Preconditioning of individual arteriolar networks in vivo

Vascular preconditioning is classically described as a protective response in which prior ischemic or pharmacologic exposure confers altered vascular response capability. This prevents hypercontractility and no-reflow phenomenon associated with reperfusion injury. There is some evidence that preconditioning of one area of, for instance, the heart, does not confer a protective effect to, “virgin,” areas of the heart that were not directly preconditioned. This led us to ask, What is the smallest vascular unit that can be preconditioned? Our prior work examines the architecture and flow conditions within arteriolar networks. These networks have a reproducible size and shape, and repeat across the tissue for skeletal muscle and for the hamster cheek pouch. We have found that the arteriolar network becomes preconditioned with a single exposure to a preconditioning agent, such as an NO-donor. Nearby networks are not preconditioned, unless they are directly stimulated. Endogenous nitric oxide and some form of reactive oxygen are essential to stimulate the preconditioning; their action appears to converge on stimulation of mitochondrial KATP channels. Importantly, preconditioning itself is initiated by a remote stimulus to a terminal arteriole of the network. Once initiated, the preconditioning signal is transmitted to the upstream portions of the arteriolar network. Transmission requires gap junctional activity. The effect is an altered vascular response capability restricted to the upper one-half to one-third of the arteriolar network where the highest shear forces occur. This effect includes enhanced dilation to NO-donors, attenuated dilation to adenosine, and a shift in phosphodiesterase maintenance of arteriolar tone. Lately we have asked, since gap junctions transmit this response, if we initiate preconditioning at two networks simultaneously, can we confer preconditioning to a nearby network that was not directly stimulated? Much work remains to explore similarities and differences between the classically described preconditioning at the organ level, and the responses we test. Our goal is to discover the smallest vascular unit that can explain organ level vascular behavior as a means to discover the root cause(s) of flow heterogeneity.