Endothelium response to supraphysiological stretch

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Abstract

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The endothelium is a cell monolayer lining the luminal surfaces of blood vessels. It forms a barrier between blood and surrounding tissues controlling the transport of molecules in both directions. Numerous clinical applications are associated with supraphysiological deformations of the endothelium, such as in angioplasty, stent placement, ventilator-induced injury, vein grafts in coronary artery bypass and blood-hammering. In such cases acute vascular damage and consequent endothelial cell loss are observed, which can lead to severe complications. In all these conditions endothelial cells undergo a mechanical loading to supraphysiological levels of stretch in short time. Our investigations aimed at determining critical conditions of endothelium stretching leading to partial or complete rupture of monolayers. To this end, we cultured endothelial cells to form a confluent monolayer on an elastomeric substrate to which we then applied uniaxial and multiaxial deformation at different strain rates. Stretch-induced damage of monolayers consisting of young, senescent, and aged endothelial populations was quantified for different stretching conditions (1). A computational discrete network model of endothelial cells under acute stretch was developed to rationalize stretch-induced damage based on phenotypic differences between cell groups (2).

High-rate experiments aimed at characterizing the instantaneous (i.e. without active cell remodeling) deformation and rupture behavior to stretches in uniaxial stress, uniaxial strain and equibiaxial conditions. The level of damage was evaluated by immunofluorescence or scanning electron microscopy as intercellular and intracellular void formation. Damage increased proportionally to the applied level of deformation, with equibiaxial stretch inducing much larger damage compared to the other conditions at the same value of maximum principal stretch.

For uniaxial strain of 40%, the aged and senescent phenotype experienced significant detachment of cells following stretch-induced damage, while the young counterpart was able to maintain or restore monolayer integrity. Larger damage in aged cells was observed also in cyclic experiments at moderate stretch levels. Based on the computational model, fragile

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behavior of aged cells was linked with their more mature focal adhesions, which lead to a more stable cell-substrate attachment of senescent cells. In fact, more affine deformation increases intracellular deformation energy, thus enhancing the tendency for cellular damage and impending detachment. Supportive of this hypothesis, cell damage was significantly reduced when senescent cells were treated to block integrin $\beta 1$, thus reducing their overall adhesion to the substrate.

Larger stretch levels, such as those associated with balloon angioplasty and stent placement, induced widespread cellular loss when applied at high rates. Remarkably, at slower rates (i.e. loading within few minutes) even for stretches larger than 200% aged cells were able to adapt, with depolymerization of the actin fibers and extension of the intermediate filaments, maintaining monolayer integrity.

In summary, the present study characterized for the first time critical levels of endothelial stretch and the rupture pattern of endothelial monolayers, depending on mechanical loading conditions. The results indicate that young cells are generally more resilient to deformation than senescent cells. Importantly, cells were able to survive very large deformations when stretching occurred at rates lower than those typically applied during clinical interventions. This may indicate a potential avenue for reducing medical complications.

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(2) R. Jakob, B.R. Britt, C. Giampietro, E. Mazza, A.E. Ehret, 2024, Discrete network models of endothelial cells and their interactions with the substrate, Biomech. Model. Mechanobiol., 23 (3)