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Is condensation the cause of plasma leakage in microporous hollow fiber membrane oxygenators

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Abstract

Extracorporeal membrane oxygenators are comprised of large bundles of microporous hollow fiber membranes (HFMs) across which oxygen and carbon dioxide are transferred to and from blood. Long term use of extracorporeal oxygenators is limited by plasma leakage through the pores of the HFM walls, requiring replacement of the oxygenator. Condensation of water vapor on the pore walls is thought to be a possible precursor to plasma leakage. To explore this mechanism, a simple theoretical analysis is used to examine the temperature of the gas flow through the HFMs. For conditions representative of two commercially available oxygenators, the analysis predicts that the gas heats up to the temperature of blood flow outside of the fibers after passing through less than 0.5% of the fiber lengths. Once the gas temperature and hence the fiber wall temperature equilibrates with the blood, condensation of water vapor is no longer possible. In vitro testing of microporous HFMs under gas flow rates and temperature conditions similar to those of extracorporeal oxygenators but with the fibers submerged in water is also presented. The fibers showed negligible degradation in carbon dioxide transfer over a four-day period. These results of both the theoretical and experimental analyses indicate that the condensation of water vapor within the pores of the HFMs is unlikely to be the cause of plasma leakage in clinically used extracorporeal oxygenators.

Keywords: Microporous fiber membranes; Artificial lung; Gas permeability; Plasma leakage

1. Introduction

The primary mode of failure for hollow fiber membrane (HFM) oxygenators used clinically for extracorporeal membrane oxygenation (ECMO) continues to be plasma leakage through the pores of the membrane walls and subsequent decay of gas exchange. Modern blood oxygenators utilize ultrathin microporous-walled HFMs made of hydrophobic materials which repel blood away from the pores resulting in high gas exchange permeability across the gas-filled membrane wall. After extended exposure to blood, however, the hydrophobic barrier breaks down and plasma passes through. With the exception of the Medtronics Maxima Plus PRF oxygenator, the time frame for plasma leakage is approximately 4–12 h. The Maxima Plus PRF oxygenator is constructed with

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fibers having a smaller pore diameter and has been shown to extend oxygenator performance for periods of 2 to as long as 18 days (patient dependent) before the onset of plasma leakage [1]. Nevertheless, the ultimate onset of plasma leakage and the consequent requirement to replace the device continues to be an impediment to the success of extracorporeal oxygenation as a method of treatment for acute or chronic respiratory distress.

Very little investigation has been reported on the mechanisms responsible for this phenomenon. Montoya et al. [2] hypothesized that adsorption of bipolar phospholipid molecules onto the surface of the fibers results in a hydrophilic interface allowing for wetting of the pores. Using both in vitro and ex vivo models, they demonstrated the dependence of plasma leakage on the phospholipid concentrations of the blood perfusing the oxygenators. Along a different line, Mottaghy et al. [3] postulated that because the entrance temperature of oxygenator sweep gas is typically lower than blood temperature, condensation of vapor within the pores might ultimately result in plasma leakage. Using a thermo-regulated box to house the entire oxygenator/gas flow system so that gas flow entered the fiber at the same temperature as the blood inside, they supported four sheep for five days using a Medtronics Maxima (Carmeda coated, but not a Plus PRF model) with no evidence of plasma leakage.

This paper specifically focuses on the potential role of condensation in plasma leakage through the pores of HFMs. Using basic heat transfer theory, we examined the temperature of the sweep gas at standard oxygenator flow velocities as a function of distance along the fibers. Condensation of water vapor transferred through the pores can only occur if the temperature of the pore walls is lower than the blood temperature. Once the gas temperature within the fibers, and hence the pore wall temperature, equilibrates with the blood, condensation of water vapor on the pore walls is no longer possible. We show that the temperature of gas entering at room temperature equilibrates with blood temperature within 0.4% of fiber length for worst case conditions, indicating that condensation is unlikely the mechanism responsible for plasma leakage. To further test this result, an in vitro system was used to experimentally evaluate the wetting of microporous HFMs in water heated to 37°C. For sweep gas entering at room temperature at flow rates per fiber equivalent to those of commercial oxygenators, no degradation in fiber gas transfer was observed over a four-day period.

2. Theoretical analysis of gas flow temperature

The temperature of the gas flow within the fibers is dependent on the rate of heat flux from the blood phase across the membrane wall into the gas phase. Heat flux is driven by the difference in the temperature of the blood and that of the gas phase within the fiber, and is inversely proportional to the overall resistance to heat transfer between the two phases. The overall resistance to heat flux consists of the serial resistances of the blood phase, the fiber wall, and the gas phase. In the blood phase heat is first transferred from the bulk flow across the thermal boundary layer to the fiber wall, and is governed by the convective heat transfer coefficient, h_b. Heat flux across the membrane wall occurs predominantly by conduction in parallel across the gas-filled pores and the membrane material. Convective heat transfer through the pores via water vapor is negligible and is thus ignored. Because its effect would result in more rapid heating of the gas flow, neglecting this component serves to make the results more conservative. The overall thermal conductivity of the membrane wall, k_m, is thus a function of the individual conductivities of the gas and membrane material, and of the wall porosity, ϵ, and is determined from the relation [4]:

$$k_m = \epsilon k_{gas} + (1 - \epsilon) k_{solid}. \tag{1}$$

Finally, in the gas phase, heat transfer from the inside fiber wall to the bulk gas phase occurs across the gas side thermal boundary layer in proportion to the heat transfer coefficient, h_g. For a cylindrical tube, the overall resistance to heat flow across the membrane wall per unit length can thus be represented by the equation,

$$R_T = \frac{1}{2\pi}\left(\frac{1}{r_o h_b} + \frac{\ln(r_o/r_i)}{k_m} + \frac{1}{r_i h_g}\right), \tag{2}$$

where r_o is the outside fiber radius and r_i the inside fiber radius [5].

As examples, the specifications and corresponding heat transfer resistances of two commercially available oxygenators, the Maxima Plus (precursor to

Table 1
Commercial oxygenator specifications and heat transfer characteristics

	Fiber specifications				Heat flux resistances $(W/m\ K)^{-1}$		
	ID/OD (microns)	Approx. length (cm)	Porosity (%)	Gas flow/fiber (ml/min)	Blood $(1/r_o h_b)$	Wall $(\ln(r_o/r_i)/k_m)$	Gas $(1/r_i h_g)$
Maxima Plus	240/300	55	40	1.1–3.2	4–23	2.0	21.0
Optima	280/380	13	45	0.4–1.8	3–14	2.9	21.0

Maxima Plus PRF, Medtronics, Anaheim, CA) and the Optima (Cobe Cardiovascular, Colorado) are evaluated. Table 1 summarizes the pertinent parameters and resulting components of the total heat flux resistance across the membrane. The blood side component to the resistance, $1/r_o h_b$, is given over a range of applicable oxygenator blood flow rates. The heat transfer coefficient, h_b, is approximated from correlations developed by Wickramasinghe et al. [6], to describe mass transfer for the case of commercial HFM modules with blood flow outside and perpendicular to the fiber. Assuming applicability of similarity rules between heat and mass transfer correlations [5], $Nu \equiv h_b d_o/k = (0.12) Re^{1.0} Pr^{0.33}$ for Reynolds numbers less than 2.5, and $Nu = (0.15) Re^{0.8} Pr^{0.33}$ for Reynolds numbers greater than 2.5, where Nu is the Nusselt number, k the thermal conductivity, d_o the fiber outer diameter, Pr the Prandtl number, and Re is the Reynolds number. For the case of commercial oxygenators, the Reynolds number is determined from the relation, $Re = Q_b d_o/\phi A_f \nu$, where Q_b is the rated blood flow, ϕ the void fraction, A_f the frontal area of the flow path, and ν is the kinematic viscosity [7]. The membrane wall resistances are calculated using the thermal conductivity of polypropylene, k_{solid} (from which the HFMs of both devices are constructed), which is approximately 0.17 W/m/K [8]. The gas side heat resistance component, $1/r_i h_g$, is approximated from the Nusselt number for fully developed laminar flow in a tube with constant wall temperature, $Nu = 3.66$ (a reasonable approximation when the gas side heat transfer resistance is dominant), where $Nu = h_g d_i/k_{gas}$, d_i is the inside fiber diameter, and the gas is assumed to be air.

In both cases, despite slightly differing wall thicknesses and porosities, both the wall heat flux resistance component (assuming the pores to be filled with air having a thermal conductivity of 0.026 W/m/K), and for higher flow rates the blood side heat flux resistance, are an order of magnitude less than that of the gas side boundary layer resistance. Ignoring the blood and wall resistances, the problem of solving for the gas phase temperature is reduced to the Graetz problem (laminar, incompressible fully developed flow in a tube with constant wall temperature) for which the mean temperature solution is well known. Neglecting all but the first term of the series solution, the mean gas phase temperature equilibrates to the blood temperature exponentially as,[2]

$$T_{mean}(z) = T_{blood} - 8\frac{G_0}{\lambda_0^2}(T_{blood} - T_{room}) e^{-\lambda_0^2 z/r_i Re Pr_{gas}}, \quad (3)$$

where $\lambda_0 (=2.704)$ and $G_0 (=0.749)$ are the first eigenvalue and eigenfunction of the full series solution, Re the Reynolds number for gas flow through the fiber, and Pr is the Prandtl number of the gas [9]. The distance from the fiber entrance to where the gas temperature equilibrates with the blood temperature can thus be estimated from Eq. (3). Assuming the blood temperature to be 37°C and the gas to be air entering at 25°C, the temperature of the gas flow through the Maxima equilibrates to within 99.99% of blood temperature after only 1.6 mm, or 0.3% of the fiber length (see Fig. 1), for maximum rated flow conditions (at slower gas flows, the gas temperature equilibrates more quickly), and through the Optima, after only 0.9 mm, or 0.7% of the fiber length, for maximum rated flow conditions.

Even if the blood side or membrane wall heat flux resistances were significantly greater than the gas side resistance, the gas flow temperature would still equilibrate quickly with the blood temperature. In the case of dominant blood side and membrane wall resist-

[2]The actual solution is a series of decaying based on the system eignevalues and eignefunctions. However, after the immediate entrance region, or approximately 1/10 of the distance to the point of equilibration, all terms but the first become negligible.

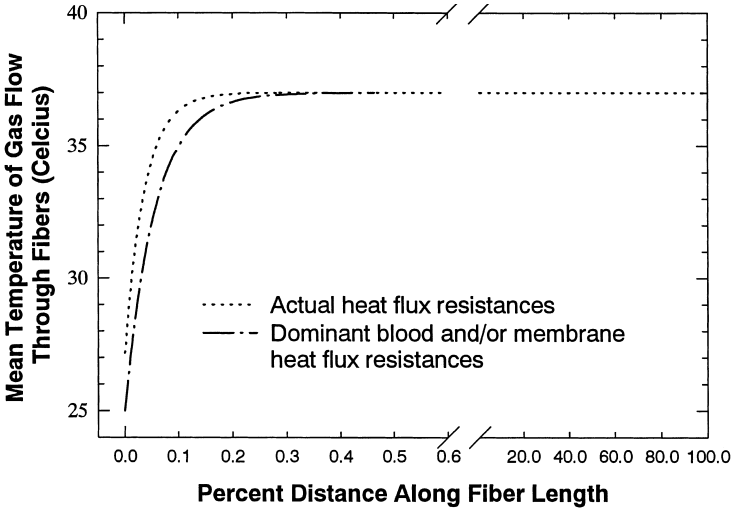

Fig. 1. Mean temperature of gas entering fibers at 25°C as a function of distance along fiber length. Gas flow velocities and fiber dimensions are based on those of the Medtronic Maxima Plus at maximum rated gas flow conditions.

ances, the radial temperature gradient will be essentially constant across the gas phase, simplifying the analytical model. The governing equation can be derived from an energy balance across the gas phase of a differential section of fiber, dz. For steady state flow of an ideal gas through the fibers, the rate of change of enthalpy across the differential fiber length will equal the rate of heat flow across the wall, or

$$\dot{m}c_p\frac{\mathrm{d}T}{\mathrm{d}z} = 2\pi\left(\frac{1}{r_o h_b} + \frac{\ln(r_o/r_i)}{k_m}\right)^{-1}(T_{blood} - T(z)). \tag{4}$$

Rearranging terms yields the following first order differential equation:

$$\frac{\mathrm{d}T}{\mathrm{d}z} + \frac{1}{\mathsf{R}}(T(z) - T_{blood}) = 0, \quad T(z=0) = T_{room}, \tag{5}$$

where

$$\mathsf{R} = \frac{\rho V c_p r_i^2}{2}\left(\frac{1}{r_o h_b} + \frac{\ln(r_o/r_i)}{k_m}\right)$$

for which the solution is

$$T(z) = T_{blood} - (T_{blood} - T_{room})\mathrm{e}^{-z/\mathsf{R}}. \tag{6}$$

If for instance the wall resistance were 100 times greater than normal, i.e. $\ln(r_o/r_i)/k_m \approx 200$, such that the gas side boundary layer resistance was negligible, using Eq. (6) reveals that for Maxima specifications and maximal gas flow conditions, the gas temperature entering at 25°C would equilibrate to blood temperature after 2.5 mm, only 0.5% of total fiber length (Fig. 1).

3. Experimental investigation

We used an in vitro apparatus, designed and reported in a previous publication [10], which measures the gas permeability of HFMs in a gas–liquid environment to further evaluate the role of condensation in fiber wetting. Approximately 100 Mitsubishi KPF 190 microporous polypropylene HFMs, 10 cm in length and having a porosity of 45%, an ID of 200 microns and an OD of 244 microns, were manifolded in a parallel arrangement to gas flow channels and submerged in a 300 cm^3 chamber filled with distilled water. The water was maintained at 37°C and stirred at 1300 rpm using a pitched blade impeller to reduce the resistance to gas transfer across the liquid side concentration boundary layer. Gas flow through the fibers was maintained at 100 ml/min, or 1 ml/min/fiber, so as to achieve a fiber gas flow rate relevant to commercial oxygenators. The gas flow entered the fiber bank at room temperature. Water vapor flux, which condenses within the fiber exit manifold due to cooling, was collected in a moisture trap submerged in ice.

The system permeability to carbon dioxide was measured by initially saturating the water with 100% CO_2, then switching the gas flow to 100% nitrogen. After switching to nitrogen, the concentration of CO_2 exiting the fibers was measured with a mass spectrometer and recorded to a computer with an A/D board. The rate of washout of CO_2 from the liquid volume determines the overall system permeability to CO_2, K (mass flow rate of the gas from the bulk liquid phase to the bulk gas phase per unit area per unit partial pressure difference), which in turn is related to the membrane permeability, K_m, and the liquid concentration boundary layer permeability, K_L, by the equation [10]:

$$\frac{1}{K} = \frac{1}{K_m} + \frac{1}{K_L}. \quad (7)$$

This equation simply states that the resistance to gas flux from the liquid into the fibers, $1/K$, is based on the serial resistances of the membrane and the liquid boundary layer.

The potential effect of condensation was evaluated by measuring the system permeability over a four-day period at a constant gas flow rate, water stir rate, and water temperature. The permeability of the KPF 190 fibers in water has been previously estimated to be 4.7×10^{-4} ml/s/cm^2/cm Hg [11], and that for the liquid boundary layer to be 3.2×10^{-4} ml/s/cm^2/cm Hg at a spin rate of 1300 rpms. Thus any changes in membrane permeability caused by condensation of water vapor in the pores would be mirrored by a corresponding measurable change in the overall system permeability, K (e.g. a 30% decrease in K_m corresponds to a 15% decrease in K for constant K_L), with a greater percent change in K as percent change in K_m increases.

Clinically, plasma leakage though the walls of fibers similar in construction to the Mitsubishi KPF 190s is observed within several hours after exposure to blood [12]. Furthermore, filling of the pores with fluid would result in a decrease in membrane permeability of two orders of magnitude, or approximately 98% [10]. This would correspond to a 98% decrease in the measured system permeability as per Eq. (7). Fig. 2 shows a plot of the system permeability to carbon dioxide as a function of time measured during the in vitro experiment described above. The results exhibited a negligible decrease in system permeability after the first three days. During the fourth day the average permeability decreased by a very small but statistically significant amount of approximately 7% compared to the average of the first day. If real, the length of time required to see this decrease, as well as its small size, makes it unlikely to have been the result of vapor condensation filling the fiber pores.

4. Discussion

Our study demonstrates both theoretically and experimentally that condensation of water vapor in the pores of clinically used oxygenator HFMs is very unlikely the mechanism responsible for plasma leakage. The resistances to heat transfer across the blood side boundary layer and the HFM membrane wall are smaller than that across the gas side boundary layer in the fiber lumen, which leads to a simple heat transfer model for determining gas flow temperature based on laminar fully developed flow through a cylinder with constant wall temperature. When solved for the conditions of two clinically used extracorporeal oxygenators, the results reveal that the gas flowing through the fibers equilibrates to blood temperature after passing through less than 0.3% of the fiber length. Further analysis reveals that even if the blood side and membrane wall heat flux resistances were significantly compromised (i.e. 100 times greater), the gas temperature would reach the blood temperature after only 0.5% of the total fiber length (Fig. 1). Once the temperature of the gas flow and hence the pore walls of the HFMs equilibrate with the exterior blood temperature, condensation of any water vapor in the gas phase within the pores will not occur.

An in vitro test was also performed to evaluate fiber performance in water where the effects of water vapor condensation are isolated from other variables potentially responsible for plasma leakage, such as blood phospholipids. Simulating gas flow rate and temperature conditions of an extracorporeal oxygenator, the permeability of microporous fibers exposed to water at 37°C over a four-day period remained essentially constant. For plasma to pass through the pores, they would have to be filled with fluid. If the pores were to have filled with water during our in vitro experiment because of vapor condensation, the fiber permeability and hence the system permeability measured in the experiment would have degraded by as much as 98%.

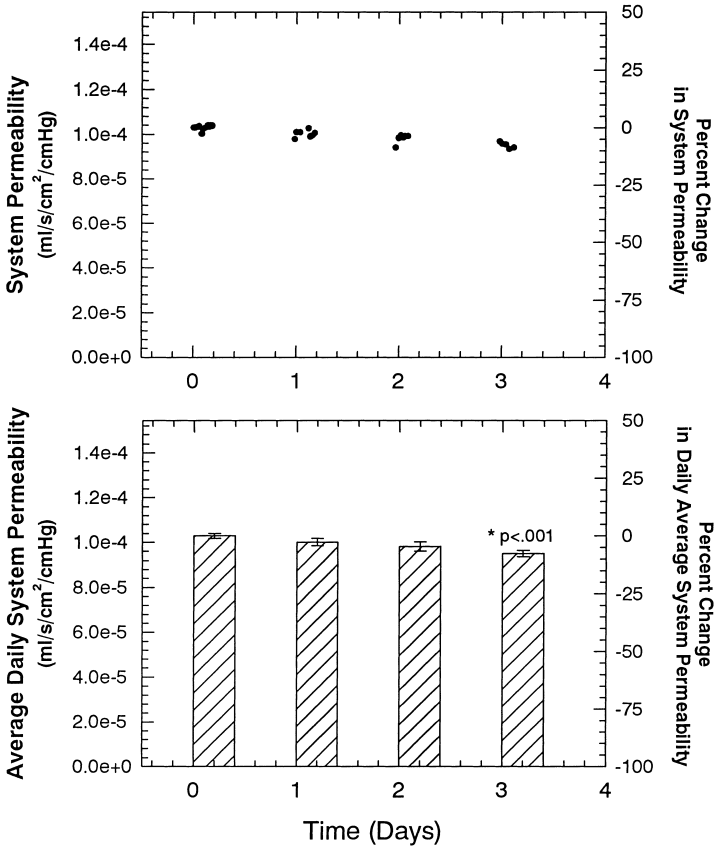

Fig. 2. In vitro carbon dioxide permeability of Mitsubishi KPF 190 HFMs submerged in distilled water stirred at 1300 rpms over a four-day period. Top graph shows actual data points while bottom graph shows daily average and standard deviations. The system permeability on the fourth day represents a statistically significant reduction with respect to the average permeability of the first day.

In the ex vivo experiments reported by Mottaghy et al. [3], the prevention of plasma leakage was attributed to the heating of the gas prior to entering the oxygenator and hence the prevention of vapor condensation in the fiber pores. By testing this theory in an ex vivo sheep model, however, the variables of plasma leakage associated with blood components and their potential role in fiber wetting were not eliminated. The mean phospholipid content of sheep blood is only 46 mg/dl [13] compared to 165 mg/dl for humans. If phospholipid content does in fact play a role in fiber wetting as shown by Montoya et al. [2], than the absence of plasma leakage in these experiments could be explained by factors other than prevention of condensation. A similar control experiment whereby the same ex vivo procedure is used without heating of the sweep gas through the oxygenator might provide further conclusions.

Based on the theoretical and in vitro analyses presented herein, vapor condensation does not appear to be responsible for plasma leakage observed during ECMO. Our investigation serves merely to rule out condensation as a plausible cause of plasma leakage, and to direct further investigation toward other possible causes such as phospholipid adsorption. This conclusion may seem counterintuitive to the clinical observation of condensate at the oxygenator gas flow exit port, which is felt to play a role in the plasma leakage process. However, in light of our results, this condensate must not originate from within the pores but rather from the cooling of the gas flow after exiting the fiber bundle and being exposed to sections of the

module gas flow path which are not warmed by the blood.

5. Notation

A_f	frontal area of oxygenator blood flow path
c_p	heat capacity of gas
d_i	inside hollow fiber diameter
d_o	outside hollow fiber diameter
h_b	convective heat transfer coefficient of the blood phase
h_g	convective heat transfer coefficient of the gas phase
k	thermal conductivity
k_{gas}	thermal conductivity of gas phase
k_m	thermal conductivity of membrane wall
k_{solid}	thermal conductivity of solid polymer from which HFMs are constructed
K	overall permeability to CO_2 of diffusion chamber system
K_L	permeability to CO_2 of liquid side concentration boundary layer adjacent to HFMs
K_m	permeability to CO_2 of HFMs
Nu	Nusselt number
Pr	Prandtl number
Re	Reynolds number
R_T	overall heat flux resistance
r_i	inside hollow fiber radius
r_o	outside hollow fiber radius
T_{blood}	mean temperature of blood phase
T_{mean}	temperature of gas averaged over inside fiber cross-section
T_{room}	room temperature
V	average velocity of gas flow through fiber
z	axial distance along hollow fiber

Greek letters

ϵ	porosity of HFMs
ϕ	void fraction of oxygenator blood flow path
ν	kinematic viscosity
ρ	density of gas

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