Featured Young Investigators' Recent Study in *Microcirculation*

Computational Network Model Prediction of Hemodynamic Alterations Due to Arteriolar Rarefaction and Estimation of Skeletal Muscle Perfusion in Peripheral Arterial Disease

Featuring: ***Joshua Heuslein, Graduate Student, University of Virginia***

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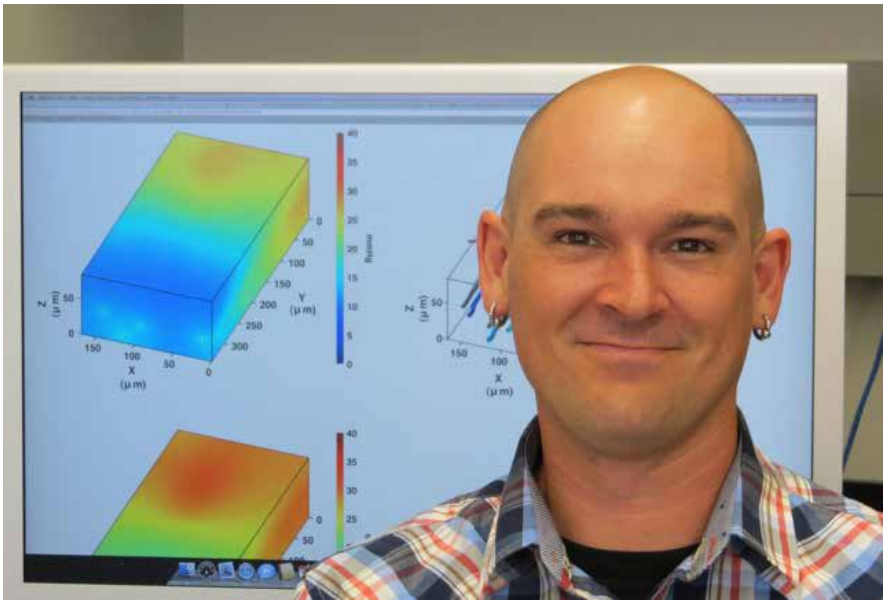
Peripheral arterial disease (PAD) is caused by atherosclerotic plaque formation in the peripheral limb vasculature, resulting in reduced blood flow to the lower extremities. While surgical and catheter-based revascularization approaches can restore ankle-brachial index (ABI), many patients experience no significant improvement in tissue perfusion. Emerging therapeutic strategies have entailed the delivery of cells and/or growth factors to restore downstream tissue perfusion via arteriogenesis and angiogenesis. However, to date, large-scale therapeutic clinical trials have been largely unsuccessful. These failures have highlighted a critical need to improve our understanding of the basic mechanisms of vascular remodeling in order to achieve eventual therapeutic success.

The lack of improved perfusion following revascularization highlights an underlying microvascular dysfunction that elevates hydraulic microvascular resistance. While the decreased capillary density observed in PAD patients may contribute toward this impaired reperfusion, blood flow is also largely governed by terminal arterioles upstream of the capillaries. Moreover, though arteriolar rarefaction had been observed in pathological conditions previously, its role in PAD remained unknown. In our study (Microcirculation 22 (5):360-369), we adapted a computational network model of the gastrocnemius muscle microcirculation in order to estimate the relative influence of input pressure (ABI) restoration and arteriole rarefaction on perfusion. We found that muscle perfusion becomes disproportionately less sensitive to ABI restoration as arteriole rarefaction increases due to a non-linear increase in microvascular resistance with increasing arteriole rarefaction. Additionally, using arteriolar density measurements from PAD patients, we simulated the isolated effects of exercise and/or percutaneous therapeutic interventions in our model. In model simulations of PAD, perfusion was restored to the greatest extent when exercise training and ABI restoration were simulated simultaneously. These results highlight the importance of restoring both microvascular structure and upstream input pressure in PAD therapy. Future strategies utilizing concomitant targeting of upstream pressure restoration via arteriogenesis or percutaneous intervention and repair of microvascular function may prove a more effective therapeutic approach for patients suffering from PAD.

Impact of Incremental Perfusion Loss on Oxygen Transport in a Capillary Network Mathematical Model

Featuring: ***Graham M. Fraser, Graduate Student, University of Western Ontario***



Our recent article modeling how progressive decreases in functional capillary density affect tissue oxygenation has important implications in mathematical modeling and experimental studies of oxygen delivery. Fundamentally one might consider how a loss of flowing capillaries would impact surface area for O2 delivery and increase diffusion distance from capillaries to tissue. This translates into a larger radius Krogh tissue cylinder and a decrease in tissue oxygenation even if capillary oxygen supply remained fixed. Our model illustrates that under normal metabolic conditions a loss of perfused capillaries decreases tissue oxygenation almost entirely due to lower red blood cell (RBC) supply rate. Restoration of total RBC supply to baseline restores oxygen delivery and improves tissue PO2. This restoration is possible through diffusional exchange within the tissue and between capillaries distributing O2 within the volume thus improving oxygenation. Therefore, under normal conditions small changes to supply rate and diffusion distance only alter tissue PO2 in a supply limited fashion.

In capillary networks, when metabolism is increased the tissue is prone to both supply limited delivery and also to diffusion limitation. Due to the spatial heterogeneity of vascular networks, some capillaries lie beyond the limits of diffusional exchange and the increased diffusion distance is a substantial barrier to oxygen delivery. Using the model we have also examined how this transition affects capillary outflow saturation, analogous to the clinical measure of venous saturation (cvSO2), and found recovery of capillary outflow saturation would occur prior to restoration of tissue PO2. This is important when considering cvSO2 as an index of oxygen extraction as it may be confounding in the transition from supply to diffusion limited delivery. In our lab, understanding this interplay between oxygen delivery and metabolism reinforces the importance of collecting detailed experimental data to properly model tissue PO2 changes in both health and disease.

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