Chronic ischemia does not impair skeletal muscle vasodilation capacity in outwardly remodeled collaterals

Matthew Yocum and Trevor Cardinal
California Polytechnic State University

Introduction
Peripheral Artery disease (PAD), an ischemic/atherosclerotic disorder of the extremities, is prevalent in 10-25% of patients over the age of 55, affecting 8 million people in the United States [1, 2]. Etiologically, atherosclerosis causes arterial narrowing at various vascular sites in the limbs (and likely elsewhere), resulting in insufficient blood delivery (ischemia) to afflicted tissues. Ischemia is a fundamentally inherent complication and the predominant cause of the disease’s deleterious symptoms. Normal revascularization (blood flow recovery) processes include angiogenesis (sprouting of capillaries) and outward remodeling (collateral enlargement). Animal ischemia models have been utilized to examine these recovery mechanisms and have led to the advent of various vascular growth promoting therapies still being tested for efficacy in PAD. Unfortunately, even when revascularization is successful and normal blood flow is regained, adequate vascular function (vasodilation and vasoconstriction) is attenuated following chronic ischemia [3]. This vascular impairment is likely influenced by a phenotypic shift in smooth muscle cells from contractile to synthetic activity. As proper vaso-active function is important for patient prognosis, we used a mouse model of ischemia to examine whether collateral expansion promoting conditions caused vascular dysfunction.

Methods
To tease apart the potential physiological conditions that would induce blood flow control impairment we utilized two surgical models of mouse hindlimb ischemia, one resulting in arteriogenic (high shear stress, normoxia, modest inflammation) and another in non-arteriogenic (decreased blood flow and more severe hypoxia and inflammation) tissue environment. The arteriogenic surgical model involved the ligation of the superficial femoral artery distal to the deep femoral artery branch point (Figure 1). Changes in the diameter of the muscular branch artery were evaluated using SDF imaging two weeks post surgery at rest and following gracilis muscle stimulation (functional hyperemia). The non-arteriogenic surgery involved the resection of the femoral artery from proximal to the muscular branch artery to mid-way between the knee and the heel (saphenous branch point) (Figure 2). The same vascular endpoints were analyzed 2 weeks post surgery.

Results
As expected arteriogenesis occurred in the muscular branch artery of the femoral artery ligation model, as the resting diameter increased by 17.4% (Figure 5A). However, vasodilatory ability of the muscular branch artery was not attenuated in this model as hypothesized (Figure 5B). In contrast, outward remodeling of the muscular branch artery did not occur in the resection model (Figure 6A). Additionally functional hyperemia was not abrogated (Figure 6B).

Discussion
Functional hyperemia following collateral enlargement was not impaired. This implies that in large arteries with modest outward remodeling (17%), such as the muscular branch, elevated shear-wall-stress does not induce endothelial dysfunction; more specifically by day 14 the smooth muscle cell contractile phenotype may be sufficiently expressed for normal vasoconstrictor response. Under conditions where neutral remodeling occurred (resection), arterial vasodilation was also not inhibited. However, following femoral artery resection the muscular branch artery was refractory to regaining resting vascular tone. After applying an electrical stimulus the artery required 30-60 minutes to reacquire its resting diameter. This was large when compared to the 4-6 minutes that were required of the alternate surgical models. Upon further reflection blood flow through the muscular branch in the resection model was particularly low and turbulent (Figure 7). This low/turbulent blood flow may have contributed to this qualitatively observed vascular dysfunction and should warrant further investigation.

References