Functional interplay between arteriolar network geometry, sympathetic regulation, and conducted vasodilation

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Introduction: Arteriolar networks that distribute oxygenated blood to tissues differ in their geometric properties (e.g., long versus short arterioles). Despite their geometric differences, arteriolar function is tightly regulated so that blood flow is distributed equally throughout the tissue, ensuring all cells receive adequate oxygenation. The sympathetic nervous system (SNS) primarily regulates arteriolar function through the release of neurotransmitters [e.g., norepinephrine (NE), adenosine triphosphate (ATP), and neuropeptide Y (NPY)] that act on their associated receptors on the surface of arterioles to cause vasoconstriction (reduction in vessel diameter) and decrease blood flow. In spite of an ongoing SNS-induced vasoconstriction, skeletal muscle contractions cause a rapid dilatory response (to increase vessel diameter) that begins in capillaries and ascends to proximal feed arteries, known as ascending conducted vasodilation (CVD). This response opposes the actions of the SNS and leads to an immediate increase in muscle blood flow so that tissue oxygenation can match its metabolic needs. It has been reported that CVD responses are spatially heterogeneous and dependent on the level of SNS activity\textsuperscript{1,2}. However, the functional relationship between arteriolar network geometry (e.g., arteriolar length), the SNS, and CVD in skeletal muscle is unknown. A better understanding of this functional interplay will provide valuable insight regarding the mechanisms that regulate blood flow in arteriolar networks that vary in their layout and geometry. Thus, this study will address the following questions:

1) Are CVD responses dependent on arteriolar segment length?
2) Does the level of SNS modulation in bifurcating arterioles depend on their lengths?
3) Is the relationship between CVD and arteriolar length dependent on the SNS?

Hypothesis:
1) The magnitude of the CVD response will be inversely proportional to arteriolar length
2) The sensitivity to sympathetic agonists at bifurcating arterioles will be inversely proportional to their lengths.
3) SNS blockade will modify the relationship between CVD and arteriolar length

Methods: For all experiments, the rat (male, Sprague-dawley) gluteus maximus (GM) muscle will be prepared for intravital video microscopy (IVVM). The planar geometry and uniform thinness of the GM enable access to its entire arteriolar network for imaging and perturbation. After baseline imaging, we will evaluate arteriole responses (vasoconstriction) to NE (10\textsuperscript{-9}-10\textsuperscript{-4}M), ATP (10\textsuperscript{-9}-10\textsuperscript{-4}M), and NPY (10\textsuperscript{-14}-10\textsuperscript{-7}M), and the results will be correlated to arteriolar length. To induce CVD, capillary beds will be stimulated with FITC-dextran labelled pinacidil (10\textsuperscript{-5}M) using a micropipette. The arteriolar tree supplying the capillary bed of interest will be imaged at baseline and during capillary stimulation to track velocity, distance, and amplitude of dilatory responses. To determine if the SNS modulates the relationship between CVD and arteriolar length, sympathetic receptors will be blocked using phentolamine (10\textsuperscript{-7}M), NF023 (10\textsuperscript{-6}M), and BIBP3226 (10\textsuperscript{-7}M). Following sympathetic blockade, CVD will be re-evaluated to determine if the interaction between arteriolar length on CVD are lost.
Conclusion: This study will be the first to quantitatively describe the relationship between arteriolar network geometry, the SNS, and CVD. We aim to build on the general concept that sympathetic regulation in an arterial network is finely tuned to its geometric properties.

References: