Respiratory Dialysis

A New Concept in Pulmonary Support

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Use of a new intravenous oxygenator made of hollow fiber membranes arranged around a centrally positioned balloon is reported. *In vitro* studies using fluorescent image tracking velocimetry and gas exchange analysis demonstrated enhanced convective mixing with balloon pulsations and augmented gas flux (100% increase in pO_2) compared with the device in its static configuration. *In vivo* observations confirmed a greater than 50% increase in O_2 flux with balloon activation. Those parameters that produce radial flow and convective mixing *in vitro* enhance gas flux *in vivo*, thus confirming that efforts to exceed the fluid limit translate into improved gas exchange. *ASAIO Journal* 1992; 38: M322–M325.

A wide variety of factors and mechanisms contribute to development of the acute respiratory distress syndrome (ARDS), which represents the end result of damage to the lung parenchyma, pulmonary capillaries, and epithelium.[1] This phenomenon, most frequently encountered in intensive care units, has an incidence estimated at 200,000 cases per year in the United States, with a fatality rate of over 50%.[2–4] Although many of these patients demonstrate multiple factors that contribute to their deteriorating pulmonary status, it is the act of mechanical ventilation and oxygen therapy itself that, while initially sustaining the patient, can eventually become a major factor in loss of pulmonary function contributing to a fatal outcome. The often disappointing results with use of ventilators and oxygen therapy have provided the experimental and clinical impetus for development of other forms of therapy; these culminated in the first success for extracorporeal membrane oxygenation in a patient with ARDS after severe trauma.[5] Although it was considered promising in theory, expected survival for ARDS in the adult using extracorporeal oxygenation and carbon dioxide removal is today approximately 50%.[6–8]

The focal point for these new forms of therapy for ARDS has been the need for treatment strategies that "rest the lung," not only from barotrauma but also from high partial pressures of oxygen. To this effect, Mortensen reported on the potential benefit of intravenous oxygenation (IVOX), with which gas exchange is promoted in the inferior vena cava by passive flow of blood past crimped hollow fiber membranes positioned in the venous system.[9,10] An alternative approach has been under development in our laboratories where we have stressed mechanisms to enhance blood oxygenation through convective mixing around hollow fibers. Here we report our ongoing experiments examining the potential benefit of balloon assisted, intravenous, hollow fiber membrane gas exchange.

Materials and Methods

Device Description

The design of our latest prototype (Prototype D) incorporates a pulsatile balloon that is centrally located and around which are mounted microporous hollow fibers (MHF-200L Mitsubishi Microporous Hollow Fibers, Mitsubishi Rayon Co., Ltd., Hiroshima, Japan). The blood-side pump provides a means of rhythmically changing fiber configuration in the venous system and enhancing convective mixing around the hollow fibers.

Prototype D consists of a polyurethane balloon that is activated by an intraaortic balloon pump console, with helium

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gas entering and exiting the base of the balloon. Oxygen flows into a receiving chamber and exits the circumferentially positioned hollow fibers through a vacuum port.

Flow Field Analysis

To visualize and measure flow fields in and around the hollow fibers and balloon, a laser-based particle tracking technique was employed. This technique, termed fluorescent image tracking velocimetry (FITV) by Shaffer *et al.*,[11,12] uses multiple exposure optical imaging to track the motion of small (30 μm) neutrally buoyant particles in a flowing fluid. A pulsed laser illuminates the seeded flow field at precisely controlled intervals. Displacement of particles between laser pulses produces a velocity vector map of the flow field. Fluorescent image tracking velocimetry involves seeding the fluid with particles that fluoresce when excited with light of an appropriate wavelength. An important property of the fluorescent dye is its Stokes shift: the difference in excitation and emission wavelengths. The light from the seeded particles consists of both scattered light at the excitation wavelength λ_1, and fluoresced light at a different wavelength (mean fluorescent emission λ_2). With measurements made adjacent to biomaterial (solid) surfaces, the light scattered by the flow boundary is at the same wavelength, λ_1, as the excitation light. The intensity of the light scattering by the solid boundary exceeds that from the seeded particles, the result of which is a low signal-to-noise (S/N) ratio for particles near the flow boundary. The S/N ratio is increased dramatically by placing an excitation filter in front of the imaging camera. The excitation filter occludes the light scattered by the particles and flow boundary at λ_1: the camera sees only the fluorescent light emitted by particles at λ_2. This approach has provided excellent S/N ratios of particles adjacent to the hollow fiber membranes both with and without balloon agitation.

The FITV system consisted of a pulsed argon laser, beam shaping optics (cylindrical lenses), a Raman holographic edge (RHE) excitation occlusion filter, an electronic camera (MTI Model 81; Kodak, Rochester, NY) with digital image acquisition (ANDROX analog-to-digital converter), and an image processing computer (SUN 670) equipped with an ANDROX parallel image processing subsystem. Additional details regarding the FITV system components can be found elsewhere.[12]

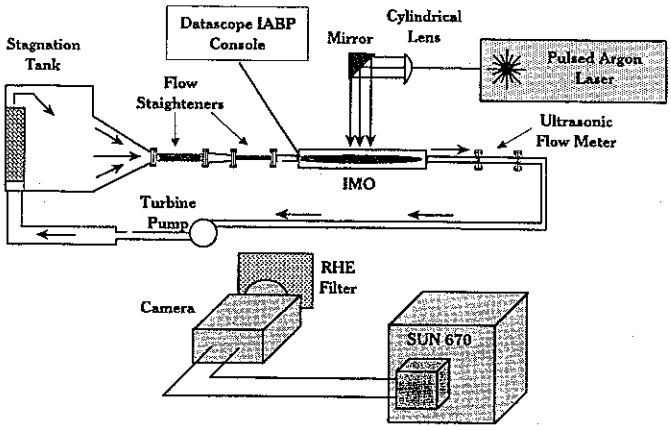

Figure 1. *In vitro* flow circuit for flow visualization and gas exchange experiments.

Table 1. Upgrade in p_{O_2} (mmHg)

Flow Rate (L/min/m^2)	Balloon On (40 beats/min)	Balloon Off
21	61	36
11	84	42
5	157	81

In Vitro Flow Loops

An *in vitro* flow loop was interfaced with the intravenous membrane oxygenator (IMO) and laser measurement system, as shown in **Figure 1**. Prototype D was housed in a specially designed chamber fabricated from cast acrylic to provide optical access for FITV. The ratio of the radius of the balloon to the radius of the housing chamber was equal to 0.5 upon maximal inflation. In operation, a transparent blood analog fluid (42% by weight aqueous spectrophotometric grade glycerin) was seeded with "red" fluorescent particles (Duke Scientific Corporation, Palo Alto, CA) and pumped around a closed loop by a rotary pump. A stagnation tank and flow straighteners insured the delivery of fully established, steady flow to the balloon housing chamber. Fluid flow rate was continuously monitored using an ultrasonic flowmeter (Transonics Systems, Inc., Ithaca, NY). The pressure drop across the IMO was measured with microtip pressure catheters (Millar Instruments, Inc., Houston, TX).

For measurements of O_2 exchange, the loop of **Figure 1** was modified to permit the flow of saline solution at room temperature (26°C). In these experiments, the flow rate was regulated by a Biomedicus pump with an on-line calibrated flow probe. Partial oxygen pressure (pO_2) was sampled immediately proximal (inlet) and distal (outlet) to the hollow fibers and measured using an ABL-3 blood gas analyzer. The saline perfusate was pre-equilibrated with room air before initiation of flow. The rate of O_2 gas flow through the hollow fibers was maintained at 5 L/min.

Animal Experiments

The IMO was inserted in the inferior vena cava of a 20 kg dog after a laparotomy and mobilization of the distal vena cava and internal iliac vein. The animal was heparinized to maintain an activated clotting time of greater than two times that of control and the device positioned so as to occupy the inferior vena cava, right atrium, and superior vena cava. Catheters were placed to monitor venous pressure proximal and distal to the IMO, arterial pressure, pulmonary artery pressure, and cardiac output. Blood samples were drawn to monitor oxygen flux at baseline and before and after activation of the balloon. A mass spectrometer allowed inlet and outlet gases to be measured. Oxygen was introduced under

vacuum (100–250 mmHg) into the hollow fibers at flow rates of 1–5 L/min.

Results

The key hypothesis underlying the development of our IMO is that the rhythmic pulsation of the balloon in the venous system will enhance convective mixing around the hollow fibers, leading to improved mass exchange efficiency. To test this hypothesis, we measured the upgrade in pO_2 generated in saline flowing across the IMO with the balloon off or pulsing at 40 beats per minute. **Table 1** demonstrates the improvement that occurred in the presence of the pulsating balloon, with an increase in pO_2 of up to 100%. Here the rate of saline flow was normalized to the surface area of our IMO prototype D. As expected, a monotonic increase in pO_2 was measured as the flow rate of saline was decreased. For all three flow rates tested, the pulsing of the balloon led to an enhanced pO_2.

In vivo gas exchange with prototype D demonstrated a >50% increase in O_2 flux upon balloon activation measuring changes in peripheral arterial saturation. Oxygen flux with the balloon off but with oxygen flowing through the hollow fiber membranes equalled 21.6 ml/min. With balloon activation at 40 BPM O_2, flux rose to 34.1 ml/min using an IMO with 0.07M^2 of surface area.

Discussion

A clinically effective intravenous membrane oxygenator capable of meeting the oxygen and carbon dioxide exchange requirements of patients with severe ARDS is the goal of this ongoing developmental work. Initial *in vivo* studies in the dog demonstrated an enhanced gas exchange of at least 50% with balloon agitation when compared with the intravenous membrane oxygenator in its static configuration. These results are to be expected based upon the previous findings of Mockros and Weissman,[13] among others, who demonstrated that the dominant resistance to gas exchange occurs in the boundary layer of the fluid phase (*vs.* the membrane). Accordingly, the focus of our current series of *in vitro* studies is to identify the balloon operational parameters (e.g., pulse frequency, inflation-to-deflation ratios, balloon filling volumes) that optimize convective mixing around the hollow fiber membranes leading to effective O_2 and CO_2 exchange. Here also, the primary effects of balloon activation are important and involve the physical motion imparted to the fibers as they move through the surrounding fluid.

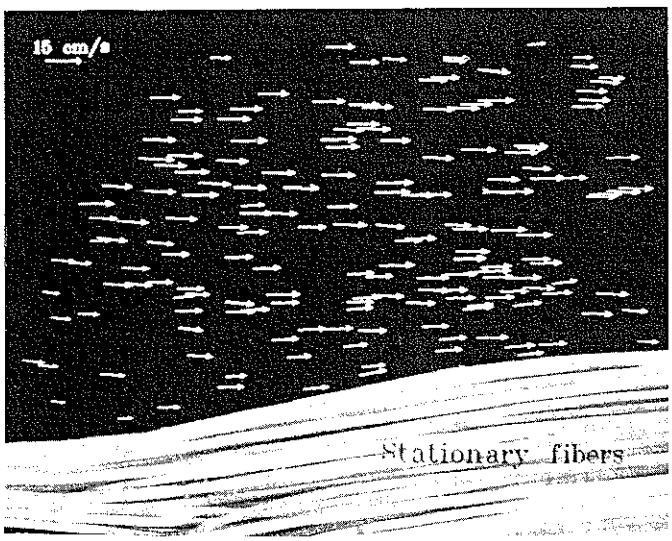

Figure 2. Measured velocity vector field over stationary IMO fibers. Velocity vectors are overlain from numerous FITV images.

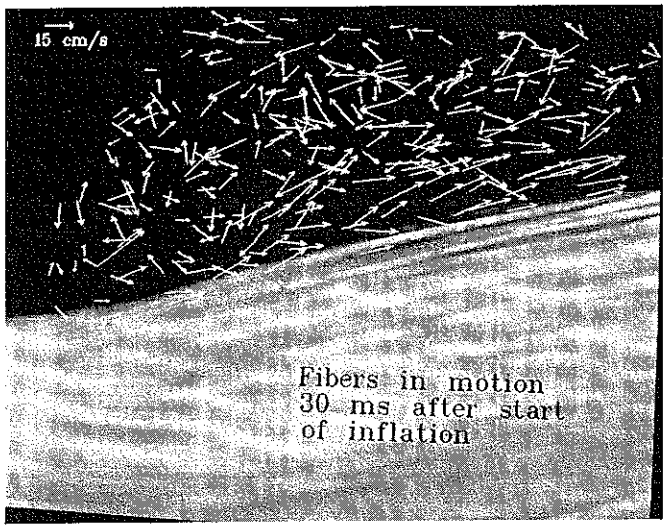

Figure 3. Velocity vector field 30 ms after start of IMO inflation. Velocity vectors are overlain from numerous FITV images at this time. There is increased dynamic range of velocity and strong mixing.

Fluorescent image tracking velocimetry has provided a useful technique for visualizing and measuring the motion of small particles close to, or even touching, the hollow fiber membrane surface. Mapping flow fields around the IMO has shown that, with balloon inflation and deflation, the velocity profiles adjacent to the surface of the fibers are markedly altered. **Figure 2** displays the characteristic parallel streamlines in the flow field when the IMO is in its static configuration (e.g., no balloon pulsation). The flow rate for the blood analog fluid is 5 L/min, which corresponds to a tube Reynolds Number of 1,200. Actuation of the balloon at a frequency of 40 beats per minute produced a marked increase in the dynamic range of velocity and strong mixing at the fluid–fiber interface **(Figure 3),** as evidenced by the presence of velocity vectors that are not parallel to the fibers. To visualize the convective mixing effect better, velocity vectors are overlaid from numerous FITV images captured at the same instant (30 milliseconds after initiation of balloon inflation). Enhanced convective mixing is present not only around the fibers but extending to the vessel wall. Ongoing image analysis involves quantitation of the magnitudes of the secondary flow components. The implications of these FITV images are that, with rhythmic balloon inflation and deflation, greater numbers of red blood cells in flowing blood will be exposed for longer residence times to the oxy-

gen rich atmosphere adjacent to the hollow fiber membranes. This will lead to more effective gas exchange compared with that associated with the static IMO configuration. This hypothesis is supported by the correlation that could be found between those parameters that produce radial flow and convective mixing *in vitro* and enhanced gas exchange *in vivo*. It therefore confirms that efforts to exceed the boundary layer effect translate into improved gas exchange.

Although it is a misnomer physiologically, the term "respiratory dialysis" has been introduced and refers to the theoretical ability to use this therapy intermittently and as needed to treat reversible respiratory failure similar to the clinical approach to renal insufficiency.

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