Multiscale, Transport-Dependent NO Signaling: Cells to Vascular Networks

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The goal of the proposed research is to develop a multi-scale mathematical model that will provide quantitative information regarding mechanisms governing nitric oxide (NO) production and activity in the microcirculation and to utilize real-time measurements to validate the model. The model will integrate intracellular NO production processes with extracellular, vascular and tissue transport, including the coupling of NO to O_2 delivery and metabolism under normal conditions and in hypercholesterolemia. It is expected that the model will help to elucidate mechanisms by which NO is produced and transported and provide greater insight into disease states marked by endothelial dysfunction. *In vitro* and *in vivo* experiments as well as results reported in the literature will be used to aid in the development of the mathematical model and validate its predictions.

Mathematical Modeling: The development philosophy is to sequentially couple lower scale with higher scale simulation: cell-scale to vessel-scale, to vascular networks. Results of the simulation will be validated using our experiments and results reported in the literature.

In vitro: A parallel plate laminar flow chamber, which enables direct, real time measurements of the kinetics of NO release under a wide range of conditions will be used for cell culture studies. The coupled effects of shear stress and altered mass transport of secreted signaling molecules on flow-induced NO production will be investigated. The role of mass transport between spatially discrete signaling domains within the cell in the pathways related to NO production will also be studied.

In vivo: Experiments will be performed using the rat mesentery and apolipoprotein-E deficient mice. Local blood flow, PO_2 and NO, combined with vessel diameter measurements, will be obtained from individual small arteries, arterioles, venules, and small veins under normal and abnormal physiological conditions to characterize relationships among vascular diameter, NO, blood flow, and O_2 delivery.

The presentation will summarize research leading to the present NIH application, describe the techniques that will be utilized in the project and report our initial results.