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EDITORIAL COMMENT

New Insights in Peripheral Arterial Disease

Novel In Silico Mouse and Disease-Based Computational Models*

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Peripheral artery disease (PAD) represents a significant burden on American health care with up to 1 in 5 Americans older than 60 years of age affected.[1] Unfortunately, it remains a complex progressive arterial disease without a robust medical therapy. Despite years of work, we are only beginning to comprehend the short- and long-term physiologic consequences of chronic tissue ischemia. One of the difficulties in better understanding and modeling the morbidity of PAD is the progressive nature of the clinical manifestations including claudication to rest pain and eventually tissue loss. More recently, there have been advances in our understanding of the effect of chronic PAD on the myocyte which suggest there is a maladaptive remodeling leading to increased fibrosis as a result of multiple mechanisms including mitochondrial damage, autophagy, and fibrosis.[2] Additional studies have focused on the changes in the microvessels themselves with thickening of microvessels from collagen deposition and a more general alteration in architecture.[3]

In addition to understanding the maladaptive effects of tissue remodeling following chronic ischemia, we need to better understand physiologic adaptations to chronic ischemia and identify "nodes" that can be pharmacologically targeted to improve patients' symptoms. Additionally, there remains a large cohort of patients for whom there are no surgical opportunities to revascularize what is otherwise unreconstructable disease. Stimulating angiogenesis has been a focus of additional study to attempt to "autorevascularize" regions of ischemia through drug or possibly stem cell-based treatments.[4] Such work requires an extensive background of understanding productive remodeling adaptations to ischemia.

In the present issue of *JACC: Basic to Translational Science,* Zhao et al[5] describe a computational biologic model of PAD based on previously published data that includes multiscale regulation of perfusion recovery in the hindlimb ischemia mouse model. They have attempted to incorporate the complex intracellular, cell-cell signaling, and dynamic temporal reperfusion effects to facilitate in silico preclinical animal testing to provide a higher-throughput and, potentially, more cost-effective method to screen for pharmacologic targets. Their in silico analysis revealed time-dependent dynamic phenotypes of macrophage phenotypes in hindlimb ischemia reperfusion model, suggesting that there was an increase in proinflammatory macrophages during the early phase of reperfusion that is followed by a decrease in macrophage number and a shift in the phenotype towards a less proinflammatory phenotype. The investigators further test and validate the use of in silico animal experiments with murine hindlimb ischemia animals to corroborate their computation model. Such a model can then be tested against U.S. Food and Drug Administration-approved medications to identify nodes for inhibition, thereby accelerating future hypothesis driven research.

One of the major downsides to such large computational models is the accuracy of such a model is

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heavily dependent on large volumes of quality data that are unbiased and reproducible. One additional concern is the model is based on only certain interactions to prevent the model from becoming too cumbersome. As an example, the model from Zhao et al[5] is dependent on endothelial cell-skeletal myocyte interaction, but it does not include upstream regulation of arterial inflow from larger vessels or interactions between endothelial and smooth muscle cells. These limitations require such computation model conclusions be validated in animal or human tissue to confirm accuracy. Zhao et al[5] have done an excellent job at validating their model, although even the best model is potentially inaccurate under certain constraints. For example, model calibration of macrophage population by their algorithm is correct for C57BL/6 but not BALB/c mice (see Zhao et al Figure 6L). These sorts of potential discrepancies are essential to better understand the generalizability of such data.

Despite limitations in computational models, such a model has significant advantages for our understanding of complex progressive disease. Models must continue to evolve with improvements and refinements in our understanding of such diseases. In comparison to more traditional preclinical trials, computational models reduce animal costs and number of animals required for multiple time points, thereby potentially reducing resource requirements over the long term. One of the major concerns with such computational models is to provide them in a manner that is open for additional refinements in the future. Zhao et al[5] use of in silico mouse experiments is intriguing to augment data collected from traditional preclinical studies. Whether such in silico animal models will serve as a replacement or continue to be an adjunct for preclinical animal trials will take years of corroboration as evidenced by the discrepancy in macrophage recruitment in the gradual hind limb ischemia mice dependent on genetic background.

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