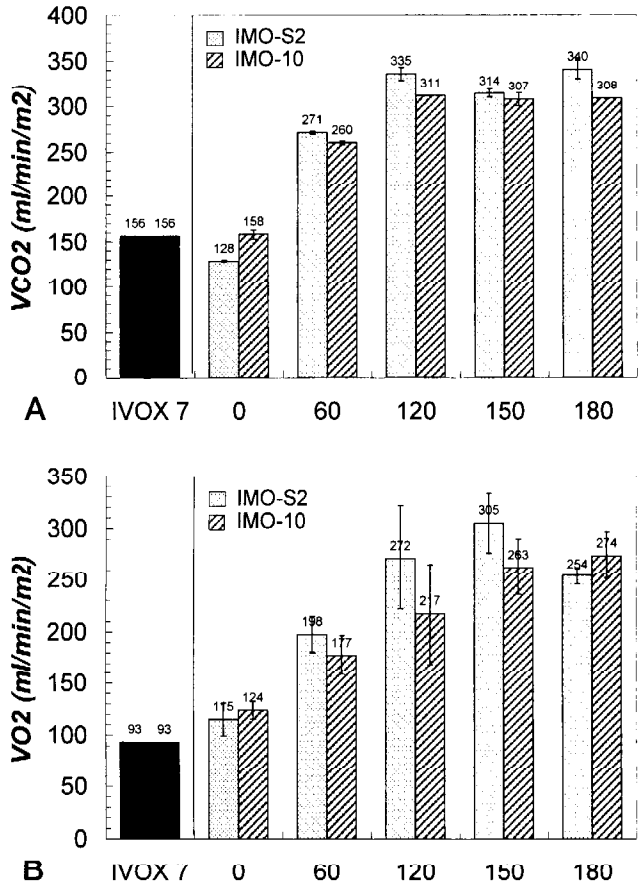

Figure 2. Effect of balloon pulsation rate on CO_2 exchange rate (A) and O_2 exchange rate (B) at 2 L/min blood flow through the MVC. All exchange rates are normalized to fiber surface area.

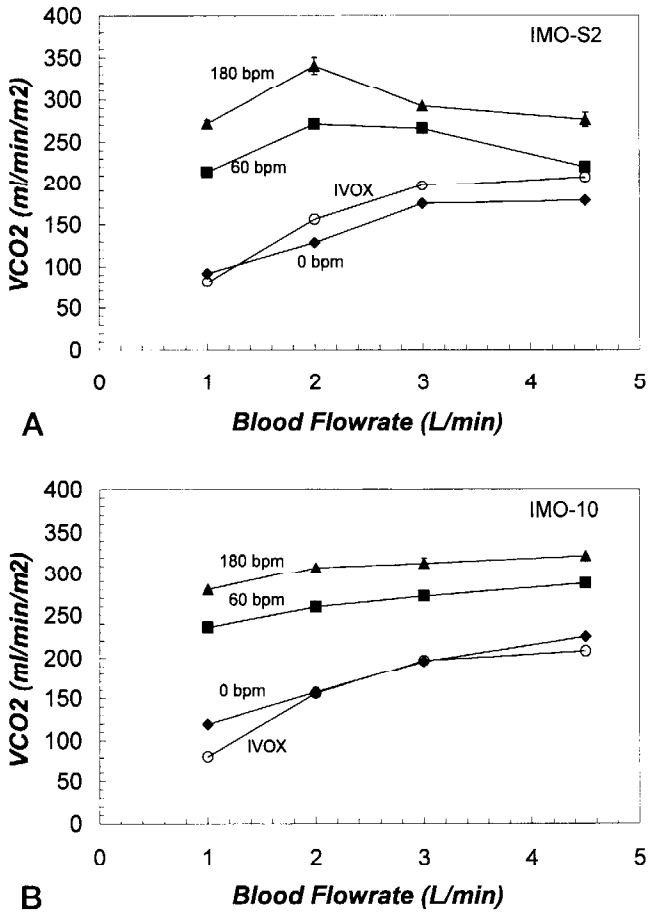

Figure 3. Effect of blood flow rate on CO_2 exchange rate at 0 (♦), 60 (■), and 180 (▲) beats per minute pulsation. CO_2 exchange rate is normalized to fiber surface area. (A) IMO-S2 test. (B) IMO-10 test.

rates 2.6 and 2.0-fold greater than the respective CO_2 exchange rates with no balloon pulsation (*i.e.*, 0 bpm). As shown in **Figure 2B**, the O_2 exchange rate also increased significantly with balloon pulsation rate at this same blood flow rate. Peak O_2 exchange rates were 305 ± 28 and 274 ± 23 ml/min/m^2 for IMO-S2 and IMO-10, respectively, which represent exchange rates 2.7 and 2.0-fold greater than the respective O_2 exchange rates with no balloon pulsation.

The variation in CO_2 exchange with blood flow rate for both IMO devices is shown in **Figure 3** for balloon pulsation rates of 0 bpm (no pulsation), 60 bpm (moderate pulsation), and 180 bpm (high pulsation). For both IMO devices, the most significant variation in CO_2 exchange rate with blood flow rate occurs in the absence of balloon pulsation. As blood flow increased from 1 to 4.5 L/min, the CO_2 exchange rate at 0 bpm rose 93%, from 92 to 178 ml/min/m^2 for IMO-S2 (**Figure 3A**), while that for IMO-10 (**Figure 3B**) rose 89% from 119 to 225 ml/min/m^2. Moderate and high balloon pulsation appeared to reduce or eliminate much of the dependence of CO_2 exchange rate on blood flow rate, as best seen in the results for IMO-10 (**Figure 3B**). At 60 bpm, CO_2 exchange rose 22%, from 236 to 288 ml/min/m^2 as blood flow rate increased from 1 to 4.5 L/min, whereas at 180 bpm, CO_2 exchange rose only 15%, from 280 to 322 ml/min/m^2 over the same blood flow range. These changes in CO_2 exchange are markedly less than the 89% change in CO_2 exchange rate seen over the same blood flow range with no pulsation. **Figure 3A** indicates that the CO_2 exchange rate for IMO-S2 at 60 and 180 bpm actually decreased as blood flow increased in the range from 3 to 4.5 L/min. This reduction can be attributed to changes in the inlet pCO_2, which began to decrease during the time period when the 3 and 4.5 L/min blood flow rates were being studied (see Discussion).

The variation in O_2 exchange with blood flow for both IMO devices is shown in **Figure 4** for the same pulsation rates explored for CO_2 exchange (see **Figure 3**). As was the case for CO_2 exchange, the absence of balloon pulsation produced the greatest variation in O_2 exchange rate with blood flow rate. Balloon pulsation at moderate (60 bpm) and high (180 bpm) rates appeared to eliminate much, if not all, of the variation of O_2 exchange with blood flow rate. At 180 bpm for example, O_2 exchange was 270 ± 9.4 and 250 ± 8.9 ml/min/m^2 at 1 and 4.5 L/min blood flow, respectively, for IMO-S2, whereas at the same pulsation rate for IMO-10, O_2 exchange was 263 ± 9.9 and 310 ± 8.3 ml/min/m^2, respectively, at the blood flow rates of 1 and 4.5 L/min.

Discussion

Our group has been actively developing an intravenous membrane oxygenator (the IMO) for acute respiratory support

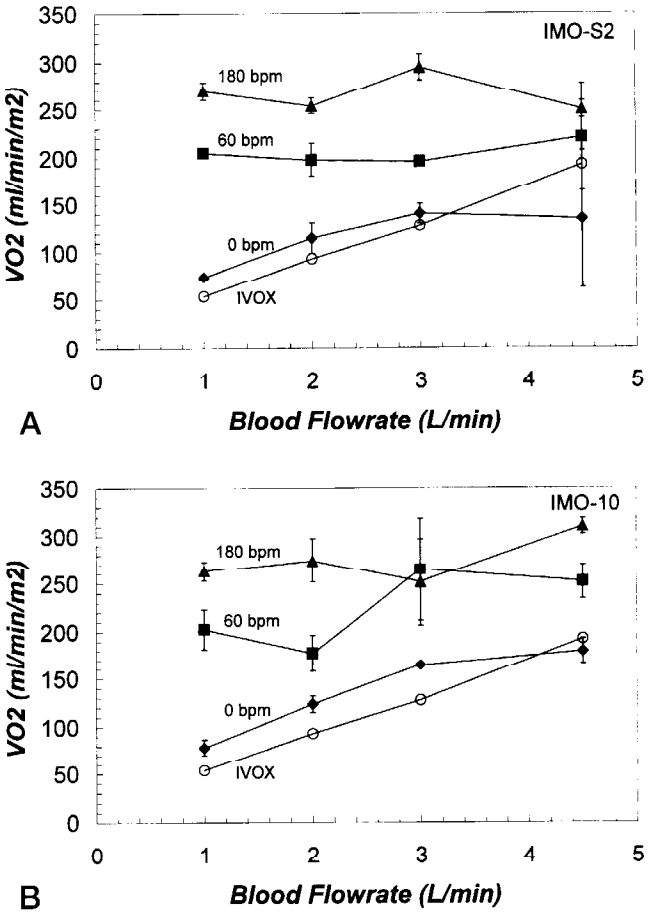

Figure 4. Effect of blood flow rate on O_2 exchange rate at 0 (♦), 60 (■), and 180 (▲) beats per minute pulsation. O_2 exchange rate normalized to fiber surface area. (A) IMO-S2 test. (B) IMO-10 test.

of the failing lung. Unlike the clinically tested IVOX device,[5,9] which is a passive intravascular oxygenator, the IMO includes a pulsating balloon for actively enhancing gas exchange with blood. In this study, we evaluated the gas exchange performance of current IMO prototypes within a mock vena cava (MVC) vessel perfused with calf blood in an extracorporeal circuit. The *ex vivo* MVC tests allow us to characterize IMO gas exchange performance within a known fixed vessel geometry, using set controllable blood flow rates, and physicochemically normal blood. Moreover, as discussed later, the *ex vivo* tests allow comparison between the performance of our intravascular oxygenator and that of the clinically tested IVOX device, which was evaluated in a comparable extracorporeal circuit by Tao *et al.*[11]

Balloon pulsation significantly improves the CO_2 and O_2 exchange rates of the IMO, with maximum exchange rates in the prototypes tested, which had 34- and 41-ml balloons, occurring at 150 to 180 bpm. Above these frequencies, pneumatic resistance in the internal catheter supplying helium to the balloon limits complete filling and emptying of the balloon. As a result, gas exchange diminishes. Over the entire flow rate range studied, the CO_2 and O_2 gas exchange rates of the IMO at maximal balloon pulsation varied, from approximately 250 to 350 ml/min/m^2. The augmentation of gas exchange by balloon pulsation was greatest at the lowest blood flow of 1 L/min, with a maximum enhancement of 200–300% (compared to exchange rates with no pulsation) for both O_2 and CO_2 exchange. At the highest blood flow of 4.5 L/min, augmentation of O_2 and CO_2 exchange rate varied from 50–100%. The dependence of augmentation upon blood flow rate resulted in maximum O_2 and CO_2 gas exchange rates that were *nearly independent* of blood flow through the MVC (see **Figures 3** and **4**, 180 bpm). In contrast, the gas exchange rate of a passive oxygenator, like the IMO with no pulsation or the IVOX, shows an appreciable dependence of gas exchange rate on blood flow rate past the device.

In passive oxygenators the gas exchange rate increases with blood flow rate because greater flow velocity past the fibers reduces the diffusional boundary layers that dictate gas exchange. In the IMO, balloon pulsation attenuates this effect because the diffusional boundary layers that dictate exchange are marshalled predominantly by the convective blood flow arising from balloon pulsation, and only secondarily by the blood flow through the vessel itself. This is so because the balloon generated blood flow is considerably greater than the blood flow through the MVC, which varied from 1 to 4.5 L/min in this study. For example, a 40-ml balloon pulsating at 60 and 180 bpm generates an *average* convective blood flow rate of 4.8 L/min and 14.4 L/min, respectively, with peak flow being greater. These larger balloon generated blood flows condition the diffusional boundary layers that dictate gas exchange to a greater degree than does the blood flow through the MVC itself. An interesting corollary to these arguments is that balloon pulsation provides more gas exchange enhancement as blood flow rate decreases. At lower blood flow, more enhancement is needed, because gas exchange under passive conditions (*i.e.*, in the absence of pulsation) would be lower. Although less gas exchange enhancement occurs at higher blood flow rates, less is needed, because gas exchange under passive conditions is higher. Thus, the pulsating balloon acts like a buffer for gas exchange, providing maximal enhancement when it is needed and maintaining relatively constant levels of gas exchange despite variations in blood flow through the vessel. This "exchange buffering" may be important in ultimate clinical application because the IMO may show more consistent levels of gas exchange in the face of variations in cardiac output in individual patients, and between patients.

Our *ex vivo* tests enable comparison of the IMO with the clinically tested IVOX device. Tao *et al.*[11] studied the gas exchange performance of an IVOX 7 device in a comparable mock vena cava (1 inch tubing) and extracorporeal circuit using the ovine model. The gas exchange rates of the IMO with maximal balloon pulsation are significantly greater than those reported for the IVOX. For example, at 2 L/min blood flow rate (**Figure 2A**) indicates that the peak IMO CO_2 exchange rate is about double the exchange rate for the IVOX 7 (156 ml/min/m^2). The lower CO_2 exchange rate of the IVOX may be due partly to different blood pCO_2 levels. In the *ex vivo* tests of the IVOX, the reported inlet pCO_2 varied from 45 to 53 mm Hg, which reflects a somewhat lower average blood pCO_2 than in our tests of the IMO.

A more meaningful comparison of the CO_2 exchange rates for the IMO and IVOX can be achieved by correcting the CO_2 exchange rate of the IMO to a lower inlet pCO_2. To do this we exploit the approximately linear relationship between the CO_2 exchange rate of an oxygenator and blood pCO_2,[11] and esti-

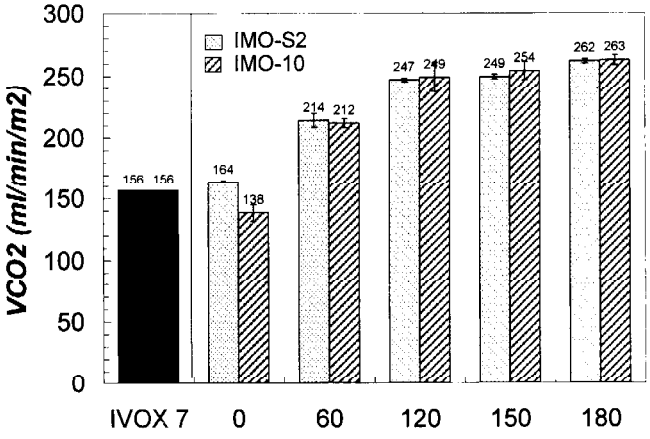

Figure 5. Comparison of the CO_2 exchange rate for the IVOX and IMO at 2 L/min blood flow through the MVC. The CO_2 exchange rate of the IMO is corrected to an inlet pCO_2 of 45 mm Hg, the reported lower boundary for inlet pCO_2 in the IVOX studies.

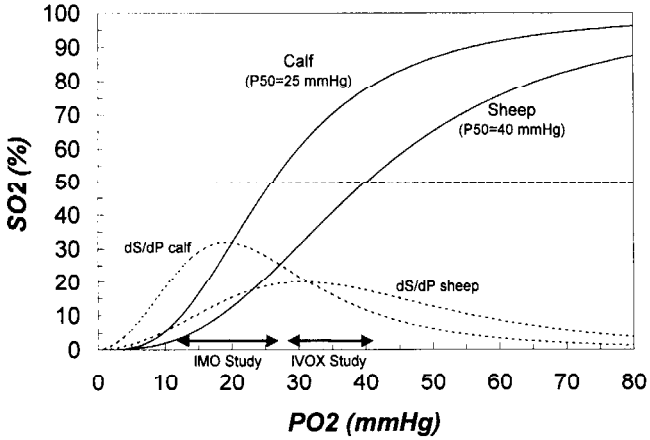

Figure 6. Oxyhemoglobin dissociation curves (ODC) for calf and sheep. Dotted lines indicate the slopes (dSO_2/dPO_2) of the respective ODC. (Slopes shown have been multiplied by 10 for graph scaling purposes.)

mate a CO_2 exchange rate corrected to an inlet pCO_2 of 45 mm Hg using:

$$\dot{V}CO_2^* = \dot{V}CO_2 \frac{45}{pCO_2^{in}} \quad (3)$$

where the * indicates the corrected exchange value, and PCO_2^{in} is the inlet blood CO_2 tension (in mm Hg) measured for each experimental condition. The chosen reference inlet pCO_2 value of 45 mm Hg represents the lower range of the IVOX studies, so that our comparison is conservative. The corrected CO_2 exchange levels for the IMO prototypes at different pulsation rates for a blood flow rate of 2 L/min are displayed in **Figure 5**. The correction of CO_2 exchange rates to a common reference pCO_2 improves the agreement between the IMO-S2 and IMO-10 rates, which suggests that the estimation analysis is reasonable. Peak corrected CO_2 exchange rates for the IMO devices are 262 and 263 ml/min/m^2, respectively, which is 68% greater than that reported for the IVOX 7. Our exchange rates are given in ml STP. The IVOX study[10] is unclear as to whether IVOX exchange rates are referenced to STP or are at the negative pressures of the sweep gas exhaust. If the latter, the IMO CO_2 exchange rate compared to the IVOX would be significantly greater than the 68% shown in **Figure 5**.

The O_2 exchange rate of the IMO also exceeded that reported for the IVOX. For example, at 2 L/min blood flow rate the peak O_2 exchange rate of the IMO was more than triple the exchange rate for the IVOX 7 (93 ml/min/m^2) (**Figure 2B**). Even in its passive mode, with no balloon pulsation, the IMO O_2 exchange rate exceeded that reported for the IVOX, which may be attributed in part to differences between calf and sheep blood and the pO_2 ranges of the IMO and IVOX *ex vivo* experiments. Even with pulsation, a small component of the increased O_2 exchange rate of the IMO compared to the IVOX may be attributed to the different experimental protocols. The extracorporeal tests of the IVOX 7 by Tao *et al.*[11] were done in the sheep model, with inlet pO_2 ranging from 28 to 41 mm Hg. Our *ex vivo* study of the IMO used the calf model, with inlet pO_2 ranging from 12 to 27 mm Hg for IMO-S2 and 16 to 28 mm Hg for IMO-10. Nevertheless, the different inlet pO_2 ranges for the IMO correspond to comparable inlet O_2 saturation ranges because calf hemoglobin has a greater O_2 affinity (P50 = 25 mm Hg) than does sheep hemoglobin (P50 = 40 mm Hg).

Some simple analysis can estimate how the differences in oxyhemoglobin dissociation curves (ODCs) between sheep and calf, combined with differences in the inlet pO_2 range, may affect the comparison of IMO and IVOX O_2 exchange. In oxygenators, the O_2 exchange per unit membrane area (VO_2/A) is proportional to:

$$\frac{\dot{V}O_2}{A} \propto K(pO_2^{gas} - pO_2^{blood}) \quad (4)$$

where K is a mass transfer coefficient accounting for the influence of diffusional boundary layers, PO_2^{gas} is the average O_2 tension in the sweep gas, and PO_2^{blood} is average blood O_2 tension. In application, PO_2^{gas} is about 500–600 mm Hg for both the IVOX and the IMO. Because gas O_2 tension is much greater than the inlet pO_2 for both the IVOX and IMO experiments, the pO_2 driving force for exchange is similar in both the IMO and IVOX experiments and does not itself contribute significantly to differences in O_2 exchange.

One important difference, however, can be ascribed to the mass transfer coefficient K and its dependence on the ODC for calf versus sheep hemoglobin. Mockros and Leonard[13] and Vaslef *et al.*[10] have shown that the mass transfer coefficient K in oxygenators varies with the *slope* of the ODC curve according to a 2/3-power dependence:

$$K \propto \left(\frac{dSO_2}{dpO_2}\right)^{2/3} \quad (5)$$

Figure 6 compares the ODC for calf and sheep using a Hill approximation to the ODC, assuming a Hill exponent of n = 2.8 and taking appropriate P50 values from the literature: P50 = 25 mm Hg for calf,[14] and P50 = 40 mm Hg for sheep.[15] The dashed lines show the values of the slope (dSO_2/dPO_2) of the respective ODCs, and the bold arrows just above the abscissa indicate the pO_2 ranges in the IVOX and IMO *ex vivo* studies. The slope of the ODC in the calf for conditions of the IMO study is 29.1 versus 19.1 in the sheep for conditions of the

IVOX studies. This translates to a ratio of mass transfer coefficients and, hence, O_2 exchange rates of $(29.1/19.1)^{2/3} = 1.32$ between the two studies. Using the maximum slopes for each ODC (calf=31.9, sheep=19.9) would yield an estimated ratio of O_2 exchange rates of 1.37. These estimates suggest that differences in the calf versus sheep ODC account for approximately 30–40% better O_2 exchange, all else being constant. Thus, at a 2 L/min blood flow rate (see **Figure 2B**), for example, the IVOX under conditions of the IMO *ex vivo* test would transfer an estimated 130 ml/min/m^2. Accordingly, the IMO O_2 exchange without balloon pulsation would be slightly less than the IVOX, but the peak IMO O_2 exchange with pulsation would still be 2 to 2.5 times larger than that for the IVOX at this blood flow rate.

Acknowledgment

We thank Sue Wanant, Joy Matoney, and Lisa Gordon for their technical assistance, as well as the laboratory of Dr. Marina Kameneva.

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