Cardiovasc Res. 2008 May 1;78(2):324-32. Epub 2008 Feb 28.

Effect of mechanical boundary conditions on orientation of angiogenic microvessels.

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Abstract
AIM: Mechanical forces are important regulators of cell and tissue phenotype. We hypothesized that mechanical loading and boundary conditions would influence neovessel activity during angiogenesis. METHODS AND RESULTS: Using an in vitro model of angiogenesis sprouting and a mechanical loading system, we evaluated the effects of boundary conditions and applied loading. The model consisted of rat microvessel fragments cultured in a 3D collagen gel, previously shown to recapitulate angiogenic sprouting observed in vivo. We examined changes in neovascular growth in response to four different mechanical conditions. Neovessel density, diameter, length and orientation were measured from volumetric confocal images of cultures exposed to no external load (free-floating shape control), intrinsic loads (fixed ends, no stretch), static external load (static stretch), or cyclic external load (cyclic stretch). Neovessels sprouted and grew by the third day of culture and continued to do so during the next 3 days of loading. The numbers of neovessels and branch points were significantly increased in the static stretch group when compared with the free-floating shape control group. In all mechanically loaded cultures, neovessel diameter and length distributions were heterogeneous, whereas they were homogeneous in shape control cultures. Neovessels were significantly more oriented along the direction of mechanical loading than those in the shape controls. Interestingly, collagen fibrils were organized parallel and adjacent to growing neovessels. CONCLUSION: Externally applied boundary conditions regulate neovessel sprouting and elongation during angiogenesis, affecting both neovessel growth characteristics and network morphometry. Furthermore, neovessels align parallel to the direction of stress/strain or internally generated traction, and this may be because of collagen fibril alignment induced by the growing neovessels themselves.

PMID: 18310100 [PubMed - indexed for MEDLINE]PMCID: PMC2840993