Air Powered Artificial Lungs and other High Efficiency Fluid Reactor Innovations

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ABSTRACT

Commercially available Hollow Fiber (HF) based Extracorporeal Membrane Oxygenators (ECMO) are presently being built using a parallel assembly of over 10-20K of porous hollow polymeric fibers as respective reactor core elements (RCE). They are currently being used during cardiopulmonary bypass or cardioplegic surgery to provide the function of a lung. The external blood circuit is driven by a blood pump while using pure O_2 as the sweep gas. We have analyzed ECMO designs for both pure O_2 and Air sweep gas operation and found that the novel ECMO designs incorporating c-VACNT™ - RCE's have the potential to reach the goal of building ECMO devices that could eventually operate at a similar performance level as conventional HF based devices, but use Air instead of pure O_2 as the sweep gas. We have also developed a non-destructive test system that allows optimization of various designs and evaluation of their potential for EMCO usage.

Keywords: ECMO, artificial lung, c-VACNT™, air powered artificial lung, fluid reactor

1 BLOOD GAS TRANSFER

Blood has two primary components that absorb and release O_2: hemoglobin molecules that chemically bind O_2 and blood plasma which dissolves O_2 according to Henry's law of chemistry. Equation (1) shows the dependence of the total amount of O_2 stored in blood C_bO_2 (mL/100mL = vol %) on the partial pressure P_bO_2 (*mmHg*) of O_2 dissolved in plasma, its active hemoglobin content *Hgb* (*g/dL)* and the O_2 saturation level S_bO_2 (%) of the blood which is the sum of the O_2 stored in the plasma and in hemoglobin.

$$C_bO_2 = \left(\frac{0.003\ mL}{mmHg*dL} * P_bO_2\right)+\left(1.392\ \frac{mL\ O_2}{g\ Hgb} * Hgb * S_bO_2\right) \qquad (1)$$

For standard blood conditions, S_bO_2 can be expressed[3] as a function of P_bO_2 as shown in equation (2)

$$S_bO_2 = \frac{1}{1+\frac{23{,}400}{150 * P_aO_2 + {P_aO_2}^3}} \qquad (2)$$

For an average adult human at rest, the heart delivers *5 L/min* of venous blood with a venous oxygen saturation level S_vO_2 *= 75%* and $pCO_2 \approx 46\ mmHg$ to a lung which then converts it to an arterial blood having an O_2 saturation level $SaO_2 > 95\%$ and a $pCO_2 \approx 40\ mmHg$ utilizing *6 L/min* of Air as breathing gas. Using equation (1) for a typical value of *Hgb = 14 g/dL* for an average adult we calculate that the human lung transfers ≈200 sccm of O_2 into the blood thus acting as a fluid reactor transforming venous blood (primary input fluid) into arterial blood (primary output fluid) while utilizing air as sweep gas. Using equation (2), we find that this corresponds to a change from a starting value $P_vO_2 = 40mmHg$ to an end value $P_aO_2 = 75.6\ mmHg$. CO_2 is getting exported from a body primarily through its lung at a similar gas transfer rate.

2 ECMO PARAMETER TRADEOFFS

During cardiopulmonary bypass surgery and/or cardioplegic surgery the heart in a human body is stopped, and an ECMO device in combination with a heart-lung machine is used to provide the necessary blood oxygenation and CO_2 removal. This gas exchange occurs while blood continues to recirculate through the body driven by a blood pump.

A usable ECMO device, therefore, needs to function as a disposable 4-port fluid reactor having at a minimum (i) a liquid-tight and blood compatible primary flow path for continuous blood (primary fluid) transport through it, (ii) a secondary gas tight flow path delivering a sweep gas (secondary fluid) for delivery of O_2 to blood and for removing CO_2 from the blood and exhausting it from the device, and (iii) gas permeable membrane with a sufficiently large total surface area S_M that isolates the blood flow path from the flow path of the sweep gas and that allows sufficient O_2 and CO_2 transfer with minimum cross-talk for the needed blood flow rate. The ISO 7199 test standard, utilizing bovine blood as a human blood substitute, is often used to evaluate and characterize the performance of a given ECMO device under application relevant test conditions and for a 510K submission.

ECMOs typically have a maximum recommended use time because plasma leaks through the membrane surface over time deteriorating the gas transfer rate. Additionally, ECMOs need to be designed so that gas bubble formation or blood vessel clogging downstream of the device does not cause formation of micro embolism in small blood vessels (i.e. the brain). These micro embolisms can kill neighboring tissue by preventing sufficient O_2 delivery and can lead to a reduction of quality of life after a surgical procedure. Arterial filters with *40 μm* pore size are therefore typically part of a heart-lung circuitry to minimize the occurrence of such incidences.

To start the blood flow circuitry of a respective heart-lung machine with an in-line connected ECMO device, blood

from the patient needs to be withdrawn which dilutes the blood's *Hgb* level, and lowers the blood's O_2 carrying capacity. To maintain the *Hgb* concentration donor blood has to be added which can lead to follow-on complications. It is therefore desirable that the blood volume needed for priming be minimized. This is one reason that smaller ECMOs with less priming volume are used for pediatric patients since they are more sensitive to Hgb dilution.

When blood components come i) in contact with external non-biological surfaces, ii) get exposed to high-pressure regions, (iii) or turbulent flows zone 1) red blood cells can get "stressed" and rupture releasing hemoglobin into the plasma, 2) platelets can get activate, and white blood cells can die. To minimize a potential coagulation reaction anticoagulants like Heparin are typically being added to the blood and their level monitored and maintained. When hemoglobin gets released into the plasma, it can no longer provide the O_2 carrying function, and it can also trigger other body response reactions and complications during and/or even after such a surgery. Minimizing the donor blood transfusion quantity and anticoagulant in the bloodstream will reduce platelet activation and blood cell rupture. Different EMCO manufacturers offer their devices with the option of one or more biocompatible coatings to make the blood exposed surfaces more biocompatible, i.e., to decrease the number of white and red blood cell ruptures compared to that of uncoated devices. ISO 7199 provides a normalized hemolysis index (grams of plasma-free hemoglobin after pumping through a circuit *100 L* of blood) quantitatively comparing the red cell rupture rate of different test ECMOs.

It is desirable to design ECMO devices in such a manner that the pressure drop across them is very low, turbulence in the blood flow path is minimum, and tortuous paths and dead ends avoid as much as possible.

When ECMOs are compared, they are typically rated (besides cost and functionality) in relationship to their (1) flow rate, (2) priming volume, (3) O_2 and CO_2 transfer rate (4) hemolysis index, (5) gas bubble formation rate and (6) the time dependence of these performance over time.

3 HF BASED ECMOS

In an HF-based ECMO device, the blood flows normally around the HFs in a tortuous way through cross-woven sub-bundles. To get the surface area needed to achieve a sufficient gas transfer rate of 400 sccm of O2 at 7 L/min of blood blow the blood contact surface area typically has to be on the order of several m^2. Given the size of these fibers and their *≈50%* packing density the priming volume amounts to about *250 sccm* and a pressure drop of *250 mmHg* for adults use.

4 C-VACNT™ BASED ECMOS

c-VACNT™ based Reactor Core Elements (RCEs) have been discussed elsewhere [1,2] and are a nano-carbon based, open-porous cellular network material having a bicontinuous phase structure that encloses the perforated fluid channels and provides a membrane functionality for gas transfer and blood confined to the flow channels. Figure 1 shows a high-resolution image of such a device, with a very high-density blood flow channel arrangement, having an ultra-straight and short *(≈2mm)* flow paths. These characteristics can result in a pressure drop on the order of tens of mmHg and have the potential to significantly reduce the hemolysis. The high-density fluid channel arrangement enables > 10X surface area/volume gains over HF allowing to significantly reduce the priming volume of a respective ECMO [2].

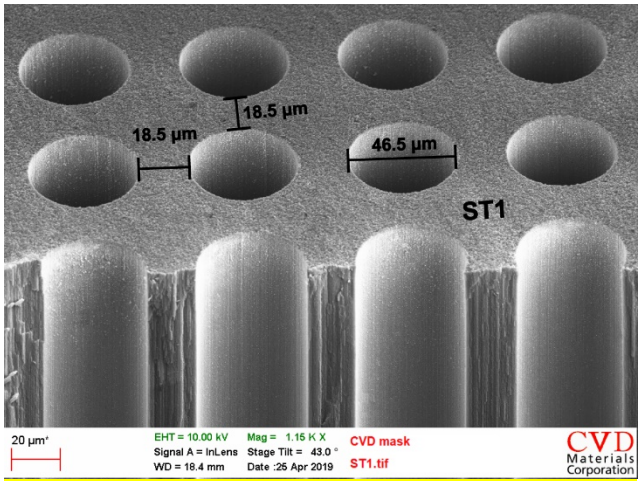

Figure 1: c-VACNT™-RCEs with non-tortuous flow path

These RCEs can be connected together in a sealed and parallel manner with a priming volume of 40 mL for a targeted *5-7 L/min* ECMO device and a potential for a 250 mL priming volume with a pressure drop <100 mmHg for a 7-9 times larger membrane surface area.

5 AIR AS SWEEP GAS FOR ECMO

The function of an artificial lung, like the temporary ECMOs device, is to transform the venous blood into arterial blood. Let us choose a test ECMO device having a maximum O_2 transfer rate of $T_{O2} = 400\ sccm$ for a pure O_2 sweep gas under ISO 7199 test conditions and analyze how the same device may perform under other test conditions utilizing equation (1) and (2) as an aid.

Table 1: shows a summary comparison for different key parameters for the same ECMO device when it uses either Air or O_2 as a sweep gas/blood flow ratio $F_s/F_b = 2/1$ for both the case of standard human and for bovine blood (ISO 7199 test condition).

Since neither have any significant CO_2 concentration to speak of, and both blood conditions have the same CO_2 gradient across the membrane, neither selection has any influence on the respective CO_2 gas transfer rate T_{CO2}. Therefore we have only to consider the consequences on the O_2 transfer rate T_{O2}. The rate of gas diffusion, i.e., gas flow

transfer rate *T*, through a membrane is governed by Fick's law.

$$T = -1 * P * SA * \frac{dC}{dx} \quad (3)$$

In equation (3) *P* representing a given membranes permeability parameter, *SA* represents its active Surface Area, and dC/dx represents the concentration gradient of the diffusing species, in our case, O_2 molecules. The minus sign assures that the flow is from the higher to the lower concentration. In the case of the c-VACNT™-RCEs the driving force for O_2 transfer is the difference between the partial pressure of O_2 in the sweep gas and average partial pressure of the venus and arterial side of the blood, i.e. $dC \sim (P_SO_2 - (P_vO_2 + P_aO_2)/2)$. This parameter can then be used as a scaling factor to predict the O_2 transfer performance for the same ECMO device under the same test condition, but with Air as sweep gas, as shown in Table 1.

	Standard blood		*ISO 7199*	
Hgb	*12 g/dL*		*12 g/dL*	
Sweep gas	O_2	*Air*	O_2	*Air*
Fs	*14 L/min*		*14 L/min*	
F_iO_2	*100 %*	*20.9%*	*100 %*	*20.9%*
P_sO_2	*760 mmHg*	*159 mmHg*	*760 mmHg*	*159 mmHg*
T_{CO2}	*same*		*same*	
S_vO_2	*75%*		*65%*	
P_vO_2	*40 mmHg*		*34 mmHg*	
F_b	*7 L/min*		*7 L/min*	
P_aO_2	*125 mmHg*	*53.4 mmHg*	*125 mmHg*	*51.1 mmHg*
S_aO_2	*99%*	*87%*	*99%*	*86%*
dC	*678*	*76.3*	*681*	*79.3*
T_{O2}	*337 sccm*	*37.9 sccm*	*400 sccm*	*46.7 sccm*
ratio	*8.9*		*8.6*	

Table 1: ECMO performance comparison: Air versus O_2 as sweep gas for standard blood and ISO 7199 type blood

Table 1 shows that if the same ECMO unit is used with Air as a sweep gas instead of O_2 about a 9x lower TO_2 value is predicted (ratio) and at the same time insufficiently oxygenated arterial blood is delivered. To overcome this problem ~ 9 ECMOs of the same type have to be connected in parallel to get the targeted O_2 transfer rate back $T_{O2} = 400$ *sccm* and $S_aO_2 > 95\%$ back. This solution, however, increases the priming volume of the total ECMO device group by over *9X* and increases the hemolysis rate (less than *9X* since a slower flow will result in a lower pressure drop and a less turbulent flow pattern which will help reduce the hemolysis index). This is the main reason that all ECMO systems based on HF technology are restricted to 100% O_2 as the sweep gas.

However, with the significant lower priming volume, pressure drop and lower hemolysis index potential for ECMOs design based on the above and elsewhere [3] discussed c-VACNT™ - RCE's and related fluid reactor technology platform [2], fully optimized ECMO devices having a similar priming volume, without a higher total pressure drop and hemolysis index than conventional O_2 powered HF based ECMOs, might become a reality.

To aid in the verification of this design potential and to help find the optimum design solutions a novel test setup [4] was developed.

6 ECMO TESTING SETUP

The standard ECMO test conditions are defined by the ISO 7199 test protocol utilize bovine blood to measure the O_2 and CO_2 gas transfer rate of an ECMO test device at a bovine blood flow rate F_b=7 L/min, a venous blood O_2 saturation of S_vO_2 = 65%, a hemoglobin concentration of Hgb = 12 g/dL, a base *0 mmol/L (= 24 mmol/L* HCO_3*-)*, and a partial CO_2 pressure $pCO_2 = 45$ *mmHg*. Most ECMO manufacturers specify the maximum O_2 and CO_2 transfer rate of their ECMO model at a sweep gas flow rate F_S with $F_S/F_b = 2:1$, i.e., $F_S = 2*F_b = 14$ *L/min* while using pure O_2 as sweep gas of $(F_iO_2 = 100\%)$.

The ISO 7199 is destructive since blood cannot be 100% removed from the interior of a test ECMO device. Therefore we developed an alternative test method [4] that uses an inert test liquid and an appropriate sweep gas to be able to measure respective gas transfer rates in a non-destructive and non-contaminating way, thereby enabling to retest an ECMO device multiple times without compromising its final use performance.

By combining equation (1) and (2), the total O_2 content of blood at normal blood conditions (37°C, base = 0 mmol/L, pH = 7.4) becomes the only function of the values of P_bO_2 and Hgb. By applying the ISO 7199 test conditions to equation (1) and (2), we find that the venus side of the blood has a $P_vO_2 = 34$ *mm Hg* instead of $P_vO_2 = 40$ *mm Hg* for the standard human blood condition. If we further use water as the inert test fluid, then we can use an in-line sensor for measuring the dissolved O_2 concentration in water. This allows us to verify the before and after dissolved O_2 concentration change for a given ECMO testing device under a chosen set of flow test conditions of F_S and F_b for a chosen test sweep gas 1. From these test results, later the respective blood oxygenation or CO_2 removal rate for blood under either ISO 7199 or human standard blood conditions can be calculated, as discussed further below.

Figure 2 shows the new gas transfer rate test setup [4] in a simplified way and with a computerized data acquisition system to record in a time-dependent manner the device gas transfer rate over time and for different programmable test conditions. A pump (preferentially a centrifugal pump, for example, a blood pump) withdraws a test liquid from a

reservoir and provides pressure to a liquid flow controller that delivers it through an inline particle filter at a targeted flow rate to the test ECMO device. The test fluid that exits the device (primary output fluid) is then piped to an inline flow cell with an optical dissolved O_2 probe (DO probe) that measures the amount of O_2 (mg/L or % saturation) dissolved in the liquid.

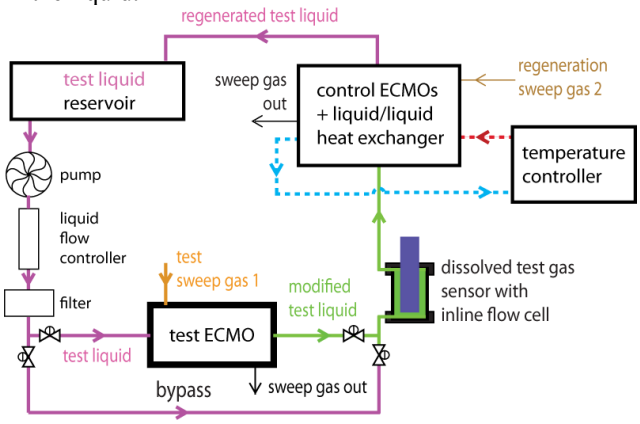

Figure 2: Non-destructive test setup for ECMO devices

The output of this flow cell is connected to a subsystem that has one or more control ECMOs (HF based) having in combination at least 2X the maximum flow capacity rating as the test ECMO device. Three-way valves allow bypassing the test cell for measuring the dissolved O_2 concentration in the test liquid. A liquid to liquid inline heat exchanger is also used in combination with a temperature controller to adjust the temperature of the liquid passing through it. This heat exchanger is either built into at least one of the control ECMO devices or connected in-line to them. By flowing a suitable sweep gas 2 at the correct flow rate and gas composition into the control ECMO device(s) with excess gas transfer capacity, the O_2 concentration of the outgoing test liquid can be transformed back into a test liquid with a targeted DO level before it gets delivered to the test liquid reservoir. By using an automated test system and a gas-tight liquid path the bypass mode allows to create different test liquids (with different DO value) on-demand and in a short time (after a few reservoir volume exchanges). If multiple dissolved gas sensors are used inline and gas mixing systems are used to generate the appropriate sweep gas 1 and gas 2 compositions, then an even wider variety of test liquids can be created. These test liquids could be used for a wide range of gas transfer tests for a given ECMO device at various flowrate F_b and F_S as well as gas 1 and gas 2 concentration conditions. With this system, an ECMO device can now be tested for its O_2 gas transfer rate for both pure O_2 and pure Air as sweep gas 1.

The ISO 7199 $P_vO_2 = 34\ mm$ can be established with this setup. For example, by using a sweep gas 2 mixture of Air/N_2 = 1/3.67, i.e. controlling two mass flow controllers at the right ratio and at sufficient high total gas flow rate to drive the modified test liquid to starting test liquid conditions. If the heat exchanger is set to the same temperature setting, i.e. 37° C no temperature compensation effect has to be taken into account. For example, if the outgoing DO test device measures a 76% DO value this means (Henry's law) that $P_aO_2 = 76\ mmHg$. From equation (2) we then derive that this would correspond to an equivalent blood O_2 saturation level of $SaO2 = 95\%$. Assuming that this test was done with a blood flow rate of $F_b = 7\ L/min$ we can then derive from equation (1) a corresponding O_2 gas transfer rate T_{O2} under the ISO 7199 test conditions of $T_{O2} = 332\ sccm$.

With the right knowledge of the material properties, temperature dependent diffusion coefficients, and gas composition and the use of the Graham's law one can use this test method to also calculate the equivalent transfer rates for other gases as well. An example of this would be calculating transfer rates for CO_2 while meassuring DO concentrations with 100% N_2 as sweep test gas 1. In a similar way, as discussed above, CO_2 transfer rates can be derived directly or indirectly with an appropiate test system configuration. A related detailed analysis is beyond the scope of this paper.

7 SUMMARY

We have analyzed ECMO designs for both pure O_2 and Air sweep gas operation and found that the novel ECMO designs incorporating c-VACNT™ - RCE's have the potential to reach the goal of building ECMO devices that could eventually operate at a similar performance level as conventional HF based devices, but use Air instead of pure O_2 as the sweep gas. We have also developed a non-destructive test system that allows optimization of various designs and evaluation of their potential for EMCO usage.

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