Arteriogenesis and ischemia impair functional vasodilation in resistance arteries

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Introduction

Patients with peripheral arterial occlusive (PAOD) disease have impaired vasodilation. Identifying the mechanism of this impaired could lead to improved therapies. Co-morbidities common to PAOD, e.g. hypercholesterolemia, are known to impair vasodilation, but arterial occlusion alone also impairs vasodilation. Although impaired vasodilation in lower-leg arterioles is well described in animal models of PAOD, the impact of arterial occlusion on collateral and resistance arteries is unknown. Collateral resistance is the last determinant of downstream flow and resistance arteries contribute up to half of the resistance to skeletal muscle blood flow, so identifying the impact of arterial occlusion on these vessels will likely provide the greatest potential therapeutic benefit. Therefore, the goal of this project is determine the impact of arteriogenesis and ischemia on collateral artery and resistance artery vasodilation, respectively. The long-term goal of this work is identify potential therapeutic targets for impaired vasodilation in patients with PAOD.

Surgical Model I - Arteriogenesis

To determine the impact of elevated flow and arteriogenesis on collateral artery vasodilation, we utilized an experimental model that involved ligation of the femoral artery between the profunda femoris and popliteal branches (proximal ligation, Figure 3a) or just distal to the popliteal (distal ligation, Figure 3b). These surgeries lead to arteriogenesis in the profunda femoris and its development as the stem region of a collateral circuit.

Surgical Model II - Ischemia

To determine the impact of ischemia on feed artery vascular reactivity, we utilized an experimental model that involved resection of the femoral artery-vein pair from just upstream of the profunda femoris to the distal saphenous. Figure 6. This surgery presumably produces ischemia in the profunda femoris artery and the downstream gracilis muscle microcirculation.

Experimental Model – Intravital Microscopy

We measured feed artery diameter using side-stream Dark Field (SDF) intravital microscopy. SDF collects the reflected light from oblique 530nm pulses, which is the isobestic point for hemoglobin, so the vasculature appears dark and the parenchymal and stromal tissue appears light. Our intravital imaging station is shown in Figure 2. Example images of the muscular branch artery (at rest and following functional vasodilation) are shown in Figure 3.

Ischemia Eliminates Functional Vasodilation in Response to Moderate Muscle Contraction

To test the hypothesis that ischemia impairs endogenous vasodilation pathways, measured profunda femoris artery diameter at day-14 following resection, before and after electrical stimulation of the gracilis muscles with tungsten microelectrodes with 1mA pulses of 200μs duration at 8Hz for 90sec, Figures 7 & 8.

Ischemia Impairs Endothelial & Smooth Muscle-dependent Vasodilation

To test the hypothesis that impaired vasodilation following ischemia was due to impaired endothelial-dependent vasodilation, measured profunda femoris artery diameter at day-14 following resection, before and application of acetylcholine, sodium nitroprusside, and norepinephrine (10μM) to the physiological salt solution. The physiological salt solution was bubbled with 95%N₂-5%CO₂, and warmed to ~35°C.

Summary

• Arteriogenesis transiently reduces functional vasodilation in collateral resistance arteries. The degree of reduction appears to be impacted by the arteriogenesis stimulus, Figures 4 & 5.
• Ischemia reduces functional vasodilation in resistance arteries, Figures 7 & 8. The extent of this reduction is impacted by the muscle contraction intensity and presumably vasodilation stimulus, Figure 9. This reduction appears to be due reduced smooth muscle responses, Figure 11.
• Ischemia delays the restoration of resting diameter in resistance arteries following intense muscle contraction, Figure 10. This delay is not due to impaired responsiveness to norepinephrine, Figure 11.

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