A NUMERICAL APPROACH TO DETERMINE THE IMPACT OF NETWORK REMODELING ON BLOOD FLOW

Trevor R. Cardinal[1], Shilpi Ghosh[1], Stephanie A. Wood[1], & Gabriel Gruionu[2]

[1]Biomedical Engineering, Cal Poly State University; [2]Vascular Surgery, Indian University

Introduction

Following arterial occlusion or resection, the hindlimb undergoes a revascularization response that includes angiogenesis and arteriogenesis. Microvascular topology is known to impact blood flow. However, it is not known how network angiogenesis and arteriogenesis impacts resting skeletal muscle blood flow and hyperemia.

Therefore, the aims of this work were to 1) apply Strahler's model of branching streams and rivulets to predict blood flow in ischemic and non-ischemic skeletal muscle and 2) perform a parameter sensitivity analysis to determine the aspects of vascular architecture that can explain differences in predicted blood flow between ischemic and non-ischemic muscles.

Hindlimb Ischemia Surgery

Chronic ischemia was used to induce vascular remodeling in the gracilis muscle microcirculation. Ischemia was induced by unilateral resection of the femoral artery & vein from downstream of the popliteal branch to the distal saphenous artery (**Figure 1**). Due to the arcade architecture within the gracilis muscle, this surgery maintains the blood supply in the proximal end of the muscle while reducing the blood supply in the distal end of the muscle and provides an experimental preparation to examine the impact of vascular remodeling on blood flow. The femoral artery of the sham control mice was exposed but maintained intact.
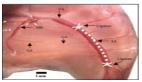

Figure 1. Photographmicrograph of medial aspect of the mouse thigh. FA, femoral artery; GA, primary gracilis arteriole; MB, muscular branch of FA; SA, saphenous artery. [1]

Vascular casting using India ink

India ink was used to visualize of the gracilis muscle microcirculation. Briefly, casting was performed by placing a left ventricular catheter through a thoracotomy and flushing the vascular space of blood with PBS containing heparin and sodium nitroprusside at -100mmHg. Ink solution was immediately perfused into the vasculature. The gracilis muscles from both hindlimbs were carefully dissected and placed flat on a microscopic slide to maintain their original length. The muscle was dehydrated in a graded series of alcohol solutions for 12 hours in each solution. Subsequently, the muscles were cleared in 100% methyl salicylate. The vasculature was then analyzed using a stereomicroscope after the muscle was sandwiched between two microscope slides and transilluminated[1].
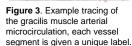

Figure 2. Example photographmicrograph of proximal region an India-ink casted gracilis muscle microcirculation. The muscular branch feed artery can be seen in the upper left corner of the image.[1]

Anatomical Characterization

Vessel diameter, length, and branching patterns were determined from photomicrographs of the India-ink casted gracilis muscle microcirculation. Briefly, arterial microvessels were traced, labeled with a unique identification number, and ordered according to the Strahler method (**Figures 3 & 4**). Segment (the region between two bifurcations) diameters and lengths were then measured using ImageJ. After initially defining orders based on the scheme presented in **Figure 4**, the diameter-defined Strahler method was used to reorder the gracilis muscle microcirculation based on segment diameters[2]

Anatomical Characterization, cont

Figure 3. Example tracing of the gracilis muscle arterial microcirculation, each vessel segment is given a unique label.
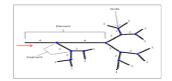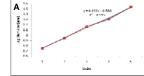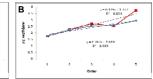

Figure 4. Schematic of the Strahler ordering scheme.

Horton's Law

Vessel element diameter, length, and quantity were compared between the diameter-defined Strahler networks for the ischemic and non-ischemic gracilis muscle microcirculation. Horton's Law of Steam Numbers (**Figure 5**) was used to determine if vessel element diameter, length, and number form an geometric sequence with order number- as would be expected for a normally branching microvascular network.
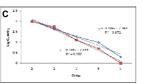

Figure 5. Log plots of element diameter (A), length (B), and quantity per order. All parameters show reasonable agreement between ischemic (red square) and non-ischemic (blue diamond) samples and with Horton's Law- diameter, length, and quantity vary from one order to the next as a geometric sequence

Network Connectivity

The ratios determined by applying Horton's Law show the trends between orders. However, not all vessels of order n branch from a vessel of $n+1$. Therefore, to examine asymmetric branching patterns impact we constructed a connectivity matrix which presents the percent of all daughter vessels of m that branch from a parent vessel of order n (**Figure 6**).
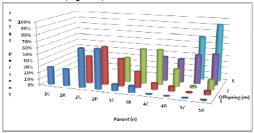

Figure 6. Connectivity matrix comparing the percent of vessels of order m that branch from a parents of order n.

Hemodynamic Predictions

To make hemodynamic predictions, we solved for our two unknowns (pressure and flow) at every microvessel segment bifurcation with two equations- conservation of mass and Poiseuille's Law (**Figure 7**).
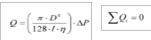
$$Q = \left(\frac{\pi \cdot D^4}{128 \cdot l \cdot \eta} \right) \cdot \Delta P \qquad \sum Q_i = 0$$

Figure 7. Poiseuille's Law (left) and conservation of mass (right) were used to calculate flow throughout the diameter-defined Strahler network
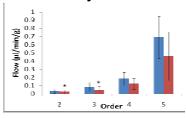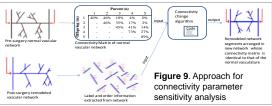
Hemodynamic Predictions, Cont

Figure 8. Predicted blood flow per order in ischemic (red bar) and control (blue bar) gracilis muscle microcirculation. *, $p<0.05$ versus control.

Parameter Sensitivity Analysis

Although diameter, length, and quantity were not statistically different between the ischemic and non-ischemic samples, predicted blood flows were significantly less in ischemic order 2 and order 3 vessels. However, although not statistically testable with our sample size, connectivity to appear to be different between ischemic and non-ischemic samples (**Figure 6**). Therefore, to determine the impact of vascular connectivity on predicted flow values we developed a coding scheme in Matlab in which the vessels segments from a disassembled network (whose diameters and lengths are left unchanged) are reassembled according to user-defined branching characteristics (**Figure 9**). In this case, we imposed the non-ischemic network connectivity onto the ischemic network segments and recalculated network blood flow (**Figure 10**).

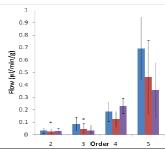**Figure 9**. Approach for connectivity parameter sensitivity analysis

Figure 10. Predicted blood flow per order in non-ischemic (blue bar), ischemic (red bar), and ischemic segments with arranged according to the non-ischemic network connectivity (purple bar). *, $p<0.05$ versus control. Imposing the non-ischemic connectivity onto the ischemic segments restores blood flow in orders 2 and 3.

Summary & Future Work

• We have developed a modeling strategy to determine the impact of vascular architecture and topology on microvascular blood flow
• This strategy involves a network characterization using a diameter-defined Strahler approach combined with a parameter-sensitivity analysis of network characteristics on blood flow
• Although not described here, code for performing parameter-sensitivity analysis on vessel diameter and length were also developed

References

1. Gruionu G, Hoying JB, Pries AR, Secomb TW, *Structural remodeling of mouse gracilis artery after chronic alteration in blood supply. Am J Physiol Heart Circ Physiol* 288: H2047-H2054. December, 2004.
2. Gan RZ, Tian Y, Yen RT, Kassab GS, *Morphometry of the dog pulmonary venous tree*, J Appl Physiol. 1993 Jul;75(1):432-40