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Original

A multiscale model of the endothelial glycocalyx as mechanosensor of hemodynamic shear forces / Gallo, Diego; Sáez, Pablo; Morbiducci, Umberto. - ELETTRONICO. - (2017). ((Intervento presentato al convegno Summer Biomechanics, Bioengineering and Biotransport Conference tenutosi a Tucson (AZ, USA) nel June 21-24, 2017.

Availability:

This version is available at: 11583/2677969 since: 2017-11-10T08:32:45Z

Publisher:

Summer Biomechanics, Bioengineering and Biotransport Conference organizing Committee

Published

DOI:

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A MULTISCALE MODEL OF THE ENDOTHELIAL GLYCOCALYX AS MECHANOSENSOR OF HEMODYNAMIC SHEAR FORCES

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INTRODUCTION

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Atheroma plaque formation is one of the leading causes of cardiovascular disorders in the developed countries. The glycocalyx (GC), a bush-like layer coating the endothelial cells (ECs), plays a key role in the mechano-sensing and -transduction processes promoting atherosclerosis [1]. In fact, GC has been identified as the mechanosensor of the forces exerted by the streaming blood onto the vascular endothelial lining [2,3,4].

The focal development of atherosclerosis has been attributed to disturbed shear forces (see, e.g., ref. [5]). However, these forces, exerted by the flowing blood, are transmitted to the endothelial cells (ECs) cytoskeleton through the transmembrane proteins, i.e. the terminal structures of the GC layer on the ECs side. Although the ECs gene expression and protein production as a consequence of disturbed shear has been extensively studied [6], the mechanisms by which fluid shear forces are transmitted to the subcellular elements through the endothelial transmembrane anchoring structures is still not fully explored.

In this study a multiscale approach is applied to analyze how fluid shear forces are transmitted to the ECs transmembrane anchors through the mechanical response of the GC layer. To do it, wall shear stress (WSS) vector time histories are calculated at the luminal surface of a carotid bifurcation, a vascular district prone to atherosclerotic lesions development, through image-based computational hemodynamic modelling. Then, a mechanical model of the GC structure, based on the Timoshenko beam theory [7], is applied to

simulate the mechanical behavior of the GC layer. Realistic atheroprone and atheroprotective WSS vector time histories, as obtained from computational hemodynamics, are prescribed to the idealized GC structure, and the dynamic forces transmitted to the anchoring elements on the EC membrane are evaluated. Finally, the comparison of the distribution of WSS phenotypes and of the corresponding mechanical forces transmitted to the anchors at the membrane level is performed, and the possible scenario opened by the presented findings is discussed.

METHODS

An ostensibly healthy carotid bifurcation geometry was reconstructed from angiographic computed tomography images [8]. The finite volume method was applied to solve the governing equations of the fluid motion under unsteady flow conditions. The general purpose computational fluid dynamics (CFD) code Fluent (ANSYS Inc., USA) was used on a tetrahedral computational mesh-grid of cardinality 1400000. Exhaustive details on the computational setting can be found elsewhere [8]. From the CFD simulation, the near-wall hemodynamics was characterized in terms of time-averaged WSS (TAWSS), and oscillatory shear index (OSI).

The endothelial GC presents a 3D bush-like structure with a constant spacing of 20 nm in all directions and a diameter of 10-12 nm [9; 10]. The anchoring locations present an hexagonal-like distribution and are spaced each other 100 nm [11; 12]. Based on these observations, Weinbaum and co-workers [13] proposed a continuum mechanics model of the endothelial GC, that has been adapted here. In detail, the hexagonal symmetric structure was simplified to a single branch centered in the anchor. This idealization relies on the assumption that the same fluid shear stress acts on all the elements of the hexagonal structure. The Timoshenko beam theory [7] was applied

in 3D to model GC deflection and to gather the reaction forces in the anchoring structures. In order to solve the Timoshenko beam theory, the finite element method-based commercial software ABAQUS was used. The shear stress was applied to 1/6 of the upper segment of the beams [13]: in fact, the GC layer acts as a dense porous medium to the blood. As a consequence, blood flow is not able to penetrate the GC layer in depth, so that the velocity profile within the layer rapidly decreases from the GC tip to the lumen surface, vanishing close to the EC membrane surface [13]. The attachment of the GC to the anchoring structures was modeled in terms of Dirichlet boundary condition, with zero imposed displacements. The fluid stimuli \mathbf{F}_{shear} (as the force derived from the WSS vector applied to the surface of the upper segment of the GC), and the mechanical forces transduced by the glycocalyx \mathbf{F}_{mem} (obtained at the GC anchor point on the EC membrane) were calculated at each node on the luminal surface of the carotid bifurcation. For a quantitative description of the role played by the GC layer in transducing the fluid stimuli to the EC membrane, we introduce here a new indicator, the Oscillatory Force Index (OFI):

$$OFI = 0.5 \left[1 - \frac{\left(\int_0^T |\mathbf{F}_{mem} \cdot dt| \right)}{\left(\int_0^T |\mathbf{F}_{mem}| \cdot dt \right)} \right] \quad 0 \leq OFI \leq 0.5$$

Inspired by the OSI, OFI is a measure of the oscillations of the mechanical force \mathbf{F}_{mem} transmitted by the GC to the EC membrane.

RESULTS

A snapshot of the deformed shape of the Timoshenko beam-based model of one GC is presented in Fig. 1, where the deformation of the structure is obtained by applying an instantaneous fluid shear force \mathbf{F}_{shear} as obtained from CFD simulations.

Among the main findings of the study, we report that: (1) discrepancies between the OSI distribution and OFI distribution at the luminal surface can be observed, in particular in the bifurcation region (Fig. 2, top row); (2) the cycle-averaged value of the magnitude of the force transmitted to the transmembrane anchor \mathbf{F}_{mem} is, in general, similar to the distribution of the fluid shear force \mathbf{F}_{shear} , in particular in the bifurcation region, where the lowest forces values can be observed (Fig. 2, bottom row). These findings suggest that the GC layer does not merely transmits near-wall forces to the EC membrane as they are: the GC mechanical transduction could lead to a modification of the sensed pattern of blood shear forces, especially in terms of direction.

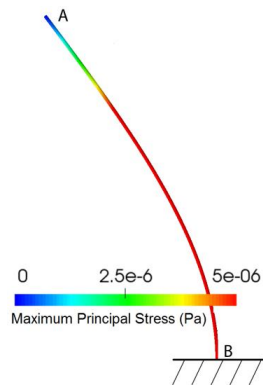


Figure 1: explanatory example of GC deformed by applying an instantaneous fluid shear force \mathbf{F}_{shear} as obtained from CFD simulations. \mathbf{F}_{shear} is applied in A, \mathbf{F}_{mem} in B. The deformed GC structure is color-coded with the instantaneous local value of the maximum principal stress.

DISCUSSION

In this study a multiscale approach is applied to analyze how near-wall fluid shear forces are transmitted to the transmembrane

anchors of ECs, through the mechanical response of the GC layer. The presented analysis, although preliminary, suggests that the presence of the GC layer alters focally both the magnitude and directionality patterns of the real forces acting on the membrane of ECs, with respect to WSS stimuli, widely considered as a localizing factor of vascular disease. This study is intended to investigate the mechanical role of the GC layer in transmitting hemodynamic shear forces to the EC membrane assuming that the acting near-wall fluid forces are not disruptive of the GC layer itself. This is like to say that the study is intended to investigate the role of GC mechanosensors at a pre-disease stage. In conclusion, the approach proposed here could contribute to clarify the mechanisms of transmission of local near-wall fluid forces sensed by the GC to the EC membrane, thus bridging the gap of knowledge still existing. In particular, mapping near-wall forces distribution at the luminal surface *versus* the forces transmitted to the EC membrane could represent a powerful tool to link hemodynamics to the mechanobiology of the endothelium.

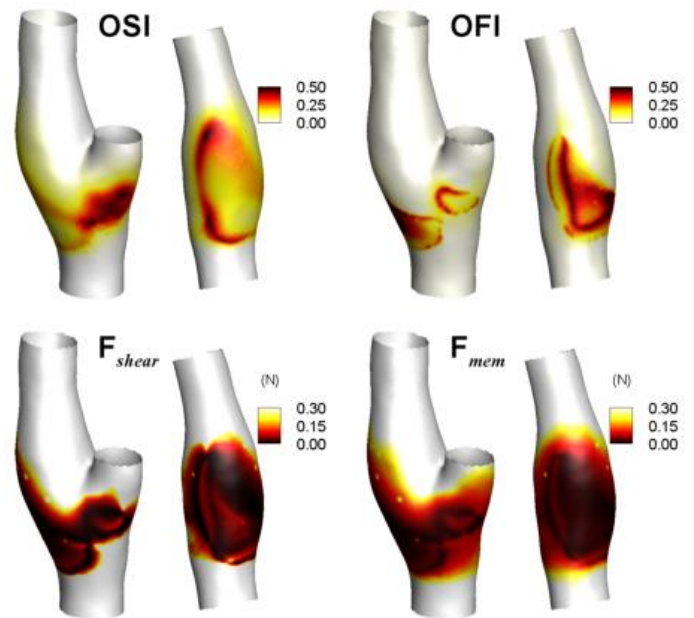


Figure 2: OFI vs OSI distributions (upper panel), and cycle-averaged \mathbf{F}_{shear} vs \mathbf{F}_{mem} distributions (lower panel) at the luminal surface of the carotid bifurcation. The role played by GC in modifying the near-wall hemodynamic forces direction, when they are transmitted to the transmembrane anchors, can be appreciated by visual inspection.

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