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Shear Stress-Dependent NO, ATP and ADP Production from Endothelial Cells – a Modeling Approach

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Abstract:

A computational model was developed to describe shear stress-dependent transport of nitric oxide (NO), ATP and ADP produced by endothelial cells (ECs) cultured in a parallel plate flow chamber.

Background:

Wall shear stress (τ_w) is the primary hemodynamic determinant of endothelial release of NO with subsequent effects on vascular tone. Adenine nucleotides (ATP, ADP) are known to modulate the NO production rate (R_{NO}) by ECs. We developed a computational mass transport simulation that allows quantitative analysis of *in vitro* experimental NO measurements obtained in our laboratory[1,2] with cultured bovine aortic ECs in the flow chamber *(Figure 1)*. Two previous models that relate ATP release to shear stress were investigated[3,4].

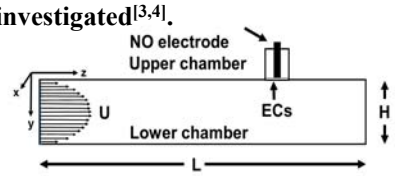

Figure 1: Diagram of parallel-plate flow chamber (Andrews *et al.*[1, 2]). A NO electrode is located in the upper chamber, isolated from the flowing steam. Dimensions of the flow channel (in cm) are W = 4.57, L = 12.19, H = 0.025.

Methods:

Computational models for the variation in R_{NO} with τ_w and total adenine nucleotide concentration ($C_{ATP} + C_{ADP}$) were used to analyze experimental data before and after degrading ATP with apyrase[2].

Simulations were run with finite element software (FlexPDE 4.2 and Comsol 5.1) using appropriate boundary conditions and parameters from the literature[3,4].

Dimensionless Governing Equations

$$\frac{dC^*}{dt^*} = \frac{d^2C^*}{dy^{*2}} + \left(\frac{H}{L}\right)^2 \frac{d^2C^*}{dz^{*2}} - \left(\frac{UH^2}{DL}\right) u^* \frac{dC^*}{dz^*} + \left(\frac{H^2 R_{max}}{DC_{ref}}\right) R^*$$

NO production (R_{NO})

$$R_{NO} = R_{basal} + R_{max} \frac{\tau_w}{(\tau_w + A)} + \beta \left[C_{ATP} + C_{ADP}\right]_r$$

ATP release

Model A by John and Barakat[3]

$$S_{ATP}(\tau_w) = S_{max} \left[1 - e^{(-(\tau_w/\tau_0))}\right]^3$$

Model B by Qin *et al.*[4]

$$S_{ATP}(\tau_w, t) = p_1 p_2$$

$$p_2(t) = e^{-t/t_2}$$

$$p_1(t) = \begin{cases} \frac{t_1 f(\tau_{w1})}{t_1 e^{(-t/t_1)}} \left[1 - e^{(-t/t_1)}\right), & 0 < t < T_1 \\ \left[f(\tau_{w1})\left(e^{(T_1/t_1)} - 1\right) + f(\tau_{w2})\left(e^{(t/t_1)} - e^{(T_1/t_1)}\right)\right], & T_1 \le t < T_2 \end{cases}$$

$$f(\tau_w) = a_1 - \frac{a_2 \tau_w}{a_3 + \tau_w}$$

Results:

A color contour map of ATP distribution predicted by Model A with the highest concentration in the EC layer for τ_w = 15 dyn/cm² is shown for a section of the flow chamber in *Figure 2* (not to scale).

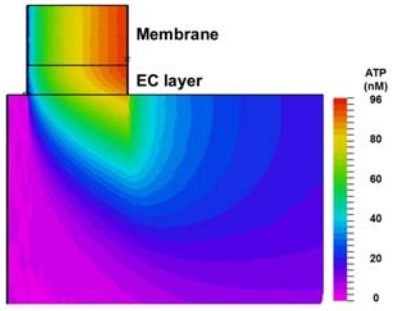

Figure 2: Spatial distribution for ATP in the membrane, EC layer, and a section of the flow stream in the chamber (0 < y < 50 µm, 4.3 < z < 12.19 cm, EC layer 4.9 < z < 7.3 cm) predicted by Model A. Concentration scale at right.

Predicted concentrations were identical for both programs. The maximum ATP and ADP in the EC layer for Model A occurs at τ_w = 15 dyn/cm² *(red curves, Figure 3A)*. With higher τ_w, convective transport progressively decreases ATP and ADP. Model B predicts a continuous increase in ATP and ADP with τ_w *(red curves, Figure 3B)*. Both models predict a decrease in ATP but an increase in ADP with apyrase.

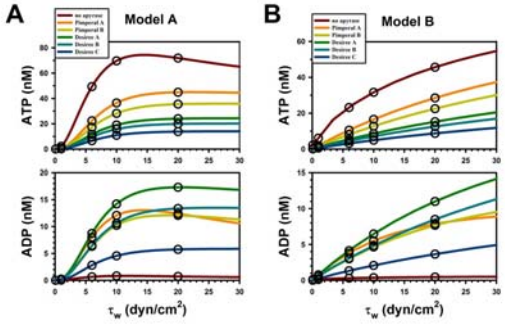

Figure 3: Maximum ATP and ADP in the EC layer predicted by Model A (A) and Model B (B) as a function of τ_w (simulations without apyrase shown by red curves), Effects of treatment with isoforms of apyrase with different kinetic parameters are shown.

Our laboratory reports that treatment with apyrase causes a decrease in R_{NO}[2]. We estimated parameters for τ_w and nucleotide dependent terms *(Figure 4)* for the models.

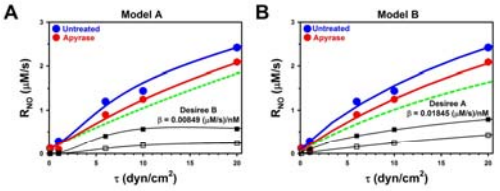

Figure 4: R_{NO} as a function of τ_w determined from NO measurements in flow chamber experiments[2] (untreated, blue circles; treated with 1 U apyrase, red circles). (A) Best fit to experimental data using Model A. R_{NO} (untreated, blue curve; apyrase, red curve). Nucleotide component (untreated, solid squares; apyrase treated, open squares), and τ_w-dependent component (green dashed curve). (B) Best fit to experimental data and individual components using Model B.

Conclusions:

- A significant portion of the total τ_w-dependent NO production (R_{NO}) is linked to adenine nucleotide signaling.
- The model predicts that R_{NO} is more sensitive to adenine nucleotide concentrations at lower τ_w (< 7 dyn/cm²) than at higher τ_w.
- Experimental studies that show a decrease in R_{NO} with apyrase treatment[2] are consistent with our model predictions.
- Our computational study suggests that adenine nucleotide signaling can be represented by a simple linear relationship (β) with the sum of adenine nucleotide concentrations, with Model B providing a closer match to the experimental data than Model A.

Selected References:

1. Andrews AM, Jaron D, Buerk DG, Kirby PL, Barbee KA. Direct, real-time measurement of shear stress-induced nitric oxide produced from endothelial cells in vitro. Nitric Oxide. 2010;23(4):335-42.
2. Andrews AM, Jaron D, Buerk DG, Barbee KA. Shear stress-induced NO production is dependent on ATP autocrine signaling and capacitative calcium entry. Cellular and Molecular Bioengineering. 2014;7(4):510-20.
3. John K, Barakat AI. Modulation of ATP/ADP concentration at the endothelial surface by shear stress: effect of flow-induced ATP release. Annals of Biomedical Engineering. 2001;29(9):740-51.
4. Qin K, Xiang C, Xu Z, Cao L, Ge S, Jiang Z. Dynamic modeling for shear stress induced ATP release from vascular endothelial cells. Biomechanics and Modeling in Mechanobiology. 2008;7(5):345-53.