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Microchannel Technologies for Artificial Lungs: (3) Open Rectangular Channels

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Abstract

Lithographic techniques were used to develop patterned silicone rubber membranes that provide 15 μm high microchannels for artificial lungs. Two types of devices were fabricated as a proof-of-concept: one has a series of parallel, straight, open rectangular channels that are each 300 μm wide, separated by 200 μm walls, and 3 mm long and the other is a wide rectangular channel with support posts, also 3 mm long. Experiments with 30% hematocrit, venous, bovine blood showed average oxygen fluxes ranging from 11×10^{-7} moles/(min·cm²) at a residence time of 0.04 sec to 6.5×10^{-7} moles/(min·cm²) at a residence time of 0.20 sec. The average oxygen flux vs residence time, which is due to transverse molecular diffusion, follows the same relation as for all membranes tested. The corresponding increase in hemoglobin saturation ranged from 9% at the residence time of 0.04 sec to 24% at the residence time of 0.20 sec. The support-post channel membranes are attractive for designers because they can be arbitrarily wide and would be less prone to blockage.

Introduction

Blood-side passages in artificial lungs that are 10 to 25 microns in size, microchannels, would alleviate the need for transverse mixing and would result in efficient, low pressure-drop, small blood prime devices. A major difficulty with attempting to develop multiple small channels is the challenge of assuring a tight uniformity of the blood-side passages. A previous study¹ investigated screen-filled blood channels with heights of 40 and 82 μm . The minimum channel height of screen-filled microchannels, however, is limited by the availability of easily-handled micro screens. Lithographic techniques are used in the present study to develop uniform channels that are smaller than 40 μm . Such techniques have been used previously to generate microfluidic devices with controlled dimensions for biological studies². The objective of the present study is to investigate the performance of microchannel devices fabricated using lithographic-patterned silicone rubber membranes and to compare them with devices fabricated using wire mesh screens.

Materials and Methods

Two types of silicone rubber membranes were developed in the present study for two types of microchannel devices (Figure 1). One is a series of straight, parallel open rectangular channels, SC, with narrow walls separating them and the other is a wide channel with periodic support posts, SP. The latter somewhat mimics the model of the natural lung microcirculation proposed by Fung³.

Most applications of lithographic techniques involve making patterns over fairly small dimensions. The practical challenge in the present case is to fabricate uniform patterned membranes over dimensions on the order of 10 cm. Details of the procedures used are listed in Table 1. The patterned membranes were prepared by molding polydimethylsiloxane, PDMS, against a master. The master was created by transferring the pattern of a photomask onto positive photoresist that was spin coated onto a silicon wafer similar to the procedure of Duffy *et al.*⁴ The photomask was generated by printing the desired pattern onto a transparency using a printer operating at 10,000 dots per inch (CAD/Art services, Brandon, Oregon). A pre-cleaned 10 cm diameter silicon wafer was primed with HMDS (1,1,1-3,3,3-Hexamethyldisilazane, Aldrich) to promote adhesion of photoresist. A positive photoresist, AZ® P4620 (AZ Electronic Materials), suitable for a film thickness ranging from 3 to over 60 μm , was spin coated onto the treated silicon wafer. At 1000 rpm, a spinning duration of 20 to 30 sec results in a photoresist thickness of between 15 and 25 μm . The photoresist was densified after a soft-bake and loaded onto the mask aligner (Quintel Corporation Mask Aligner Q-2000 with UV Broadband radiation). A UV exposure time of 90 sec was found to be appropriate to decompose the photoresist in the transparent region of the photomask. Thirty min after the UV exposure, the master was developed by an immersion process using a 1:4 dilution of AZ® 400K (AZ Electronic Materials) in water. In this process, the area of the photoresist exposed to the UV light was removed. For complete development of 10 to 20 μm thick patterns (the thickness of which defines the channel depth), the process was monitored with optical microscopy. In the last step, 30 min after treatment with the developing solution, the master was silanized with tridecafluoro-1,1,2,2,-tetrahydrooctyl trichlorosilane (Gelest) vapor at room temperature for two hours in a desiccator. This latter procedure increased master lifetime by promoting PDMS release. Optical microscope pictures of the masters are shown in Figure 2. The photoresist coating thickness was measured with SEM. Highly reproducible resist-coat thickness in the range of 10 to 20 μm can be fabricated using these procedures. To prepare an imprinted silicone rubber membrane, a 10/1 mixture of silicone elastomer/curing agent (SYLGARD® 184 Silicone Elastomer Kit, Dow Corning Corporation) was well mixed and degassed in a vacuum desiccator. It was spin-coated onto a master containing the patterned microchannels. The thickness of the membrane is dependent both on the spin rate and duration of the spin coating and the relationship is shown in Figure 3. From this relationship, the appropriate spin parameters were determined to generate a membrane thickness of 130 μm . Right after spin-coating, the coated master was baked on a hot plate at 80°C for 20 min to semi-harden the elastomer so that it can be transported without damaging the pattern. It was then baked in an oven at 70°C for an additional two hours. After cooling down, the patterned silicone rubber membrane was peeled from the master.

For this study, two different masks were used; a straight-pattern mask (300 μm dark straight stripes with 200 μm open space between them) and a cross-patterned mask (200 $\times$ 200 μm open squares with 300 μm dark space between them) (Figure 2). The former is used to create straight rectangular microchannels that are 300 μm wide, 15 μm high and separated by 200 μm wide walls, and the latter is used to create wide rectangular microchannels with 200 $\times$ 200 μm square 15 μm high support posts that are spaced 500 μm apart center-to-center. Figure 4a shows a top view SEM of a patterned silicone membrane, used to create a wide rectangular microchannel with support posts. Figures 4b and 4c are side views showing the membrane thickness and the height of the walls and support posts for the SC and SP membranes, respectively. Four devices were investigated; one with straight rectangular channels, device SC, and three with wide rectangular channels with support posts, SP-1, SP-2 and SP-3 which were generated from the same master and essentially identical. Schematic drawings and calculations of the gas exchange areas and liquid volumes of these microchannels are shown in the appendix.

Polycarbonate support plates for the blood side were fabricated with inlet and outlet manifolds, each 5 mm wide and 69 mm long. They are separated from one another by a distance of 3 mm

and have a depth that varies linearly from 9 to 0.5 mm (Figure 5). The deep ends of the two manifolds are at opposite ends of the plate and are connected to openings that serve as the inlet and outlet for blood. A membrane was glued onto the support with the pattern side facing the plate. The glue covered the entire plate except in the 3 mm region separating the two manifolds, the gas exchange region. In addition, five strips of glue in the gas exchange region were applied to further secure the membrane onto the support. These strips reduced the effective width of the gas exchange area from 69 mm to 46 mm. The straight channel, SC, membranes were aligned such that the channels were at a 90 degree angle to the long axis of the manifolds, i.e., the channels were directed straight across the exchange region. To avoid the potential for stagnant regions between posts, the support post, SP, membranes were aligned such that the rows of posts were at a 45 degree angle to the long axis of the manifolds, as depicted in Figure 1b. The gas channel, running perpendicular to the blood channel, was on top of the membrane. The device was always operated with higher blood-side pressure, and in order to minimize deformation of the top membrane due to the blood-side pressure, a coarse 280 μm wire screen (McMaster Carr) was placed on the gas passage side of the membrane. The wire screen was sandwiched with a second polycarbonate block that had a corrugated surface. Silicone grease was applied around the outer edge of the screen to prevent any gas leakage. During operation, oxygen or air flows over the wire screen. The gas exchange took place from the gas side to the blood side through the membrane. Each membrane was 130 μm thick and the walls or support posts were 15 μm high.

Two types of blood were used in the experiments: slaughterhouse-collected bovine blood and drawn bovine blood obtained from Lampire Biologicals. Both were treated with anticoagulant heparin 15,000U/L and EDTA (0.75 g/l), both were adjusted to have hematocrits between 28 and 31%, and both were conditioned with sodium bicarbonate buffer to a pH between 7.35 and 7.5. Before using the blood for tests the hemoglobin saturation was adjusted to about 68% by recirculation with a peristaltic pump over a ventilating gas of an appropriate pO_2 and pCO_2 . During the recirculation, the blood was passed through a 20 μm transfusion filter to remove any of the larger particles or debris that may be present. After achieving the desired condition, the blood was pumped into the test device. The pH, CO_2 and O_2 contents of the blood entering and exiting the device were analyzed with a Ciba-Corning Model 860 blood-gas analyzer.

In a typical experiment, the blood was first pre-conditioned while the device was primed with 0.15 M NaCl. Care was taken to avoid trapping any gas bubbles in the device. Two lead crystal blocks, 471 g each, were placed onto the top of the devices to hold the silicone membrane in place and minimize bulging of the membrane. Switching the inlet liquid flow to the preconditioned blood started the experiment. Oxygen or air was fed into the gas passage. The gas-side exit was submerged in water and typically the gas exit pressure was adjusted to 1-2 cm of water.

The microchannels of the present study are 15 μm in height and should be large enough to pass all constituents of normal blood. Although the slaughterhouse blood was filtered during preconditioning, it contained some tissue debris, up to 20 μm , that tended to periodically clog the 15 μm blood-side passages and cause some fluctuations in the oxygen uptake with the straight channel devices at low blood flow rates. The only reliable data with the straight channel pattern, thus, were those with relatively high flow rates, i.e., short residence times, where the blood could push any debris through the channel. The channels in the support-post devices are interconnected and the blood can take alternate routes to circumvent any blockages. Any *in vivo* applications should not be hindered by the blockage problem. Post-experiment washing of the membranes did not reveal the presence of any clots on any of the membranes.

Results

Table 2 shows the results of 18 *in vitro* experiments using four different patterned microchannel membranes. The experiments with the SC, SP-1 and SP-2 were with slaughterhouse blood. The experiments with membrane SP-3 were with drawn blood from Lampire Biologicals. Oxygen was the ventilating gas in these 18 experiments.

Figure 6 shows the oxygen flux in $\text{moles.cm}^{-2}.\text{min}^{-1}$ as a function of residence time for one SC device and three SP devices, all with $15\text{ }\mu\text{m}$ channel heights. Figure 7 shows the same data as an increase in hemoglobin saturation. Each steady state condition was maintained for anywhere from 52 to 190 minutes, and each data point at a given residence time is an average of several uptake readings during that steady state condition. The data shows a consistent flux and saturation change for all four devices. The saturation increases, as expected, with increased residence time. Since the average blood-side pO_2 increases with increased saturation, the average flux decreases with increased residence time.

The pressure drop across both the SP and SC devices was small, about 2 to 4 mmHg. The oxygen uptake was also measured using air as the ventilating gas instead of oxygen. With air, the uptake was $3.4 \pm 0.4 \times 10^{-7} \text{ moles}/(\text{min.cm}^2)$ at a residence time of 0.099 sec, about one third of that with oxygen.

Figures 8a and 8b compare the oxygen flux and the change in the percent saturation for the $15\text{ }\mu\text{m}$ SP and SC devices with those for 40 and $82\text{ }\mu\text{m}$ screen-filled channel devices.¹ The oxygen flux decreases smoothly as a function of residence time and, within experimental uncertainties, is device independent. In contrast, the change in percent saturation, Figure 8b, is dependent on the channel height. The $15\text{ }\mu\text{m}$ SC and SP devices appear to have the same profile and are distinct from both the 40 and $82\text{ }\mu\text{m}$ devices fabricated with wire screens.

Discussion

The microcirculation in the lungs has been modeled^{3,5} as blood flow between parallel plates that are held apart by support posts. The height between the anatomical plates is 5 to $10\text{ }\mu\text{m}$. The present two types of artificial lung devices also have blood flow between parallel plates; in one case, they are straight rectangular microchannels separated by parallel vertical walls, and in the other case, they are wide rectangular microchannels with support posts, similar in structure to the natural lungs. In both types of devices the channel heights are $15\text{ }\mu\text{m}$, which is about twice as high as that in the natural lung. In both the natural lungs and the devices, the blood flow is laminar and parallel to the plates. The gas transport is essentially by transverse diffusion. The oxygen transport into the 5 to $10\text{ }\mu\text{m}$ high blood channels of the natural lungs is from the alveolar space, i.e., one-sided transport through only one of the parallel plates. The oxygen transport into the $15\text{ }\mu\text{m}$ high blood channels in the devices of the present study is also one-sided. Although these devices are shown to be very efficient in oxygen uptake, they could be made even more efficient, perhaps comparable to the natural lungs, by configuring the devices for two-sided transfer as proposed by Lee *et al.*⁶ The measured pressure drops in these tested microchannel devices were small, 2 to 4 mmHg, suggesting that the exchange paths could be longer than the 3 mm used, flow rates could be faster, and/or residence times longer with larger percent saturation increases.

Figure 8a shows consistency in flux between the data of the present study using $15\text{ }\mu\text{m}$ high channels with the data from a previous study¹ using screen-filled 40 and $82\text{ }\mu\text{m}$ high channels. The oxygen transport in the $15\text{ }\mu\text{m}$ channels is, as mentioned, by transverse diffusion. On the other hand, transverse convective mixing due to the presence of the screens overcomes the much greater transport distances in the larger channels and makes them just as efficient, in term of flux, as the very small channels. Figure 8b, on other hand, shows a much greater increase

in saturation in the small channels than in the large channels at a given residence time. The larger channels, of course, contain a larger blood volume and with the same flux would be expected to show a smaller saturation increase.

The decrease in flux with increased residence times is a result of the decreased pO_2 differential from the gas-side to the blood-side as the saturation increases. The observed three-fold decrease in flux using air instead of oxygen, rather than a five-fold decrease that might be expected based on the five-fold decrease in gas-side pO_2 , is also a result of the fact that average blood-side pO_2 remains lower in the experiment using air than when using pure oxygen.

The data of Page *et al.*⁷ show that saturation increase depends on the residence time in microchannels. They show, for instance, that the saturation will increase, for 30% hematocrit blood, from 66% to 98% flowing for 0.15 sec in a 10 μm circular channel. Figure 8b shows a 24% increase in saturation for a 0.20 sec residence time, with one-sided transport, in the 15 μm high rectangular microchannels of the present study, which is somewhat comparable.

Lee *et al.*⁶ use some simple calculations to estimate the required characteristics of several different microchannel configurations for full size artificial lungs. Assuming a 4 L/min blood flow, a limiting pressure drop of 10 mmHg and two-sided transfer, they considered two different cases of wide rectangular channels with support posts: one with 12 μm high channels and the other with 25 μm high channels. The channels were assumed to be 15 mm wide. The former would require 87,000 channels that are one mm long. The overall size of the device, not including any manifolds, would be 252 mL with a blood prime of only 13 mL. The latter would require 40,000 channels that are 3.9 mm long. The overall size, not including any manifolds, would be 453 mL with a blood prime of 50 mL.

A major challenge in developing full size devices with the techniques described in this study, however, is to be able to fabricate devices in which the blood-side channels are homogeneous enough to assure a uniform distribution of the blood flow. Lithographic techniques are shown to be suitable for preparing reproducible, patterned, silicone rubber membranes for microchannel artificial lungs. Techniques for mounting the membranes, however, whether using the gluing method of the present work or some other method, need to be carefully controlled. Perhaps the developed technology from the field of microfluidics could be adapted and the use of glue can be avoided.⁴ Gilbert *et al.*⁸ recently evaluated a microfluidic blood flow device in PDMS with channels that were 100 μm high and 1197 μm wide.

Acknowledgments

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Appendix

The black stripes, walls between channels, are 15 μm higher than the white stripes, the blood channels. The gas exchange takes place along the white area. For each white stripe, the gas exchange area = $0.3 \text{ mm} \times 3 \text{ mm}$ (the blood path is 3 mm long). Since the width of the gas exchange area is 46 mm, there are a total of 92 stripes. Therefore the total exchange area is 0.83 cm^2 . Since the height of the channel is 15 μm , the liquid volume is 0.00124 mL.

Wide rectangular channels with support posts

The gas exchange area of each repeating unit is 0.0021 cm^2 . The number of such units in the area where blood crosses over from inlet to outlet manifold is 552. Thus the total exchange area is 1.16 cm^2 . Since the channel height is 15 μm , the liquid volume is 0.00174 mL.

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Figure 1. Schematics of test devices. (a) Straight, parallel rectangular channels, SC. (b) Wide rectangular channels with support posts, SP.

Figure 2. Optical microscope pictures of the masters for making (a) straight channel membranes and (b) support-post channel membranes.

Figure 3.
Effect of spin speed and spin duration on membrane thickness.

Figure 4a **Figure 4b** **Figure 4c** **Figure 4.**

(a) Top view SEM of a support-post channel membrane, (b) side view SEM of a straight channel membrane showing the height of the side walls, and (c) side view SEM of a support-post channel membrane showing the height of the posts.

Figure 5.
Schematic of polycarbonate support plate for the blood side with inlet and outlet troughs.

Figure 6. Comparison of oxygen flux as a function of residence time for devices SP-1 ($\diamond$) and SP-2 ($\blacksquare$), SP-3 ($\triangle$) and SC ($\otimes$).

Figure 7.
Percent changes in saturation as a function of residence time for devices SP-1 ($\diamond$) and SP-2 ($\blacksquare$), SP-3 ($\triangle$) and SC ($\otimes$).

Figure 8a **Figure 8b** **Figure 8.**

Comparison of (a) oxygen flux and (b) change in percent saturation for devices of different channel height. (◆) 15 μm straight channels, (◇) 15 μm support-post channels, (□) 40 μm screen-filled channels, and (▲) 82 μm screen-filled channels.

Table 1**Procedures for UV-photolithography**

Process Step	Procedure
Coating with HMDS prime	Spin at 500 rpm for 5 s then spin at 4,000 rpm for 45 s.
Coating with AZ P4620 photoresist	Spin at 300 rpm for 4 s then spin at 1,000 rpm for ~ 25 s
Soft bake	At 110°C for 10s with gap between wafer and heater then at 110°C for 4 min with full contact
UV exposure	For 90 s
Develop	For ~ 6 min immersed in AZ 400K developer then rinse with deionized water

Table 2

Experimental data from SP and SC devices with oxygen as the ventilating gas. Suffices a1, b1, etc. denote experiment number. Experiments conducted on the same day with a specific membrane have the designation SP-1-a1, SP-1-a2, etc. Experiments conducted on a different day with that same membrane, after a saline wash, have the designation SP-1-b1, SP-1-b2, etc. The conditions for SP-1-c1 and c2 were identical, so the results were averaged and listed as SP-1-c1.

Experiment (time, min)	Residence time, s	Fractional Saturation		O ₂ Flux Moles min ⁻¹ cm ⁻² *10 ⁷
		Inlet	Outlet	
SP-1-a1 (97)	0.11	0.68±0.002	0.82±0.016	7.18±0.8
SP-1-a2 (90)	0.075	0.69±0.01	0.81±0.021	8.6±1.4
SP-1-a3 (66)	0.062	0.71±0.01	0.79±0.018	7.8±0.9
SP-1-a4 (109)	0.206	0.72±0.016	0.95±0.02	6.5±0.8
SP-1-b1 (78)	0.092	0.66±0.013	0.80±0.017	8.2±0.4
SP-1-b2 (54)	0.053	0.66±0.013	0.75±0.012	9.3±1.9
SP-1-b3 (93)	0.14	0.65±0.007	0.83±0.037	7.1±1.5
SP-1-c1 (148)	0.099	0.67±0.002	0.85±0.029	9.1±1.5
SP-1-c3 (52)	0.099	0.66±0.004	0.84±0.107	9.3±2.1
SP-2-a1 (190)	0.086	0.69±0.02	0.82±0.04	8.1±2.5
SP-2-a2 (108)	0.054	0.67±0.006	0.76±0.02	8.7±2.5
SP-3-a1 (56)	0.059	0.70±0.0007	0.79±0.02	8.3±1.8
SP-3-a2 (89)	0.163	0.70±0.008	0.87±0.03	6.0±0.7
SP-3-b1 (52)	0.052	0.67±0.005	0.77±0.018	10.1±2
SP-3-b2 (59)	0.072	0.67±0.004	0.79±0.011	8.8±0.9
SP-3-b3 (33)	0.052	0.68±0.01	0.78±0.01	10.2±1.5
SC-a1 (75)	0.047	0.68±0.007	0.77±0.024	10.7±2.8
SC-a3 (18)	0.039	0.61±0.008	0.69±0.011	10.7±0.4