Branched vascular network architecture: A new approach to lung assist device technology

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Objective: A lung assist device would serve an important clinical need as a bridge to transplant or destination therapy for patients with end-stage lung disease. A new lung assist device has been developed that incorporates a branched network of vascular channels adjacent to a gas chamber, separated by a thin, gas-permeable membrane. This study investigated 2 potential gas exchange membranes within this new architecture.

Methods: Oxygen and carbon dioxide exchange within the device was tested in vitro using 3 gas-permeable membranes. Two of the membranes, silicone only and silicone-coated microporous polymer, were plasma impermeable. The third, a microporous polymer, was used as a control. Gas exchange testing was done using anticoagulated porcine blood over a range of flow rates.

Results: Oxygen and carbon dioxide transfer was demonstrated in the device and increased nearly linearly from 0.6 to 8.0 mL/min blood flow for all of the membranes. There was no significant difference in the gas transfer between the silicone and the silicone-coated microporous polymer membranes. The transfer of oxygen and carbon dioxide in the device was similar to existing hollow fiber oxygenators controlling for surface area.

Conclusions: The silicone and silicone-coated microporous polymer membranes both show promise as gas-permeable membranes in a new lung assist device design. Further optimization of the device by improving the membranes and reducing the channel diameter in the vascular network will improve gas transfer. The current device may be scaled up to function as an adult lung assist device. (J Thorac Cardiovasc Surg 2010;140:990-5)

Lung assist devices have been in development for several decades.[1-4] The 2 fundamental implantation approaches for these devices have been in an arteriovenous shunt position principally for intensive care unit-based care of acute lung disease[5] or as an ambulatory lung assist device with abdominal or intrathoracic placement in parallel to the native lungs.[6] For ambulatory lung assist devices, the goal is to develop a device that can be implanted in patients to improve their quality of life and reduce the mortality while awaiting a lung transplant.

The central aim of this work is to explore the application of a branched vascular network-based scaffold to create a lung assist device that closely matches physiologic flow and is minimally damaging to the blood while achieving satisfactory gas exchange. For the past 2 decades, nearly all of these devices have had the same basic design architecture using a porous hollow fiber oxygenator with blood flowing outside the fibers.[7] The hollow fiber design approach achieves efficient packaging of a large surface area of fibers for gas exchange into a small cartridge. However, it is a significant deviation from the physiologic flow in the bifurcated vascular network of the native lung.

In an effort to develop a tissue engineered liver, it was proposed[8-10] that a solid organ scaffold with a preformed vascular network would be a means of delivering needed oxygen and nutrients to the tissue. This architectural concept of a tissue scaffold has been successful for in vitro development of liver tissue.[11] By applying this preformed vascularized scaffold approach, a branched vascular network of microfluidic channels analogous to capillaries were developed for a lung assist device. A gas-permeable membrane separates the vascular channels from the adjacent gas chamber that carries oxygen. Gas exchange occurs across the thin membrane.

This study compared the gas exchange characteristics of the lung assist technology with 2 different plasma impermeable gas-permeable membranes: silicone and silicone-coated porous polycarbonate. The gas exchange membranes were evaluated within the vascular network architecture to determine the feasibility of this approach as a long-term implantable lung assist device.

MATERIALS AND METHODS

Device Architecture

The vascularized scaffold approach for a lung is composed of 3 fundamental components. A branched vascular network divides the blood flow into multiple parallel microfluidic channels to create significant surface area for gas exchange. Adjacent to the vascular network is an alveolar

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Abbreviations and Acronyms
PDMS = polydimethylsiloxane

chamber for the flow of oxygen analogous to the alveoli in the lungs. The channels of the vascular network and the alveolar chamber are separated by a thin gas-permeable membrane. This membrane allows the exchange of oxygen and carbon dioxide between the blood and the alveolar chamber. The vascular network and cross-section of the device are shown in Figure 1.

Vascular Network Design

The vascular network was designed to divide the flow from a single inlet into a high density of capillary-like network with significant surface area. The design has a single depth of 200 μm for all of the channels, and the width of the channels varies from several millimeters at the inlets to 200 μm in the 23 capillary-like subunits of the design. The network was designed to achieve a high density of channels across the entire surface area and then optimized to achieve low shear stress within the capillary-like subunits.

The vascular network design was drafted in 3 dimensions using SolidWorks (SolidWorks Corp, Concord, Mass). Computational fluid dynamics analysis (FloWorks, SolidWorks Corp) using a non-Newtonian blood model was performed over a range of flow rates to determine the shear stress and blood velocity within the channels.

Alveolar Chamber

The alveolar chamber for the device shown in Figure 1, *B*, consists of an open chamber 200 μm deep with an array of posts to maintain a constant chamber depth. The posts are 140 μm in diameter and spaced 300 μm apart to achieve relatively unimpeded oxygen flow within the chamber.

Photolithography manufacturing was used to create silicon molds of the vascular network and alveolar chamber. The vascular and alveolar layers were made with traditional soft lithography techniques by casting Sylgard 184 polydimethylsiloxane (PDMS) (Dow Corning, Midland, Mich) on the molds and heat curing at 70°C for 2 hours.

Gas Exchange Membranes

Two silicone-based gas exchange membranes were developed and tested in the device. The silicone gas exchange membranes were made by thinning 1 mL of silicone pre-polymer (MDX4-4210, USP Class VI polymer; Dow Corning, Midland, Mich) on a plain silicon wafer using a plate spinner (Model 100; Brewer Science, Rolla, Mo). The silicone membranes were then cured at 70°C for 30 minutes.

The porous polycarbonate membrane, used as a control, had a pore size of 1 μm with a pore density of 1.0×10^7 pores/cm^2 for a resulting 8% porosity (GE Water & Process Technologies, Trevose, Pa). The silicone-coated porous polycarbonate membranes were made by spin coating the porous polycarbonate membranes with the silicone pre-polymer using a plate spinner at 3000 rpm for 15 minutes. The silicone was then cured at 70°C for 30 minutes.

The gas exchange membranes were bonded between the vascular and alveolar chambers by applying a thin layer of PDMS pre-polymer to the top of the layers and then joining the respective layers to opposite sides of the membrane and heat curing the PDMS. Inlet and outlet tubing was attached to the vascular and alveolar layers using silicone glue.

The thickness of the membranes for each of the devices was measured after the gas exchange testing by dividing the device in half and imaging the cross-section of the membrane with light microscopy at 200×. The membrane thicknesses were measured at 5 points across each device and calculated by image analysis in Photoshop (Adobe Systems Inc, San Jose, Calif).

Gas Exchange Testing

An in vitro gas exchange test was developed to evaluate the potential of the lung assist technology. The gas exchange test is similar to tests performed by Page and colleagues[12] and more recently by Lee and colleagues.[13] A schematic of the test setup is shown in Figure 2. The test setup consisted of a syringe pump (PHD 2000; Harvard Apparatus, Holliston, Mass) that pumped 37°C anticoagulated porcine blood (Lampire Biologics, Pipersville, Pa) through the vascular chamber of the lung assist device at flow rates of 0.6, 1.0, 2.0, 4.0, and 8.0 mL/min. Oxygen (100%; Air Gas, Hingham, Mass) was delivered through the device at a flow rate of 400 mL/min. Blood and oxygen inlet pressures were measured using a pressure transducer (Model PX209-30V15G5V; Omega Engineering, Stamford, Conn) connected to a digital display (Model DPi8-EI, Omega Engineering). For each device, blood was sampled before and after flowing through the device to determine baseline and post-device blood gas values. Four devices were tested in each of the 3 membrane types. Blood gas values (P_{O_2}, P_{CO_2}, H_{CO_3}, % hemoglobin saturation) were measured using an iSTAT portable clinical analyzer with CG8+cartridges (Abbot Point of Care Inc, East Windsor, NJ). Oxygen transfer[14] and carbon dioxide transfer rates[15] were calculated using established equations.

Statistical Analysis

Results are expressed as mean ± standard deviation. The gas transfer results were compared between groups using the Student *t* test.

RESULTS

This vascular network design achieved a high degree of density with a repeating design of 23 capillary-like modules and interconnecting transit channels. The area of the entire vascular network is 30.8 cm^2, and the area of just the vascular channels is 18.0 cm^2 with a resulting 58.4% of the area of the vascular network comprising an actual channel. Low capillary-like shear stresses were present in the capillary-like portions over a range of flow rates. For the 4 mL/min flow rate, the shear stress within the capillary-like channels of the devices ranged from less than 1 to 26.6 dynes/cm^2 (Figure 1, *D*).

The resistance of this initial vascular network was designed for arterial input pressures and may be redesigned to match the input pressures of its intended vascular connection (eg, the pulmonary artery). Accordingly, the blood inlet pressure ranged from 19.8 mm Hg at 0.6 mL/min to 123.1 mm Hg at 8.0 mL/min. The oxygen inlet pressure averaged 4.75 ± 0.9 mm Hg for all devices.

The devices were reliably fabricated with each of the membrane types. The device units were tested as single units consisting of a vascular network and an adjacent alveolar chamber separated by a gas-permeable membrane. The resulting membrane thicknesses are as follows, the porous polycarbonate control membranes were 12 μm thick as measured by the manufacturer. The silicone-coated porous polycarbonate membranes were 15 ± 2 μm thick with a resultant 3-μm thickness of the silicone portion. The thickness of the silicone only membranes was 63 ± 19 μm.

The blood used for the testing was stored in a hard plastic container between being drawn and used for testing. This resulted in the blood being similar in gas content to that

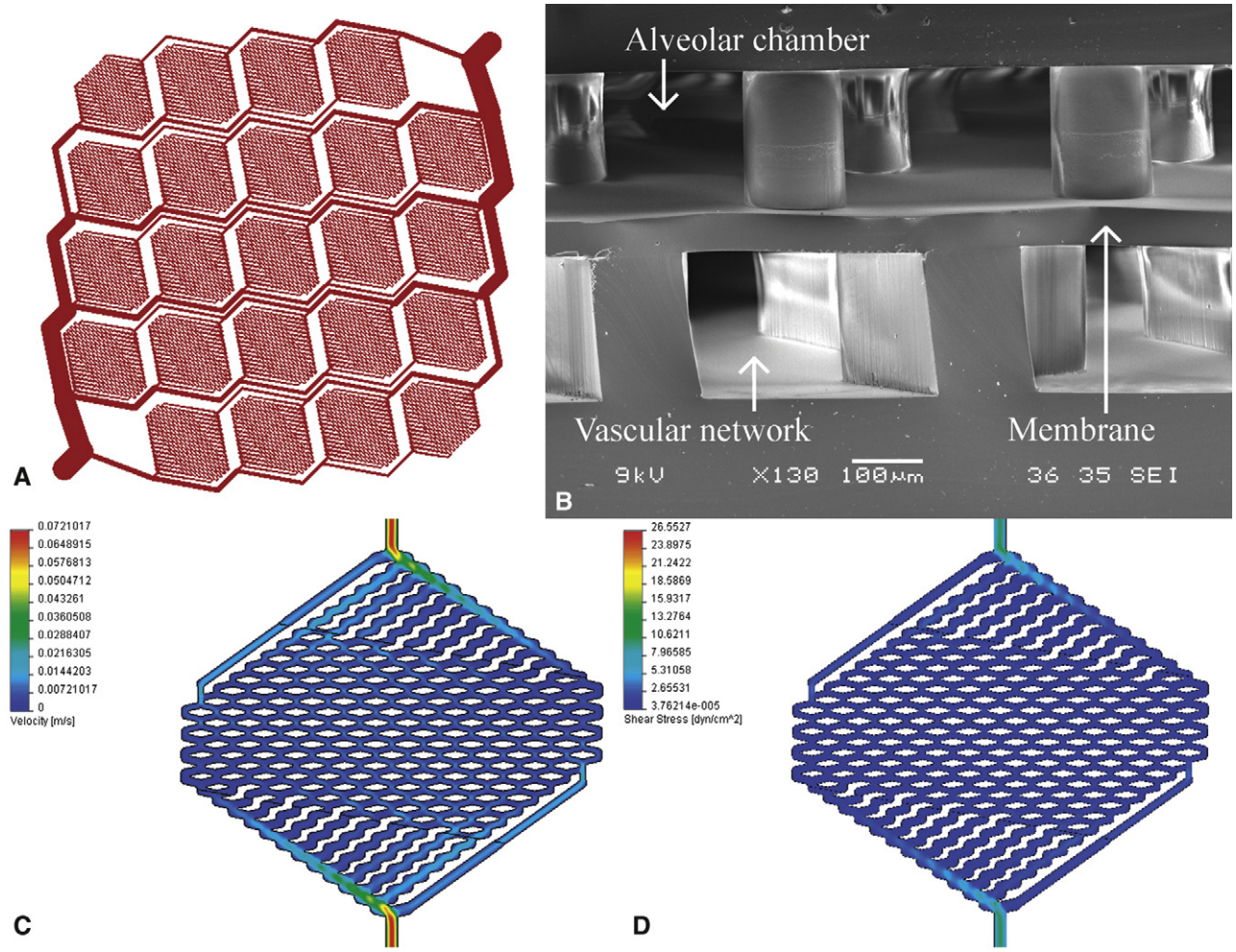

FIGURE 1. Design of vascular network-based lung assist device. A, Top view of branched vascular network design with single blood inlet and outlet. B, Cross-sectional scanning electron microscope image of cut edge of device with silicone membrane. Velocity plot (C) and (D) shear stress plot from computational fluid dynamics analysis of capillary-like area of vascular network at blood flow rate of 4 mL/min.

of an adult patient with end-stage lung disease. The baseline P_{O_2} of the blood was 53 ± 4.5 mm Hg, and the baseline P_{CO_2} of the blood was 86.9 ± 5.3 mm Hg. The oxygen transfer in the devices increased with increasing blood flow for the device over the range of blood flow rates is shown in Figure 3. The carbon dioxide transfer also increased with increasing flow over the range of flow rates for all of the membranes except for the silicone membrane, which trended lower at the higher flow rates shown in Figure 4. By using the entire area of the vascular network, the oxygen and carbon dioxide gas exchange was 89.3 and 78.1 mL/min/m^2, respectively, at 4 mL/min blood flow in the device. These values for oxygen and carbon dioxide exchange are similar to hollow fiber-based oxygenators, including the Biolung[16] (oxygen transfer rate 64 mL/min/m^2) and the Ambulatory-AVCO2R prototype[17] (carbon dioxide transfer rate 84 mL/min/m^2). The challenge in this technology is to create high-density vascular networks with minimal total scaffold material to maximize gas transfer area and minimize overall size.

DISCUSSION

Ambulatory lung assist devices may offer patients with end-stage lung disease new clinical options, including a bridge to transplant or eventually a destination therapy. This article describes a new architectural design for a lung assist device. In this device, a branched vascular network divides blood flow into many parallel capillary-like channels analogous to the native lung architecture. A thin gas-permeable membrane functions similar to the alveolar membrane of the lung to effect oxygen and carbon dioxide exchange with the alveolar chamber. This approach has many theoretic benefits. The vascular network can achieve physiologic blood flow, including physiologic shear stress throughout the network, and thereby minimize platelet activation and thrombus formation within the device. The entire blood contact surface of the device is

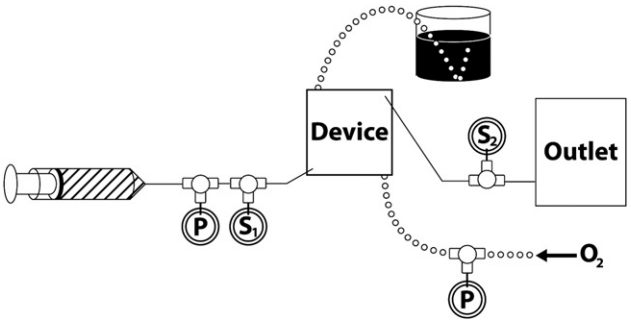

FIGURE 2. Schematic of in vitro gas exchange testing setup. Blood was pumped through vascular network using syringe pump and oxygen delivered through the alveolar chamber. Samples for blood gas analysis were taken before (S1) and after (S2) the device to calculate the gas transfer rates.

silicone, which is both biocompatible and eliminates the risk of plasma leakage during long-term implantation.[14] The device is scalable by stacking layers of the device units consisting of the vascular network and alveolar chamber. The resulting device can be a single module of stacked units or multiple modules arranged in parallel to achieve adequate gas transfer for a range of patient needs.

In this study, the devices had effective gas transfer over a wide range of flow rates. Both the oxygen and carbon dioxide transfer increased in a nearly linear fashion for each of the membranes with increasing flow rate. The exception was the silicone membrane where the carbon dioxide transfer decreased at the higher flow rates; however, this was not statistically significant. There was no difference between the gas transfer of the 2 silicone-based membranes and the control membrane used in this initial study. The standard deviation at the higher flow rates was large and may be minimized in the future by increasing the sample size.

Extrapolating the data of this experiment with single-layer devices (joined vascular network and alveolar chamber) can formulate a picture of an implantable adult lung assist device that could be made by scaling up this technology. The amount of CO_2 removal required for an effective bridge to transplant device is not known. For a device to remove 20% of baseline CO_2 (50 mL/min), the device would require 357 layers (using a silicone-coated porous membrane and flow rate of 4 mL/min) and would have a total surface area of 0.64 m^2. The device would require approximately 25% of the cardiac output and could be expected to increase the Po_2 from 57 to 79 mm Hg.

With its current size, a 357-layer device would be more than 20 cm tall and 6 $\times$ 12 cm in breadth and width. Although this size is too large to be clinically useful, the size will decrease significantly in future iterations of the technology by decreasing the size of each layer through manufacturing optimization and reducing the total number of layers required. Decreasing the thickness of the membrane will also decrease the total number of layers required.

In comparison, the Novalung assist device (Novalung GmbH, Baden-Württemberg, Germany) is currently clinically available for peripheral placement principally as a ventilatory support device.[18,19] The arteriovenous placement of the device limits oxygenation capacity but has excellent CO_2 transfer capacity of 201.3 mL/min/^{2}.[20] This therapy requires full anticoagulation and uses a traditional hollow fiber architecture.

In this study, there were no significant differences in gas exchange between the 2 plasma-impermeable membranes,

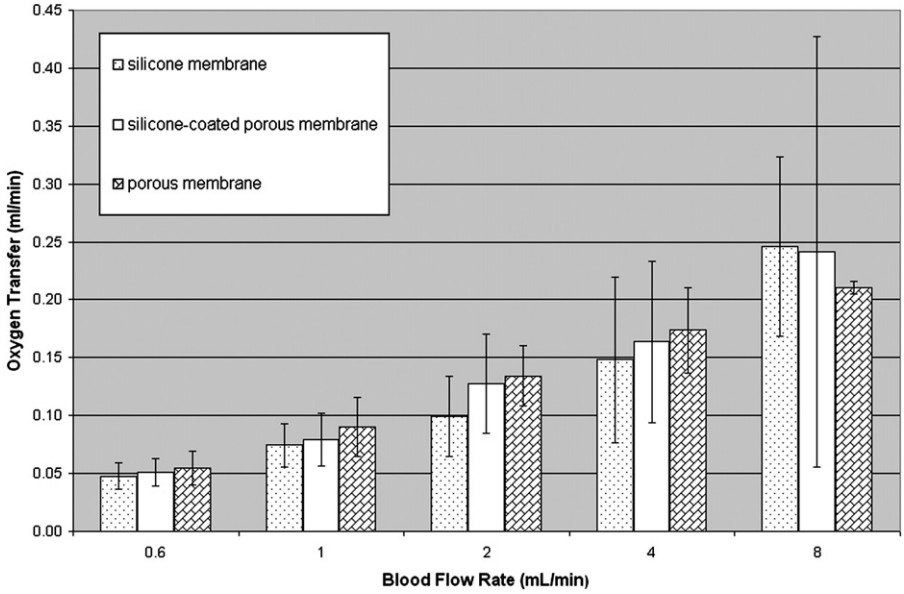

FIGURE 3. Oxygen transfer in lung assist device over range of blood flow rates. There was no statistically significance difference between the membranes at any of the flow rates.

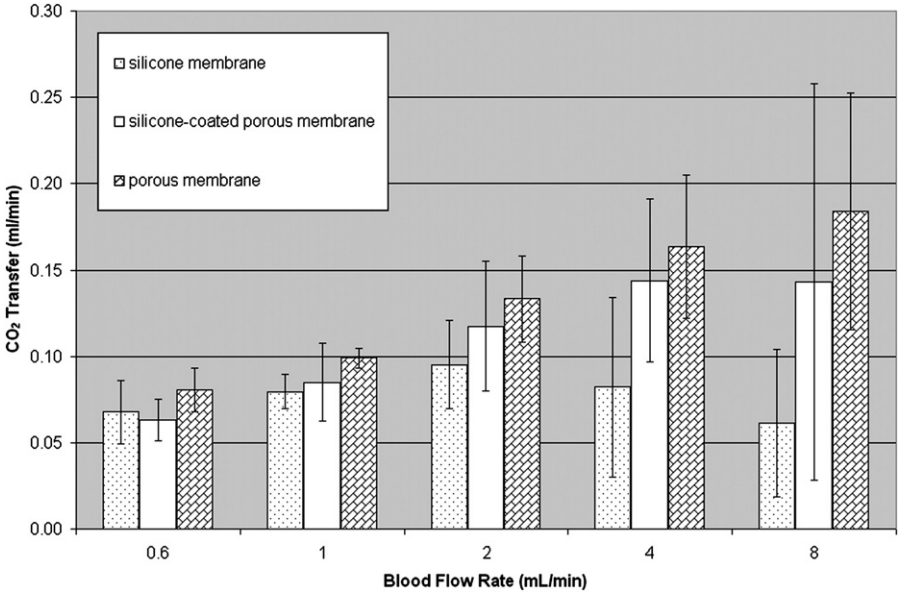

FIGURE 4. Carbon dioxide transfer in lung assist device over range of blood flow rates. There was no statistically significance difference between the membranes at any of the flow rates.

silicone and silicone-coated microporous membranes. In another study, a significant gas transfer difference was noted between silicone coating (0.2 μm coating) on a microporous hollow fiber oxygenator and a silicone fiber oxygenator (100 μm wall).[14] In contrast, the membranes used in this study were approximately 40% thinner at 63 μm, whereas the silicone coating on the porous membranes was substantially thicker at 3 μm. Both silicone and silicone-coated porous membranes can be optimized, warranting further investigation of each to determine which may be the best option. Increasing the porosity of the sheet-based microporous membrane and minimizing the silicone coating thickness by using plasma polymerization or chemical vapor deposition may be ways of optimizing the gas permeability of the silicone-coated porous membrane. For the silicone-only membrane, the silicone membrane thickness may be reduced, and one can expect a corresponding linear increase in gas transfer. We expect that a silicone membrane thickness of less than 10 μm is possible using this architectural approach.

Although the gas transfer increase is linear with increasing flow rate for each of the membranes, it does not double with the flow rate. Thus, there is a loss of efficiency of gas exchange with increasing flow rates. The central difference between the native lung and this first-generation vascular network device (and hollow fiber oxygenators) is the size of the blood channels versus native lung capillaries. It is expected that this difference accounts for loss of gas exchange efficiency as flow rate increases. Hollow fiber oxygenators have diffusion distances on the order of 200 to 300 μm,[21] and the channels in this device are 200 μm deep while a native capillary is 5 to 10 μm in diameter. Page and colleagues[12] described the kinetics associated with oxygen transport in capillaries and showed that full saturation of the hemoglobin in a 25-μm diameter capillary takes approximately 4 times as long in a 10-μm diameter capillary.[12] The channels in this vascular network are larger than the 25 μm used by Page and colleagues and are comparable to traditional oxygenators. There is significant shunting of blood at higher flow rates and a decrease in the efficiency of gas transfer. This can be improved by minimizing the diameter of the smallest capillary-like channels and increasing membrane permeability. Lee and colleagues[21] have begun to build on the work by Page and colleagues to optimize the balance of channel depth, blood velocity, and membrane permeability. Further work in this area is required to optimize gas exchange of these channel-based networks.

As channel diameters are decreased to improve gas exchange, the risk of thrombosis increases. Continued refinement of the design of the vascular network to achieve physiologic shear stress and minimal flow disturbances within the network is paramount. Because these vascular networks are designed to mimic native blood vessels, they may be endothelialized to greatly reduce the risk of thrombus. This would require a different scaffold material but has been demonstrated in principle by our group[22] and others.[23]

The central limitation of the initial testing of this device is the small overall size of the device tested. Development of a scaled-up clinically sized device is an important next step in validating this technology. High oxygen flow rates were used in this initial evaluation; however, it is expected that much lower oxygen flow rates will affect similar gas transfer. Variation in the oxygen flow rates is a principle element of the next step in testing. Similarly, demonstrating the effectiveness of the device in a small animal model is

also an important near-term goal to confirm the gas exchange function. The durability of the device with regard to supporting blood flow for an extended period of time will need to be assessed in vivo. The devices have supported sustained blood flow for hours in vitro with pressures exceeding 120 mm Hg, but longer term durability has not been assessed. Although the blood flow is more physiologic than hollow fiber-based devices, some level of anticoagulation will be required for this device without endothelial cells. The exact level of anticoagulation required will need to be assessed with in vivo studies.

CONCLUSIONS

A new architectural approach toward creating a lung assist device based on a bifurcated vascular network has been developed. Initial testing using silicone and silicone-coated microporous membranes demonstrate gas transfer of oxygen and carbon dioxide similar to existing hollow fiber oxygenators when normalizing by surface area. Optimization of this technology will focus on increasing the permeability of the gas transfer membrane and decreasing the diameter of the vascular network channels while optimizing physiologic blood flow.

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