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Project Title: Early Microvascular Rarefaction in Metabolic Syndrome

Project Summary:

The metabolic syndrome (MS) represents an integrated metabolic and cardiovascular disorder reflecting the development of multiple risk factors for a poor cardiovascular outcome, including obesity, insulin resistance, dyslipidemia, hypertension and the genesis of pro-inflammatory and pro-oxidant environments. The obese Zucker rat (OZR) represents an excellent model of MS, and develops this condition due to chronic hyperphagia. While impairments to vascular reactivity with MS have been well established and are partly a function of reduced nitric oxide bioavailability and altered arachidonic acid metabolism, we have made the novel and consistent observation that reductions to skeletal muscle microvascular density (rarefaction) also develop in parallel with reactivity alterations, and that this plays a key contributing role in poor perfusion outcomes. While our previous publications have demonstrated that the full extent of rarefaction is well predicted by a chronic loss of nitric oxide bioavailability, our most recent data strongly suggest that an early pulse of rarefaction develops very rapidly in the OZR model of MS which significantly precedes any demonstrable loss in NO bioavailability. Our advanced statistical analyses have suggested that the strongest associated parameter with the early pulse of microvascular rarefaction is a shift in vascular arachidonic acid metabolism from prostacyclin (PGI₂) to thromboxane A₂ (TxA₂). Preliminary experiments have supported this concept, as chronic blockade of TxA₂ action via receptor antagonism completely abolished the development of this early pulse of microvascular rarefaction. The experiments proposed in this predoctoral fellowship application will build on this compelling preliminary data by determining the spatial and temporal characteristics of this early pulse of rarefaction and its impact on the ultimate extent of microvessel loss (Specific Aim 1) as well as evaluating the relative roles of progressive elevations in systemic oxidant stress and sub-acute inflammation in this early structural degradation of the peripheral microcirculation in the metabolic syndrome (Specific Aim 2).