
Discrete network simulation of the multiaxial rupture properties of the endothelium

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Abstract

Lining the luminal surface of blood and lymphatic vessels, the endothelium is exposed to various mechanical stimuli such as variable hydrostatic pressure, shear stress due to blood flow, and circumferential stretch due to the heart's pulsatility. Under physiological conditions, these stimuli contribute to endothelial homeostasis, ensuring its biological functions. However, in certain clinical conditions such as altered vessel properties, use of venous grafts in arterial bypass, or coronary angioplasty and subsequent stent placement, mechanical stimuli can reach supraphysiological levels. Specifically in angioplasty and stenting, the vessel is dilated to a multiple of its original diameter in a matter of seconds, thus acutely stretching the endothelium. As complications of these interventions, endothelial denudation and impaired endothelial repair lead to inflammation, platelet activation, and smooth muscle cell proliferation, resulting in neointimal hyperplasia, restenosis, and adverse clinical outcomes. Thus, improved understanding of the rupture properties of endothelial monolayers is of importance for the improvement of clinical outcome.

We recently investigated the behavior of endothelial monolayers when exposed to acute stretch as a result of uniaxial tensile loading with lateral contraction of their substrate up to magnitudes of 87%, comparing the response of young and aged cells (1). We revealed that aged cells were more susceptible to stretch-induced damage, characterized by intercellular and intracellular void formation, which increased with the level of deformation. Under in-vivo conditions, however, the load state can be highly heterogeneous. In the case of coronary angioplasty, for example, the placement of the stent leads to states of stretch that vary locally in magnitude and directionality. Thus, the kinematic configurations assessed based on uniaxial tensile loading do not yield sufficient information to characterize stretch induced damage in endothelial monolayers in clinically relevant cases. We therefore extended the analysis to include both equibiaxial and uniaxial (i.e. no deformation in the direction perpendicular to the loading axis) stretch conditions. The experiments indicated clear differences in the amount of damage, quantified as the area of voids formed within the monolayer depending on the loading conditions.

In order to rationalize the observations, we aimed at identifying a kinematic variable which could characterize void formation for all three kinematic states considered in the experiments. Attempts based on the maximum principal stretch or the area stretch did not yield satisfactory results. To fill this gap, we developed a computational model of endothelial monolayer deformation and damage. The model aims at representing the extensibility of intracellular cytoskeletal structures as well as intercellular connections, with consideration of corresponding failure conditions. Moreover, as the cells bind to their substrate via protein complexes

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called focal adhesions, through which the deformation of the substrate is transmitted to the cells, representation of these links, their density and failure properties is an important aspect of the analysis. To this end, we created a discrete network model of a single endothelial cell's actin cytoskeleton, linked with elements representative of nucleus, cellular membrane, and focal adhesions. After calibrating the model of a single cell to experimental data from traction force microscopy (2), we were able to capture the endothelial cell's contractile behavior on unstretched substrates as well as the local stiffening caused by a contracting cell on a soft substrate subjected to equibiaxial stretch (3). We then extended the model to represent a monolayer through connection of many of the single-cell models by incorporation of cell-cell junctions. This allowed us to create endothelial monolayer models consisting of hundreds of cells with subcellular cytoskeletal resolution.

Because the single endothelial cell discrete network representation consists of thousands of intracellular connections, the setup and simulation of a mechanical boundary value problem of endothelial monolayers consisting of hundreds of cells is computationally demanding. Additionally, simulation of sub-isostatic networks (4) as well as implementation of the breaking of connections within the network pose further challenges to the solver. Conventional numerical techniques such as finite element modelling are ill-equipped for this kind of problem. Since solvers used in molecular dynamics are designed to handle such conditions, we implemented our mechanical boundary value problem in the Largescale Atomic/Molecular Massively Parallel Simulator (LAMMPS). Inspired by the representation of covalent bonds in LAMMPS, we designed custom bond potentials to define the required mechanical behavior of the cytoskeletal components. These potentials exhibit a stretch-dependent bilinear material law with different moduli under tension and compression, respectively, as well as a stretch-dependent bond-failure criterion. The boundary value problems were solved by minimizing the potential energy by means of the Fast Inertial Relaxation Engine (FIRE).

The distribution of bond-failure properties of the intercellular connections in the computational model was determined such that good agreement was achieved with the experiments in terms of void area for the different amounts of applied stretch. This also led to sound agreement in terms of the void morphology, i.e. the endothelial damage patterns observed in the experiments. By means of the model we could confirm a correlation between the amount of void area and the total elastic energy stored in the different cytoskeletal elements. Moreover, using a hyperelastic model, the latter was expressed in terms of a strain-energy density function dependent on the isotropic strain invariants representative of the kinematic boundary conditions, so that the experimental void formation could be related to these invariants of macroscopic substrate strain. These results allow to predict the expected void area in endothelial monolayers for any arbitrary kinematic state of their substrate, thus creating a tool for estimating the expected damage during angioplasty and stenting. The model further allows us to analyze the influence of each cytoskeletal component on void formation, and thus provides a basis for biochemically modifying the properties of endothelial cells to increase their stretching resistance, or to reduce endothelial damage through an optimized application of vascular devices.

References

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