Breathing. Empowered.™

Oxygenator Design
Present & Future Challenges

Daniella Yeheskely – Hayon, PhD, MBA
Chief Technology Officer

An overview based on the presentation given within the Technology and Physiology session at the Israeli ECMO conference - Nov 10, 2022.

Introduction – Key Oxygenator Design Considerations

Blood oxygenators are a core component of extracorporeal life support (ECLS) systems, and their design has a significant effect on patient outcomes.

Ideal oxygenator device characteristics should include:

- Efficient gas exchange - to maintain physiological oxygen (O_2) and carbon dioxide (CO_2) levels in the blood
- Compact size
- Minimal priming volume to avoid patient hemodilution
- Minimal contact of blood with foreign materials
- Laminar blood flow path
- Minimal shear stress

The last three characteristics are most crucial to avoid blood trauma which is the main drawback of current ECMO oxygenators.

There are two central factors that should be considered when designing blood oxygenators:

(A) Gas Exchange Matrix

Refers to material characterizations such as the type of material, porosity and required surface area for diffusion. These should be considered based on Fick's first law of diffusion[1] which defines that substance flux is proportional to material properties. According to this law, the rate of diffusion is determined by four criteria: material diffusion coefficient, concentration gradient between two media, surface area, and the thickness of the barrier to diffusion (Equation 1). For instance, a thicker membrane (larger physical barrier) will result in slower diffusion, while the greater the gradient, the faster flux will be.

$$Vgas = \frac{D\ x\ (P1 - P2)\ x\ A}{T}$$

D – Diffusion Coefficient

P – Pressure

A – Surface Area

T – Thickness of the barrier

Equation 1. Fick's 1st Law of Diffusion

(B) Device Structure

Refers to characteristics such as geometry of the device, length of the blood path within the device and type of blood flow path, that should be carefully selected in order to minimize the pressure drop across the membrane. Pressure drop (i.e. the pressure gradient between the inlet and the outlet of the oxygenator), is an important parameter that is found to be a key factor in inducing blood trauma.

1. Fick, A. (1855), Ueber Diffusion. Ann. Phys., 170: 59-86. https://doi.org/10.1002/andp.18551700105

As depicted in Equation 2, the pressure gradient increases as the resistance to blood flow increases. Maintaining minimal pressure drop is crucial to avoid high blood shear stress [2,3] (Equation 3), which is found to be a major factor in activating blood coagulation. It has been shown by numerous research groups [4,5] that high shear stress significantly affects blood components such as Von-Willebrand factor, leukocytes, platelets, and red blood cells [6,7].

$$R = \frac{\Delta P}{Q}$$

ΔP – Pressure Gradient
Q – Flow Rate

Equation 2. Resistance to Flow

$$\tau = \sqrt{\frac{Q \ x \ P \ x \ \mu}{V}}$$

Q – Flow Rate
ΔP – Pressure Gradient
μ - Dynamic Viscosity
T – Priming Volume

Equation 3. Shear Stress Calculation (De-Somer F. er al, 1996)

Commercial Oxygenator Design

(A) Gas Exchange Matrix

Current oxygenators are based on polymethyl pentene (PMP) microporous hollow fibers. While the gas continuously flows inside the hollow fiber ("sweep gas"), the blood flows exterior to it. The gas exchange occurs through the fiber wall when oxygen and carbon dioxide diffuse as a function of the partial pressure gradient (Figure 1).

a. b.

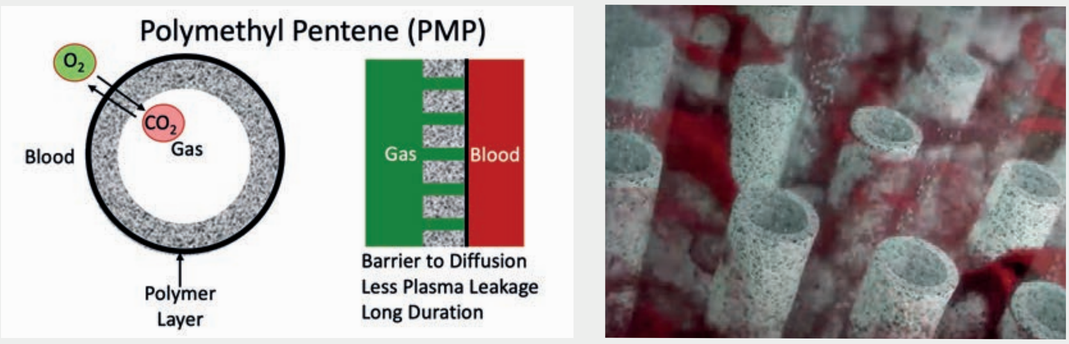

Figure 1. Current oxygenators gas exchange membrane design (a) and blood flow path (b)

Unlike the Polypropylene (PP) microporous hollow fibers, used in oxygenators for short duration during CPB procedures, the PMP fibers are covered with a thin polymeric layer that prevents plasma leakage while enabling gas exchange for prolonged use. The PMP fibers are manufactured mainly by 3M™.

2. De Somer F. et al., (1996), Journal of cardiothoracic and vascular anesthesia vol. 10,7: 884-9. doi:10.1016/s1053-0770(96)80050-4
3. De Somer F. et al., (2013), Perfusion, 28(4) 280–285 DOI: 10.1177/0267659113483803
4. Gu Y.J, et al., (2000)., Artif Organs.;24(1):43-8. doi: 10.1046/j.1525-1594.2000.06351.x. PMID: 10677156
5. Hong J.K. et al., (2020), Biomater. Sci.,8, 5824-5845, https://doi.org/10.1039/D0BM01284J
6. Tsai, Han-Mou, (2012): 163-9. doi:10.1097/MAT.0b013e31824363e7
7. Meyer AD et al., (2020). J Thromb Haemost;18(2):399-410. doi: 10.1111/jth.14661

The limitations of this design are:

- Fiber polymer wall is a barrier to diffusion - large surface area is required.
- PMP polymer is a synthetic foreign material - anti-coagulation coating is required to prevent blood clotting.
- PMP fibers are relatively expensive, and availability is limited by production capacity.

(B) Blood Flow Path

In current oxygenators, blood flows in between PMP fibers in a turbulent, tortuous flow path. This enables a larger surface area for diffusion which is required for efficient gas exchange. However, the turbulent blood flow also leads to multiple collisions of blood components with the fiber wall, high pressure drop and high shear stress. These result in multiple harmful effects on blood components and activation of blood coagulation, inflammation, complement activation, hemolysis and more.

Although all current oxygenators are based on similar material and same turbulent flow path, they slightly differ in their geometry, blood flow length, location of blood inlet and outlet and additional minor design aspects. Available oxygenators are composed from different arrangements of the fiber bundles which can be woven either parallel, perpendicular or with an angle one to each other[8]. Some oxygenators have a circular design while others are square-shaped oxygenators. The main advantage of the square shape is shorter blood flow length which results in reduced pressure drop. A reduced pressure drop may potentially minimize blood shear stress. However, the square structure occasionally causes blood to clot at the square corners of the device, due to uneven blood flow distribution (i.e., blood flows at slower rate in the corners). Newer square-shaped oxygenators address this limitation by blocking the blood flow at the corners. However, this is viewed as a gross waste of surface area within the oxygenator, considering the high cost of the porous fiber hollow tubes.

Thus, the current oxygenator design is not ideal – on one hand it is characterized with efficient gas exchange, compact size, and relatively low priming volumes, but on the other hand, it is extremely harmful to blood components which leads to major adverse effects and fatal patient outcomes[9].

The above limitations, mainly the gas exchange material and the problematic turbulent flow path, encourages several research groups to explore and develop novel designs that can address some of the key pitfalls of current design, potentially resulting in better performance and patient outcome.

8. Nagase K. et al., (2005), Biochemical Engineering Journal 24 105–113, https://doi.org/10.1016/j.bej.2005.02.003
9. The ELSO Red Book, 6th edition section I-6

Novel Technologies

There are several new approaches currently in research and development, none yet reaching maturity to become a real product. Herein are two concepts that have the potential to disrupt the field of blood oxygenators.

(A) Microfluidic Oxygenators

This concept is based on microfluidic fabrication technologies allowing to design a device that closely bio-mimics the human vasculature. Many efforts have been invested over the years to fabricate microfluidic blood-gas exchange systems that are superior to the current oxygenators regarding flow paths, blood gas interfaces, volume and more, potentially resulting in reduced trauma to the blood. [10,11,12] Most microfluidic-based devices are composed from sheets of Polydimethylsiloxane (PDMS, a type of silicone which enables gas diffusion but prevents liquid leakage), having multiple microchannels for blood flow.

The blood flows laminarly, and the gas exchange occurs through the PDMS. The main drawback of this technology is the inadequate hemocompatibility of the design: although this technique prevents turbulent flow, blood tends to clot, probably due to the high resistance to flow through the micron size channels. According to the Hagen-Poiseuille formula for laminar flow, the resistance to flow increases when the channel diameter decreases. Moreover, once a coagulation process is initiated, it rapidly blocks the micron-scale blood channels. Thus, this critical matter needs to be addressed and resolved to advance this technology toward clinical use.

(B) Carbon Nanotube-Based Oxygenator

An attempt has recently been made to develop an oxygenator based on novel material and novel flow design. This concept was invented in 2014 by Prof. Yoram Palti[13]. His invention was based on carbon nanotubes (CNTs), a hexagonal structure of carbon atoms with unique chemical and electrical properties. Currently, CNTs are used mainly in the electronics, automotive and aerospace industries. The high hydrophobicity, which allows liquid to flow on the surface without any friction and with reduced resistance to flow, and the high porosity make a matrix build from vertically aligned carbon nanotubes (VACNT), an ideal material for gas exchange. Flowing blood laminarly through multiple channels in parallel, results in efficient gas exchange between the blood and the gas molecules that can easily diffuse between the carbon nanotube fibers, with minimal pressure drop and reduced shear stress (Figure 2). This innovative technology potentially results in reduced blood trauma.

9. The ELSO Red Book, 6th edition section I-6
10. Kniazeva, A.A. et al., (2012), Lab Chip, 2012, 12, 1686 DOI: 10.1039/C2LC21156D
11. Potkay J.A. et al., (2011), Lab Chip,11, 2901-2909, https://doi.org/10.1039/C1LC20020H
12. Thompson A.J. et al., (2017), Biomicrofluidics 11, 024113; https://doi.org/10.1063/1.4979676
13. https://patents.google.com/patent/US20150360182A1

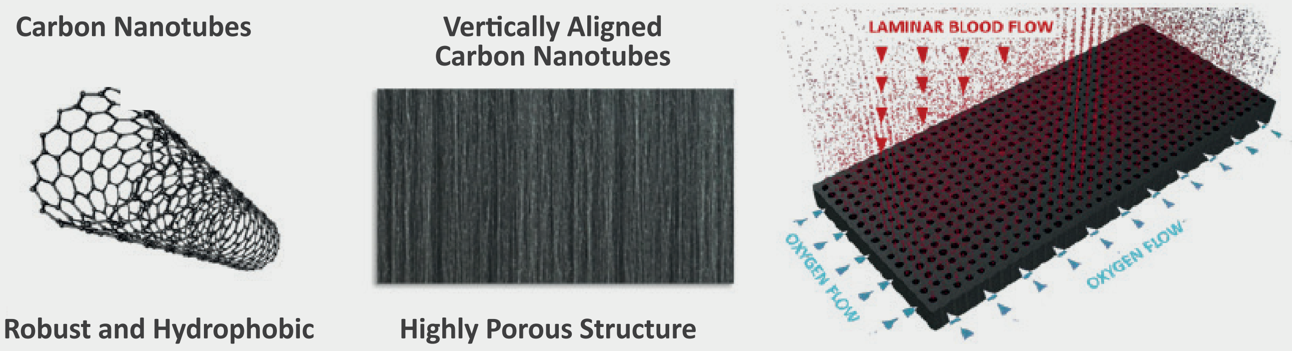

Figure 2. Pictures were taken with permission from Prof. Yoram Palti

The main challenges of the above design are the manufacturing process and the associated costs of the structure, as well as the burdensome regulatory pathway.

Conclusion

The blood oxygenator is a critical component that plays a central role in ECMO systems and has a significant effect on ECMO procedures efficacy and safety. Even though ECMO has become a more widespread procedure for numerous conditions, it is important to understand the limitation of commercially available products and the requirements for better future products.

Clearly, advanced new technologies will encourage the expansion of current ECMO indications and may pave the way for new ones.

While recent research has demonstrated some innovative and potentially clinically effective designs, the barrier to entry for new extracorporeal oxygenator technologies remains extremely high. The substantial financial investment required to develop and obtain market clearance for a new technology makes innovation in this field a difficult milestone to achieve.

Only highly audacious entrepreneurs who are driven by the need to innovate and improve medical care will be able to succeed in bridging the gap and deliver such technological advancement.

MRK-ARS-046 Date of preparation: December 2022