Do changes in the vascular bed contribute to the development of denervation atrophy in skeletal muscle?

Olga Hudlicka

Department of Physiology, University of Birmingham, Birmingham B15 2TT, UK

In one of his early papers, Ernest Gutmann described that muscle ischemia impaired denervation atrophy. However, neither blood flow nor transcapillary transport decreased in muscles for several weeks after denervation, possibly due to the vasodilator action of various metabolites released by degenerating muscle fibers. Velocity of flow and thus possibly shear stress enables the maintenance of the capillary bed in these earlier stages, but with long lasting atrophy (several months) capillaries degenerate and the increased amount of extracellular collagen impairs the diffusion of substrates towards the muscle fibers.
Electrical stimulation and /or long-term increase in blood flow stimulate capillary growth via release of NO and activation of VEGF and its receptor 2, in normal muscles, and capillary density also, in denervated muscles.
Key words: atrophy, denervation, skeletal muscle, vascular bed.

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Bowden and Gutmann [2] described changes in capillaries and arterioles in denervated human muscles that would imply impairment of blood delivery and diffusion of nutrients across the capillary wall. However, numerous studies on blood flow showed no change, decreased or increased blood flow days and even months after denervation. Our own studies showed that blood flow increased immediately after sectioning of the nerve and stayed elevated for up to six weeks in muscles that lost almost 50% of their weight. Many authors explained the high blood flow in denervated muscles by the removal of the effect of the sympathetic vasoconstrictor fibers. Sympathetic fibers in cats and dogs leave the spinal cord at the level of lower thoracic and upper lumbar region while motor neurons supplying the lower limb muscles (e.g. gastrocnemius) leave the spinal cord at the lower lumbar and upper sacral level. Thus gastrocnemius muscle in animals with section of the ventral roots at the level of L5-S1 would be denervated with the sympathetic neurons intact, while sectioning of the sciatic nerve would remove the influence of both motor and sympathetic nerve fibers. Experiments performed in cats in this way revealed that blood flow after section of the sciatic nerve increased shortly after denervation and remained elevated for the following 4-6 weeks while blood flow after ventral roots section increased only later with developing atrophy. However the blood flow was elevated similarly in both cases 4-6 weeks after any intervention. When referred to the whole muscle weight it was the same as in the contralateral control muscle, when calculated per 100g of tissue it was twice as high [4]. Thus while the muscle fibers atrophied the size of the vascular bed during the firsts 4-6 weeks after denervation did not change.

However, many data showed decreased capillary supply (estimated on the basis of capillary: fiber ratio) in denervated muscles. Electron microscopic studies showed normal [8] as well as distorted [1] capillaries in rat extensor digitorum muscle 2 months after denervation. To assess whether the capillaries that are present are perfused and whether the diffusion of substances to muscle fibers was maintained at a normal level, we estimated the total capillary diffusion capacity and blood flow in muscles that had been denervated for 2-60 days [5]. Both blood flow and total capillary diffusion capacity were elevated in absolute terms (per muscle) up to 30 days and diffusion capacity was the same as in control muscle even at 60 days after denervation. We hypothesized that metabolites released from atrophic muscle fibers produce dilatation of arterioles and thus capillaries that are present are better perfused. Increased capillary perfusion in muscles denervated for 2 months was indeed reported by Tyml et al. [7]. They showed a higher number of capillaries with flow, higher velocity of red blood cells and higher red blood cell flux in rat extensor digitorum longus that had been denervated by infusion of tetrodoxin for 8 weeks than in control muscles. All these changes in capillary perfusion would result in a higher capillary shear stress which, in normal muscles, leads to generation of nitric oxide (NO) that in turn can trigger upregulation of vascular endothelial growth factor

(VEGF), a factor important in stimulation of growth and the maintenance of capillaries.

In a normal muscle, capillary shear stress in increased during muscle contractions, and even under resting conditions in capillaries of muscles that had been made to contract over several hours per day by chronic electrical stimulation. This increased shear stress led to release of NO from the endothelial cells and upregulation of the VEGF and its receptor two (VEGFR-2) and vigorous capillary growth (Hudlicka et al. [6].

Levels of VEGF and VEGFR-2 are decreased in denervated muscles long before the capillary: fiber ratio decreases [9]) Although it is not known whether chronic electrical stimulation reverses this trend in denervated muscles, it was shown that 10 weeks of electrical stimulation increased capillary supply to a normal level in muscles that atrophied as a result of spinal cord injury [3].

In conclusion, muscle atrophy during the first two months after denervation cannot be explained either by deficiency of muscle blood flow or capillary perfusion. Metabolites released by atrophying muscle fibers cause dilatation of arterioles and perfusion of the remaining capillaries is thus improved and the overall transcapillary diffusion is maintained. The decreased capillary supply is preceded by decrease in the expression of vascular endothelial growth factor and its receptor. Chronic electrical stimulation increases the expression of VEGF and VEGFR-2 in normal muscles and stimulates capillary growth in normal as well as denervated muscles, but so far it is not known whether it improves capillary perfusion and blood flow.

Address correspondence to:

Olga Hudlicka, Department of Physiology, University of Birmingham, Birmingham B15 2TT, UK
E-mail: o.hudlicka@bham.ac.uk

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