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Authors

Wang, Xianglong

Meyerhoff, Mark

Bull, Joseph

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SIMULATING THE RELEASE PROFILE OF A NITRIC OXIDE RELEASING CATHETER IN PHYSIOLOGICAL CONDITIONS

Xianglong Wang (1,2), Mark E. Meyerhoff (3), Joseph L. Bull (2)

(1) Department of Biomedical Engineering
University of Michigan
Ann Arbor, MI, USA

(2) Department of Biomedical Engineering
Tulane University
New Orleans, LA, USA

(3) Department of Chemistry
University of Michigan
Ann Arbor, MI, USA

INTRODUCTION

Intravascular catheters are essential for long-term vascular access in both diagnosis and treatment. However, these catheters can trigger the thrombotic pathway since the blood recognizes them as foreign surface. Bacteria can also adhere to the surface of these catheters and form biofilms. [1] Due to these problems, these catheters are often replaced at a 3-7 day cycle [2]. Having to be constantly replacing these catheters can be a burden for physicians and a pain for patients. Even though the recommended guideline is followed, catheter-related infections can still occur and claim lives.

Nitric oxide (NO) is a potent antimicrobial and antithrombotic agent. Although healthy vascular endothelial cells release NO into the bloodstream, the effective concentration of NO may be too low to exhibit physiological effects around the surface of intravascular catheters. [3] Higher local concentration is needed to activate the desired physiological properties of NO to be used in catheters, requiring the catheter to provide a source of NO.

Recent approaches to provide a source of NO in the catheters include electrochemical reactions [4] or impregnation of the catheter with a NO-releasing compound [5]. Evidence can be seen through bench and animal models associated with these approaches. However, the release profile of NO in animals is largely inaccessible in situ and the measurements are mostly performed post-experiment, showing a significant different result compared to lab bench models largely due to convection by blood flow.

Computer simulation provides a cost-effective solution to estimate the release profile of NO inside the animal. The simulated results can also be used as a platform to design optimal shapes of the catheter, placement of the NO source, and NO release profiles without dedicating excessive resources and efforts to performing animal experiments.

METHODS

The solver used in the simulation is a custom second-order accurate finite volume solver developed in house, specifically designed to capture the concentration drop across interfaces separated by boundaries of flow. [6] The solver numerically solves the convection-diffusion equation over a body-fitted hexagonal grid. The solver computes the convective flux using gradient-limited Gudonov type flux and the diffusive flux using the multi-point flux approximation (MPFA) L-method. The chosen flux schemes stabilize the solution to give positive solutions to the simulations.

This simulation is based on the approach of impregnating the catheter using a NO-releasing compound [5]. A catheter is assumed to be placed at the center of a jugular vein. The catheter is made of an Elast-eon polymer with a concentric cylinder shape. The catheter polymer contains three layers: original polymer, active (impregnated) polymer, and another layer of the original polymer. The thickness of these three layers is 1:5:1. Figure 1 shows a diagram of the catheter.

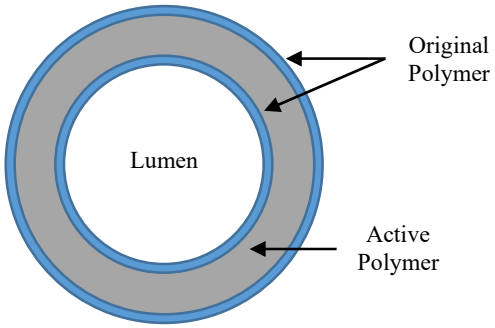

Figure 1: A diagram of the catheter, with a 1 original:5 active:1 original composition.

We simulated the concentration of NO with or without flow in the jugular vein. The length of the jugular vein is selected to be 30 cm. Without flow, the transport of NO is assumed to be pure diffusion. If flow is present, the flow in the jugular vein is assumed to be fully developed and Newtonian. Therefore, we impose the analytical solution for Poiseuille flow in concentric cylinder in the region outside the catheter and inside the jugular vein with respect to a reference flow rate, as shown in Equation (1)(2). The lumen is simply treated as a sink since the inside surface of the catheter does not contact blood and is not of interest.

$$p_x = -\frac{8\mu Q}{\pi}\left(r_2^4 - r_1^4 - \frac{(r_2^2 - r_1^2)^2}{\ln(r_2/r_1)}\right)^{-1} \quad (1)$$

$$u(r) = -\frac{p_x}{4\mu}(r_1^2 - r^2) - \frac{p_x}{4\mu}(r_2^2 - r_1^2)\frac{\ln(r/r_1)}{\ln(r_2/r_1)} \quad (2)$$

A set of symbols, their physical meanings, and values used in the simulation can be seen in Table 1. For initial conditions, we set the NO concentration in the active layer to be 3.0×10^{-5} mol/cm^3, which is approximately the solid concentration of the NO releasing compound in the catheter [5]. The time for simulation is 180 seconds.

Table 1: Symbols, physical meanings, and values used in simulation

Symbol	Physical Meaning	Value	Source
Q	Flow rate (jugular vein)	18.168 cm^3/s	[7]
μ	Blood viscosity	3.8 cP	[8]
r_2	Radius (jugular vein)	0.324 cm	[7]
r_1	Radius (catheter, outer)	0.165 cm	[5]
r_{in}	Radius (catheter, inner)	0.104 cm	[5]
D_w	Diffusion coefficient, NO in water	2.21×10^{-5} cm^2/s	[9]
D_p	Diffusion coefficient, NO in catheter polymer	8.5×10^{-6} cm^2/s	[9]

RESULTS

The simulation is performed on a $55 \times 55 \times 55$ domain. The initial distribution of NO can be seen in Figure 2, showing a band of NO at higher concentration.

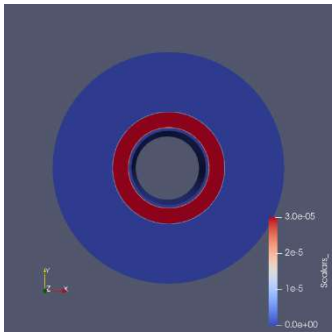

Figure 2: Initial condition of the simulation.

The numerical solution at t=180 for pure diffusion can be seen in Figure 3, and the solution with blood flow is shown in Figure 4. The concentration as a function of the radius at z=15cm is shown in Figure 5 for both cases. We can see increased consumption of NO when flow is present, and a sharp drop of NO concentration at the interface of flow. A plot of the concentration vs. the axial coordinate z at r=0.1651, just outside the catheter, is shown in Figure 6. We can see that the concentration of NO increases with increased z.

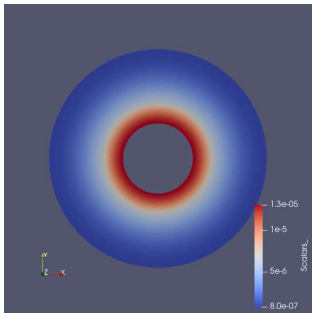

Figure 3: Solution from pure diffusion

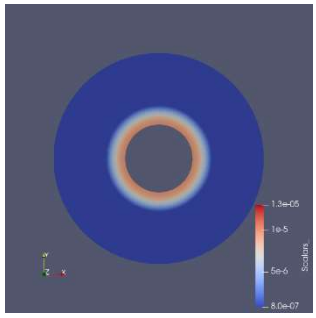

Figure 4: Solution from diffusion and convection

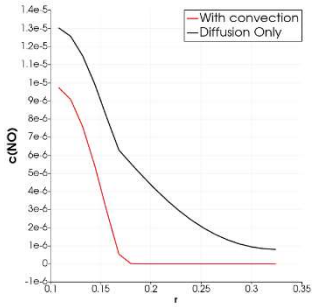

Figure 5: Concentration vs. r coordinate with and w/o flow

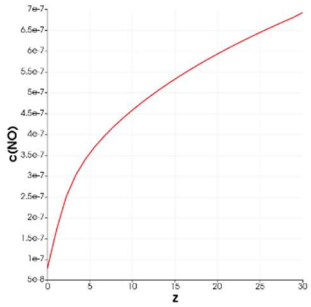

Figure 6: Concentration vs. z with convection at r=0.1651

DISCUSSION

The simulations presented above presented critical information about the effect of blood flow in nitric oxide releasing catheters – the consumption of the NO releasing reservoir is much faster when blood flow is present, requiring higher initial NO deposit, or a way to replenish NO releasing compound to match the lab bench results.

The simulation is a simplified model of the physical process. It does not account for non-Newtonian or pulsatile flow of the blood, reaction between NO and hemoglobin, or partition coefficients of NO between water and catheter polymer. The catheter is also placed at the center of the vein as an ideal situation. These aspects will be addressed in future iterations of the simulation.

It is also debatable whether the approximation of setting the concentration of NO in the active layer to be the solid concentration of the NO releasing compound is accurate. This compound, S-nitroso-N-acetyl penicillamine (SNAP), exists as solid crystals in catheter polymers, and the kinetics of NO release from SNAP is yet to be fully understood.

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