Title: Theoretical, experimental, and translational studies of RBC flow distribution through capillary networks in the microcirculation

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Structured Abstract:

The distribution of erythrocytes (RBCs) through the microcirculation is the central mechanism for regulating oxygen delivery to match metabolic demands of the tissue. Oxygen is delivered fundamentally at the level of the capillary network where RBCs travel in single file as discrete cellular units and the diffusion distance to adjacent tissue is minimized. Given the overwhelming complexity of capillary networks, questions still remain regarding how they contribute to the physiology of oxygen delivery and flow regulation.

We first approach this problem at the level of the basic microvascular unit (MVU) – from terminal arteriole, through a capillary bundle (CB), and into a post-capillary venule. Using a dual-phase blood flow computational model, we demonstrate the impact of biophysical parameters on the distribution of RBC and plasma flow within CBs. Increasing capillary length reduces mean RBC flow in a nonlinear fashion with an inflection point occurring at capillary lengths of 200 microns. Increases to arteriolar and venular diameter above 10 microns have little additive effect on the magnitude or distribution of RBC and plasma flow through the MVU. Changes to the driving pressure across the MVU has a linear effect on RBC and plasma flow with no impact on the relative distribution between capillaries.

Next, we relate this basic MVU to the broader architecture of the microcirculation using intravital videomicroscopy of rodent skeletal muscle. We propose the microvascular lattice (MVL) as an updated paradigm for describing RBC flow through capillary networks. The key feature of the MVL is the highly-interconnected organization of CBs such that terminal arterioles supply multiple CBs and post-capillary venules receive blood for multiple CBs; these bundles are linked together in long columns that orient with the direction of the muscle fascicle. We quantify RBC flow characteristics of the MVL in vivo and discuss the potential impact of the MVL structure on the mechanisms of RBC flow regulation.

Finally, we apply our pre-clinical approach to develop an optical system for measuring RBC flow distribution in humans at the bedside. Isosbestic NIRS can track changes in microvascular hemoglobin content (MHC) and can provide a functional assessment of the microcirculation in peripheral tissue. In a pilot study in the ICU, we demonstrate the functionality of our NIRS system and also highlight the value of high-frequency sampling to quantify the dynamic variability of MHC in real-time. ICU interventions including mechanical ventilation directly impact MHC. We observe slow (~0.033Hz) oscillations in MHC in patients with severe sepsis that are highly comparable to our septic animal models. These findings will be further characterized with a frequency-domain analysis of MHC time series.

Taken together, these three studies provide complementary techniques to evaluate the physiology of RBC distribution in the microcirculation on multiple levels of scale.