Endothelial cell (EC) responses to shear stress generated by vascular perfusion play an important role in circulatory homeostasis, while abnormal responses are implicated in vascular diseases such as hypertension and atherosclerosis. EC subjected to high shear stress *in vitro* alter their morphology, function, and gene expression. The molecular basis for mechanotransduction of a shear stress signal, and the identity of the sensing mechanisms, remain unclear with many candidates under investigation. Translating these findings *in vivo* has proved difficult. The role of VEGF flow-dependent NO release in remodelling of skeletal muscle microcirculation is established for elevated (activity, dilatation) and reduced (overload, ischaemia) shear stress, although their temporal relationship to angiogenesis varies. It is clear that growth factor levels *per se* may offer only a permissive environment, and alteration of receptor levels may be a viable therapeutic target. Angiogenesis *in vivo* appears to be a graded phenomenon, and capillary regression on withdrawal of stimulus may be rapid. Combinations of physiological angiogenic stimuli appear not to be additive.