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Abstract

Atherosclerosis is a systemic disease that leads to accumulation of deposits, known as atherosclerotic plaques, within the walls of the carotids. In particular, three types of plaque can be distinguished: soft, fibrous and calcific. Most of the computational studies who investigated the interplay between the plaque and the blood flow on patient-specific geometries, used non standard medical images to directly delineate and segment the plaque and its components. However these techniques are not so widely available in the clinical practice. In this context the aim of our work was twofold: i) to propose a new geometric tool that allowed to reconstruct a plausible plaque in the carotids from standard images and ii) to perform 3D FSI simulations where we compared some fluid-dynamic and structural quantities among 15 patients characterized by different typologies of plaque. Our results highlighted that both the morphology and the mechanical properties of different plaque components play a crucial role in determining the vulnerability of the plaque.

1 Introduction

Carotid arteries represent a preferential site for the development of atherosclerosis, a pathological condition corresponding to the reduction of the arterial lumen due to the formation of deposits of calcium, fat substances or abnormal inflammatory cells that occur in the innermost layer of arteries, the intima. The accumulation of such deposits leads to the atherosclerotic plaques, which can grow producing stenosis. The major complications of atherosclerotic plaque development are the thrombotic occlusion of arterial lumen and the cerebral embolization both from plaque's inner content or dislodgement of thrombus. [1].

Based on the histology, the structure and the mechanical properties, three types of plaques can be distinguished: soft, fibrous and calcific [2, 3, 4, 5]:

- *Soft plaques* mainly comprise high lipid content covered by a thin fibrous cap. This type of plaque has a low mechanical stiffness due to the presence of a large lipid pool;
- *Fibrous plaques* are made by packs of collagen fibers, small amount of lipid pool, and possible small calcifications. This type of plaque has an intermediate mechanical stiffness due to the presence of collagen fibers;
- *Calcific plaques* are composed by compact calcium crystals covered by a fibrous cap. This type of plaque has a high mechanical stiffness due to the presence of calcium deposits.

Computational methods, based on patient-specific geometries obtained from medical images, represent a non-invasive way to describe the interplay between plaque and blood dynamics [6]. For example, low and oscillating Wall Shear Stresses (WSS) have been shown to correlate positively with plaque formation, intimal thickening [7, 8, 9, 10], and re-stenosis after carotid endarterectomy [11], whereas high values of WSS and Von Mises (VM) stresses acting on the fibrous cap are considered as haemodynamic indicators of plaque rupture [12, 13, 14, 15].

The geometric identification and reconstruction of the plaque are considered a challenging task due to the difficulty to detect its three-dimensional extension from standard imaging techniques and to the available reconstruction tools for the vessel wall that are often based on extrusion strategies and thus scarcely adaptable to the plaque. For this reason, Computational Fluid-Dynamics (CFD) studies in a rigid domain have been often considered. These accounted for the presence of the plaque in a "geometric" way, through the stenosis appearing in the lumen as a consequence of the plaque. Several groups considered simplified idealized models of carotid arteries obtained by geometric-shaped narrowings [16, 17, 18]; others, instead, proposed studies in patient-specific geometries, obtained with medical imaging techniques [19, 20, 21, 22, 23].

To obtain a better characterization of blood dynamics and accurate results also for the internal structural stresses, several works considered a Fluid Structure Interaction (FSI) approach. This allowed to include the presence of the plaque in the structure model with different approaches to account for the changes in geometry and mechanical properties determined by its morphology and composition. Early FSI works were performed in idealized geometries of carotid arteries [24, 25, 26]. In order to provide clinically useful information, several groups conducted studies in patient-specific geometries. First works which involved the presence of plaque in the structure model were performed in 2D [27, 28] which evaluated the mechanical stresses acting on plaques with lipid filled necrotic core.

Regarding 3D FSI models, there were different strategies to account for the presence of the plaque. In [29] the changes in geometry were modeled through the inclusion of a stenosis in the fluid lumen. The presence of the plaque was however ignored in the structure model. In [30] the authors proposed a surrogate model based on substituting the plaque with a set of springs applied at the external surface of the stenotic carotid wall.

Other works used a specific, non-standard imaging based on multi-contrast MRI techniques to detect and segment directly the plaque. For example, in [31] the 3D plaque was considered in the structure model, however with no specific mechanical and morphological characterizations since it was embedded as part of the healthy tissue; in [32, 33] the effects of varied lipid pool volumes on distribution of mechanical stresses were studied; in [34, 35] the detailed modeling of the atherosclerotic tissue allowed a better understanding of the rupture of the plaque; in [36] the effect of calcification patterns in plaques with different fraction volumes has been investigated.

All the previous works suffer from the limitation that are all based on clinical data that are not commonly acquired in the clinical practice for diagnostic purposes. To overcome such limitation, in [37] the authors proposed a new strategy to obtain a plausible plaque starting from standard MRI imaging. This method is based on the (non-constant in space) extrusion of the stenotic lumen and on the assumption that at an external view the carotid appears as the healthy one, since the plaque grows up from the internal side, that is towards the lumen.

In this context, the aim of our work was twofold. The first one, in a effort of using clinical data coming from the daily clinical practice, was to propose a new geometric tool that allowed to reconstruct a plausible plaque in stenotic carotids starting from standard AngioTC images. In more details, this strategy allowed us to differentiate the mechanical properties of the single plaque components, such as the lipidic core and the calcifications. This new tool could be useful when one directly build the structure computational mesh, without reconstructing a structure geometry. The second aim of the work was to perform, starting from this tool, 3D FSI simulations where, for the first time at the best of the authors knowledge, we compared fluid-dynamic (velocity and WSS) and structural (displacements and Von Mises Stresses) quantities among patients characterized by different typologies of plaque, namely soft, fibrous, and calcific, all with severe degrees of stenosis (>70%).

2 Materials and Methods

2.1 Patients recruitment and images acquisition

Fifteen asymptomatic patients who underwent ECD with an Affinity 50 ultrasound scanner and linear 8MHz probe (Philips Ultrasound, Bothell, WA) as preoperative evaluation of the degree of stenosis and plaque typology, were selected at the Operative Unit of Vascular Surgery of the Istituto Auxologico Italiano in Milan, Italy. The percent of stenosis was classified according to the guidelines of the European Society for Vascular Surgery (ESVS) [38], based on the NASCET measurement method, referring to the peak systolic velocity (PSV), end-diastolic velocity (EDV) and their ratios in the internal carotid artery (ICA) and common carotid artery (CCA) [39]. Ethical review board approval and informed consent were obtained from all patients.

The acquisitions of AngioTC images were performed with a GE Light Speed VCT 64-slice 3T (GE Healthcare, Little Chalfont, U.K.) with the following main acquisition parameters: slice thickness 0.625 mm, reconstruction matrix by 512×512 pixels and a final resolution of $0.39 mm \times 0.39 mm \times 0.625 mm$.

In Table 1 we reported some information about the patients. In particular, the population analyzed is composed by five patients with soft plaques (S), five patients with fibrous plaques (F) and five patients with calcific plaques (C).

Patient	Age	Sex	% Stenosis	enosis Type of plaque	
S1	62	Μ	75	Soft	
S2	71	Μ	75	Soft	
S3	81	Μ	80	Soft	
S4	84	Μ	85	Soft	
$\mathbf{S5}$	82	Μ	90	Soft	
F1	74	М	75	Fibrous	
F2	84	Μ	85	Fibrous	
F3	66	Μ	90	Fibrous	
F4	84	Μ	90	Fibrous	
F5	83	Μ	90	Fibrous	
C1	84	М	80	Calcific	
C2	61	F	80	Calcific	
C3	71	Μ	85	Calcific	
C4	68	F	90	Calcific	
C5	74	F	90	Calcific	

Table 1: Data-set of the population under investigation.

2.2 Geometric reconstruction of the lumen

In Figure 1 we reported the flow chart summarizing the steps and the strategy to obtain the geometry of the lumen, of the vessel wall, and of the plaque. In particular, the surface model of the interface between the blood and the arterial wall for each of the fifteen stenotic carotids was reconstructed starting from the AngioTC images (Figure 1.a). This segmentation was performed by using a level-set technique with a colliding fronts initialization provided by the Vascular Modeling Toolkit (VMTK) [40]. The output represents the surface geometry of the stenotic lumen (Figure 1.b), describing the vertices of triangles using a 3D Cartesian coordinate system.

To generate the computational fluid meshes, the surface models of the stenotic lumen were successively turned into volumetric meshes of about 220K tetrahedra with 3 boundary layers (Figure 1.c). This corresponds to a representative value of the space discretization h, which was about $0.05 \, cm$ far from the stenosis and about 0.01 cm at the stenosis. This value was set after a mesh refinement study, with the aim of obtaining a mesh-independent numerical solution.

2.3 Geometric reconstruction of the vessel wall and of the plaque

To include the physical presence of the plaque in the solid model and generate the corresponding structure mesh, we proposed a new geometric pipeline based on differentiating the mechanical properties of the structure to account for plaque and healthy vessel. The final results of our pipeline were reported in Figure 1.h and 1.i.

To do this, we followed two steps. In the first one we reconstructed a *plausible healthy lumen* (Figure 1.d) by reinflating the stenotic areas of the lumen. To do this we used the software *MeshMixer* (http://www.meshmixer.com).

After, we performed a Boolean difference between the plausible healthy lumen and the stenotic lumen to obtain the contour of the plaque (Figure 1.e). In this case we used the software *NetFabb* (https://www.autodesk.com/products/ netfabb/). This output allowed us to distinguish the plaque region with respect to the healthy vessel one.

In the second step we generated the healthy vessel wall by combining two constant in space extrusions, leading to two different solid meshes: the *stenotic solid mesh* obtained by extruding the stenotic lumen (Figure 1.f) and the *plausible healthy solid mesh* by extruding the plausible healthy lumen (Figure 1.g), in both cases with a thickness equal to 20% of the radius of the lumen [41]. After, we created a new geometry whose interface was given by the stenotic solid mesh (f), whereas the external surface by the plausible healthy solid mesh (g). Then, the volume subtended by the contour of the plaque found at previous step was joined to this geometry. The output was the final structure (healthy vessel + plaque) geometry (Figure 1.h). The final model was meshed in *Gmsh* (http://gmsh.info/) in order to realize the plaque and healthy structure meshes (Figure 1.i).

With this geometric tool we generated the 15 plaques related to the patients. We observed that, based on the observation of the lumens that presented noneccentric stenosis and on the indications of vascular surgeons who removed the plaques, we considered for all the cases a cylindrical plaque that spreads out along all the lumen circumference with one or even two pronounced thickening, see Figure 2.

As stressed, the tool we have described has been thought for standard images which are not able to detect the different plaque components. In order to delineate the latter, such as the lipidic core and the calcifications, we referred to some general properties reported in the literature.

In particular, regarding the soft plaque, we assumed that the contour of the internal lipidic core featured the same shape of the external surface of the reconstructed plaque [26], see Figure 3. Moreover, the area comprised between the core and the external plaque surface was assumed to composed by the fibrous cap [26], see Figure 3. The thickness of this cap was assumed to be constant along the plaque and equal to about 100 μm , which is a typical value of plaques with thin fibrous caps [42, 43].

Instead, for the fibrous plaque we did not identify different components since this plaque was formed only by fibrotic material [44], see Figure 3.

Regarding the calcifications, we modeled them as a compact, dense, coherent material [45], immersed in the fibrous cap [46]. In particular, we assumed them of ellipsoidal shape occupying a percent of volume of the total plaque volume



Figure 1: Flow chart summarizing the steps and the strategy to obtain the geometry of the lumen, of the healthy vessel, and of the plaque



Figure 2: Plaques reconstructed by the proposed tool. In grey: contour of the plaque. In green: plaque on an internal section.

equal to 60%, see Figure 3, in accordance with studies based on medical imaging which highlighted a fraction of volume greater than 50% [47]. The location of this deposit was close to the lumen, with a thickness of the fibrous cap equal to 50 μm [48].

Once the plaque with its components has been reconstructed, the corresponding 15 structure meshes composed of about 300K tetrahedra were generated. The value of space discretization h for healthy volume and plaque was set for all the meshes equal to 0.1 cm. This value was obtained after a mesh refinement study, with the aim of obtaining a mesh-independent numerical solution.



Figure 3: Geometric reconstruction of the each component of the plaque. Red: healthy vessel; Green: fibrous cup; Blue: lipidic core; Yellow: calcifications; Pink: lumen.

In Figure 4 we reported all the structure meshes, together with the components of each plaque typology.

2.4 Mathematical and numerical model

We considered the blood as a Newtonian, homogeneous, and incompressible fluid, and, accordingly, we numerically solved the Navier-Stokes equations written in the *Arbitrary Lagrangian-Eulerian* (ALE) formulation [49, 50]. Regarding the structure, both the healthy vessel and the plaque components were modeled by means of the linear infinitesimal elasticity (Hooke's law) to study the wall mechanics [51, 52]. The elastodynamics problem was written in the Lagrangian configuration [53].

The fluid and structure problems were coupled through the no-slip condition and the third Newton law (kinematic and dynamic conditions) [54].

For the computation of the fluid domain, we used an harmonic extension of the fluid-structure interface displacement [55, 56]. This led also to a geometric



Figure 4: Structure meshes generated by the proposed tool. Red: healthy vessel; Green: fibrous cup; Blue: lipidic core; Yellow: calcifications; Pink: lumen.

coupling between fluid domain and structure problems [57].

For the numerical solution of the FSI problem, we considered a first order time discretization based on Finite Differences for the fluid and structure subproblems and for the kinematic interface condition. The convective term and the geometric coupling were both treated implicitly. The resulting non-linear problem was solved monolithically by means of first order Finite Elements stabilized by means of SUPG-PSPG technique [58, 59], with an inexact Newton method given by an approximation of the Jacobian matrix [60]. The resulting linear system arising at each Newton iteration was solved by using the GMRES method with block parallel preconditioner FaCSI [60].

2.5 Boundary conditions

At the inlet of each computational fluid domain, we imposed a parabolic velocity profile in order to guarantee the physiological representative flow rate reported in Figure 5 [23], whereas at the outlet sections we considered a 3-elements windkessel lumped parameter model (formed by two resistances, the proximal and the distal one, and by a capacitance), which provides a dynamic relationship between pressure and flow rate accounting for the downstream circulation [61, 62]. In particular, the proximal resistance was set as the one obtained in the case of a resistance absorbing boundary condition [63] in order to avoid spurious numerical reflections given by the truncation of the fluid computational domain. Instead, the values of the distal resistance and of the capacitance were chosen in order to guarantee an appropriate flow division between the common carotid artery (CCA) and the internal carotid artery (ICA) at the systolic peak, according to the literature [15]. In Table 2, we reported, for each degree of stenosis, the corresponding flow division prescribed in the simulations.

% Stenosis	(Q_{ICA}/Q_{CCA})
75	0.7
80	0.625
85	0.55
90	0.475

Table 2: Relationship between the degree of stenosis and the flow division given by the ratio between the flow rates at the common carotid artery (Q_{CCA}) and at the internal carotid artery (Q_{ICA}) at the systolic peak [15].

Regarding the computational solid domain, we imposed null displacements at the inlet and outlet rings, whereas on the external surface, we prescribed a Robin condition with parameter α assuming an elastic behavior of the surrounding tissue represented, for example, by the jugular vein [30, 64].



Figure 5: Flow rate prescribed at the inlet of each the computational fluid domain.

2.6 Settings of the numerical simulations

Unsteady numerical simulations have been performed by using the parallel Finite Element library *LifeV* (https://bitbucket.org/lifev-dev/lifev-release/wiki/Home).

Regarding the fluid problem, we used the following data: kinematic viscosity $\mu = 3.5 \cdot 10^{-3}$ Pa· s and density $\rho = 1.05 \ g/cm^3$. The Young moduli of the structures were:

- 300 KPa for the healthy vessel [30];
- 3 KPa for the lipidic core, that is 1/100 of the value of the healthy vessel [65];
- 300 KPa for the fibrous cap, that has the same mechanical properties of the healthy vessel [5, 65];
- 30 MPa for the calcifications, that is 100 times greater than the value of the healthy vessel [66].

For all the structures we used a Poisson coefficient $\nu = 0.45$ [27, 52] and an elastic surrounding tissue with $\alpha = 2 \cdot 10^5 Pa/cm$ [30].

For the time step discretization we selected $\Delta t = 1 \cdot 10^{-3} s$. The absolute tolerance for the inexact Newton method was set equal to $1 \cdot 10^{-6}$, whereas the relative one used for the convergence of the linear system to 10^{-10} .

For each patient we ran two heartbeats and we discarded the first one, thus our results referred to the second heartbeat. In more details, our analysis was focused on the systolic instant t = 0.31 s.

2.7 Quantities of interest

The major consequence of atherosclerosis in carotid arteries is the rupture of the plaque. To describe the vulnerability of each plaque typology, we introduced the following post-processed quantities:

- *Peak Systolic Velocity (PSV)* is the value of the velocity magnitude at the systolic peak obtained at the tightest stenosis level. In presence of atherosclerotic plaque, values higher than 200 cm/s are considered as fluid-dynamics indicator that enhances plaque vulnerability, increasing the risk of plaque rupture [67];
- Wall Shear Stresses (WSS) are defined as the magnitude of tangential force per unit area that are exerted by the flowing fluid on the surface of the vessel. In particular, high values of WSS might be detrimental for patients and lead to the rupture of the plaque [12]. Accordingly, we introduced the function of time $WSS_{max}(t)$ of the maximum-in-space WSS and its systolic value \widehat{WSS}_{max} ;
- Displacements of the structure (vessel wall and plaque) due to the interaction with blood, especially in correspondence of the plaque. In our work the motion analysis could provide important information about the plaque stability [68]. In particular, we computed the maximum value in space of the systolic displacements magnitude, \hat{D}_{max} ;
- Von Mises (VM) stresses are often used in determining whether an isotropic and ductile material will yield when subjected to a complex loading condition. In our work we employed VM stresses because areas with high values were seen to be correlated with a large rupture risk [13]. To be more precise, we introduced the function of time $VM_{max}(t)$ of the maximum-inspace VM stresses and its systolic value \widehat{VM}_{max} .

3 Results

In Figure 6 we reported the streamlines at the systolic instant to describe the velocity field. From this figure we observed that the different plaque typologies were characterized by different blood velocity field. In particular, the velocities were significantly higher in the calcific plaques, due to the small displacement of the lumen induced by the calcifications in correspondence of the stenosis. Accordingly, in the fibrous plaque we found intermediate values, whereas the lowest values were found in the soft plaques.

Patient	Stenosis	PSV	WSS_{max}	D_{max}	VM_{max}
	[%]	$[\mathrm{cm/s}]$	[Pa]	[mm]	[KPa]
S1	75	179	63	0.22	41
S2	75	191	55	0.21	40
S3	80	230	76	0.23	36
S4	85	255	62	0.16	36
S5	90	263	140	0.22	33
F1	75	210	66	0.05	13
F2	85	310	118	0.08	18
F3	90	300	116	0.09	14
F4	90	289	117	0.07	14
F5	90	327	110	0.11	18
C1	75	237	92	0.03	6
C2	80	304	112	0.037	5
C3	85	351	140	0.039	9
C4	90	385	250	0.05	8
C5	90	422	360	0.042	10

This was also confirmed by the PSV values reported in Table 3. In particular, the average values obtained, for each type of plaque, among the five patients, featured differences up to 29% and 52% for the fibrous and calcific plaques, respectively, with respect to the soft plaques.

Table 3: Values of maximum-in-space systolic velocity, PSV, and WSS, \widehat{WSS}_{max} , at the stenosis, together with maximum systolic displacement, \widehat{D}_{max} , and VM stresses, \widehat{VM}_{max} , within the plaque.

In Figure 7 we reported, for all the patients, the spatial distribution of the systolic WSS magnitude. Again we observed significantly higher values featured by the calcific plaques, intermediate values in the fibrous plaques and the lowest values for the soft plaques, see also Table 3 where we reported the values of WSS_{max} . In Figure 8, *left*, we reported the time behavior of the average, among the five patients, $WSS_{max}(t)$ for each type of plaque. We observed a significant difference between fibrous and soft plaques and an even more pronounced discrepancy with calcific plaques. In particular, we found an increment of average \widehat{WSS}_{max} (that was at the systole) equal to 33% and 140% for the fibrous and calcific plaques, respectively, with respect to the soft plaques. To better quantify these differences, in Figure 9, left, we reported a histogram showing the 100 highest values of systolic WSS magnitude at the stenosis and clustering them in five intervals. From this graph we observed that the most of the values of the soft plaques fell within the range 0-100 Pa, whereas that for the fibrous plaques in the range of 51-100 Pa. Regarding the calcific plaques, we found greater values, even greater than 200 Pa.



Figure 6: Streamlines of the velocity field at systolic peak. Up: soft plaques; Middle: Fibrotic plaques; Bottom: Calcific plaques.



Figure 7: Spatial distribution of WSS magnitude at systolic peak. Up: soft plaques; Middle: Fibrotic plaques; Bottom: Calcific plaques.



Figure 8: Trend in time of the average of the WSS_{max} and VM_{max} for each type of plaque, among the five patients.



Figure 9: Distribution of the systolic WSS stresses and VM stresses in the different plaques.

In Figure 10 we reported the spatial distribution of the magnitude of the systolic structure displacement. From this figure we observed that the highest values were featured by the soft plaques, especially in correspondence of the plaque, and the lowest in the calcific plaques. This was also confirmed by the values reported in Table 3, where we computed the values of \hat{D}_{max} . In particular, we noticed differences of the average values among the five patients up to 160% and 425% for the soft plaques with respect to fibrous and calcific plaques, respectively.

In Figure 11 we reported, for all the patients, the spatial distribution of the systolic VM stresses. From this figure we noticed that in the soft plaques areas with high concentration of stresses, located in the thin fibrous cap, were present. Instead, for the fibrous and calcific plaques we found lower VM stresses values and no presence of peak stresses. In Table 3 we reported the values of VM_{max} , which confirmed this trend. Morever, in Figure 8, right, we reported, for each type of plaque, the time behavior of the average, among the five patients, of $VM_{max}(t)$. In this case, we had important differences between calcific and fibrotic plaques and even more larger discrepancies with respect to the soft plaques. In particular, the average systolic values of the soft plaques featured differences, up to 113% and 393% with respect to the values of fibrotic and calcific plaques, respectively. To better quantify these differences, in Figure 9, right, we reported a histogram showing the 100 highest values of systolic VM stresses within the plaque, clustering them in four intervals. From this graph we noticed that the most of the values of the calcific plaques were within the range 0-10 KPa, whereas that for the fibrous plaques in the range of 11-20 KPa. Regarding the soft plaques, the VM stresses values were characterized by larger values, almost all higher than 21 KPa.

4 Discussion

4.1 The role of the different plaque components

Aim of this work was to propose a new geometric tool that allowed us to reconstruct the plaque in the carotids starting from standard medical images, with the final goal of performing a computational FSI analysis. Often, from standard medical images the contour of the 3D plaque is scarcely detectable. On the contrary, other patient-specific studies used multi-contrast MRI techniques to directly visualize and segment the plaque and its components. However the main drawback of such techniques is that often they are not available for standard diagnostic purposes [30].

At the best of our knowledge, this is the first computational analysis who compares fluid-dynamic and structural quantities among patients characterized by different typologies of plaque. In particular, our computational results highlighted considerable differences among the plaque typologies. These great variations led to a different behavior of the plaques once subjected to the impinge-



Figure 10: Spatial distribution of the displacement magnitude at systolic peak. Up: soft plaques; Middle: Fibrotic plaques; Bottom: Calcific plaques.



Figure 11: Spatial distribution of the VM stresses at systolic peak. Up: soft plaques; Middle: Fibrotic plaques; Bottom: Calcific plaques.

ment of blood flow. In more details, we modeled the soft plaques with a large lipidic core, covered by a thin fibrous cap. This morphology made this type of plaque prone to the highest values of displacements \hat{D}_{max} and Von Mises stresses \widehat{VM}_{max} . Accordingly, due to the large motion of the lumen in correspondence of the stenosis, the fluid dynamic quantities (peak velocity PSV and maximum Wall Shear Stress \widehat{WSS}_{max}) were considerably lower with respect to the other plaques.

Instead, the fibrous plaques can be considered a 'special' version of the soft ones, where the lipidic core is absent or located far from the lumen where its effects on the fibrous cap can be negligible. In our work we modeled it without the lipidic core. This choice underlined that the displacements within the plaque were lower, because the global stiffness of the plaque was higher and thus we found higher values of PSV and \widehat{WSS}_{max} whereas lower values of \widehat{VM}_{max} with respect to the ones of the soft plaques.

This different behavior of the fibrous plaques with respect the soft plaques resulted to be even more evident if we analyze the calcific plaques. In our work we modeled this typology by including a coherent mass of ellipsoidal shape occupying the 60% of the volume of the plaque, covered by a thin fibrous cap. From this model we noticed that they were the less stressed (lowest \widehat{VM}_{max}) and the most stable, due to the lowest value of \widehat{D}_{max} occurring within the plaque, making this type of plaque the most similar to a rigid wall. Accordingly, this morphology led to the highest values of PSV and \widehat{WSS}_{max} in correspondence of the stenosis.

Therefore, our results highlighted a positive correlation between the global Young modulus of the plaque (fibrous cap + component) and the fluid-dynamic indexes. Indeed, a greater stiffness led to lower lumen expansion in correspondence of the stenosis and thus increased PSV and \widehat{WSS}_{max} .

WSS, that are the forces that the fluid exerts on the surface of the vessel due to its viscous nature, cause a state of stress within the plaque that can be quantified by employing the VM stresses. However, looking at Figures 7 to 9 and Figure 11 and at Table 3, VM stresses resulted highest in the soft plaques, where the WSS had the lowest values compared with the other plaques typology. This is due to the nature of the different plaque components: the lipidic core and the calcifications. Indeed, the large lipidic core acts in two ways: its great compliance (large displacements) makes the entire soft plaque the less stiffer structure with respect to the other typologies, leading to the lowest values of PSV and \widehat{WSS}_{max} , but it is not able to bear the loads given by the WSS. Thus, a great amount of deformations and loads are transmitted over a smaller area, i.e. the thin fibrous cap, that is stiffer with respect to the lipidic core, leading to a focal increase of the mechanical stresses [69]. Thus, even if in the soft plaques PSV and \widehat{WSS}_{max} were the lowest, the nature of the lipidic core gave rise of a hot-spot of structural stresses in the thin fibrous cap. Accordingly, in Figure 11 we noticed that in the soft plaques, the lipidic cores did not support a great

amount of mechanical stresses. This behavior is in agreement with other studies [46, 70].

On the contrary in the fibrous and calcific plaques we found higher values of \widehat{WSS}_{max} and PSV, but lower values of \widehat{D}_{max} and \widehat{VM}_{max} . In particular, in the fibrous plaques, the absence of the lipidic core increased the global stiffness with a consequent increase of \widehat{WSS}_{max} and PSV. However, the loads given by WSS are more homogeneously concentrated and less high because distributed over a greater fibrous cap with respect to the one of the soft plaques.

This behavior was amplified in the calcific plaques, modeled by macro calcifications which were stiffer than the covering fibrous cap. Thus, the macro calcifications increase the global stiffness of the plaque, and lead to the highest values of PSV and \widehat{WSS}_{max} , but at the same time they are able to carry a higher fraction of the loads given by WSS. Indeed, macro calcifications reduce the deformations of the adjacent layers and thereby VM stresses are below those the thin fibrous cap can carry [71].

Summarizing, these results suggested that the different plaque components submitted the fibrous cap to different states of mechanical stresses. From a mechanical point of view the rupture of the plaque occurs when the stresses acting on the fibrous cap exceed the cap strength [72]. Based on this and previous considerations, in what follows we referred to the VM stresses to assess the plaque vulnerability because they are suited to describe the distribution of load between the plaque components.

4.2 Plaque vulnerability

One of the major complication related to atherosclerosis development in carotids is the rupture of the plaque with consequent formation of a thrombus and possible embolism. Plaque rupture is rapid and, in most cases, unpredictable. Based on what previously discussed, we used the VM stresses as suitable quantity to predict the risk of plaque rupture, see Figures 8, 9, 11 and Table 3. Our results suggested that the large lipidic core, present in the soft plaques, exerted a key role in making the thin fibrous cap vulnerable and led to the highest values of VM stresses among all the plaque typologies. In particular, if the thickness of the fibrous cap is small and the lipidic core volume is large, then the probability to have peak concentrations of high VM stresses in the fibrous cap is large.

In literature there is a great consent about the fact that the soft plaques are the most unstable due to the presence of a great amount of lipidic core that makes the structure vulnerable to rupture [32, 33, 71]. Regarding the fibrous plaque, we found that the presence of the only fibrotic material led to a homogeneous state of stresses within the plaque with the presence of intermediate values of VM stresses. This is due to the fact that the fibrous tissue provides a more structural integrity to the plaque, with respect to the lipidic core [73]. Instead, in the calcific plaques, the role of the calcium deposits and the effect on the plaque stability is still unclear [36]. Our results highlighted that, the presence of thick calcium deposits stabilized the structure, by lowering the displacements and VM stresses, making the whole plaque stiffer and less prone to rupture. This is in agreement with previous studies [71, 74].

Notice that the calcium deposits may form a dense and coherent material (as in our work), but also be present as micro-calcifications, namely inclusions that do not coalesce into a compact calcified deposit but are scattered in the fibrous cap with a dimension less than 0.05 mm [45].

4.3 Clinical relevance

We found that the soft plaques are the most vulnerable and thus the first candidates to rupture and embolism, whereas the fibrous and calcific plaques seem to be more stable, without the presence of hot spots of high stress concentrations that could lead to rupture (see Figures 8, 9, 11 and Table 3). Therefore, together with the morphology, also the components of the plaque play a crucial role in determining the stress configuration. This suggests, to model the plaque as discrete structure [66] in order to study how components affect the stresses distributions acting on the fibrous cap.

Currently, the major surgical guidelines advise carotid revascularization in asymptomatic patients when the percent of stenosis detected is equal to 60% or more, while in symptomatic patients, revascularization is advised in 50-69% of stenosis and recommended in 70% or more of stenosis [38, 75]. In addition to the degree of carotid stenosis, even the nature and composition of carotid plaques are elements that must be taken into consideration in the risk assessment of plaque vulnerability [76]. Heterogeneous and soft plaques result more frequently correlated with symptoms and, in case of intraplaque hemorrhages associate to ulceration, rapid plaque volume progression that can result in severe narrowing of arterial lumen [77, 78].

Carotid plaques more prone to be symptomatic usually have larger lipid cores, thinner fibrous caps, and/or intraplaque hemorrhages [79, 80, 81, 82]. If both fluid dynamics and mechanical studies confirm different stress configurations of lipid plaques with respect to the fibrous and calcific ones, a closer stratification of stroke risk would be needed and a more aggressive approach to some categories of asymptomatic patients could be justified. Advance in the knowledge of the carotid plaque behavior can give, to the medical community, opportunity to develop new methods of assessment for stroke risk prediction more based on individual setting.

4.4 Limitations and future developments

The main limitations of the work are summarized in what follows.

First, we modeled the macro calcifications with an idealized geometry of elliptical shape based on the assumptions supported by the literature. We believe that this shape should not affect too much the results because they are more sensible to the global stiffness of the plaque rather than to the shape of the calcifications.

Secondly, the plaque components and the healthy vessel were modeled with the linear infinitesimal elasticity. We believe that possible inaccuracies introduced by this hypothesis should not influence too much the conclusions of the results, which were mainly focused on the comparison between different scenarios, all affected by the same approximation.

We also observe that blood in carotid with severe degrees of stenosis (in our study up to 90%) may become disturbed or even feature transition to turbulence [35, 83, 20, 84]. In this preliminary study, laminar flow has been assumed for all the simulations, which however should not influence so much the results in terms of their comparison among the different plaque typologies.

Future developments of this work may focus on conducting parametric studies by modifying different plaque lengths (longer or shorter) or positions (close or after the bifurcation) to investigate how these factors can affect the vulnerability of the plaque.

Moreover, we have in mind to investigate not only different shapes of macro calcifications, but also the location of these inclusions within the plaque and possible effects on the plaque vulnerability.

Future works could also consider non-linear laws for the healthy vessel and for the plaque components to study the wall mechanics, and turbulence models to study the blood flow behavior. These choices would allow us to obtain a more complete description of the physical processes and to provide a deeper comparison among plaques.

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References

- Libby, P., Buring, J., Badimon, L., Hansson, G., Deanfield, J., Bittencourt, M., Tokgözõglu, L., and Lewis, E., 2019. "Atherosclerosis". *Nature Reviews Disease Primers*, 5(56), pp. 1–18.
- [2] Maher, E., Creane, A., Sultan, S., Hynes, N., Lally, C., and Kelly, D., 2009. "Tensile and compressive properties of fresh human carotid atherosclerotic plaques". *Journal of Biomechanics*, 42(16), pp. 2760–2767.

- [3] Ebenstein, D., Coughlin, D., Chapman, J., and Pruitt, L., 2009. "Nanomechanical properties of calcification, fibrous tissue, and hematoma from atherosclerotic plaques". *Journal of Biomedical Materials Research. Part* A, 91(4), pp. 1028–1037.
- [4] Maher, E., Creane, A., Sultan, P. S., Hynes, N., Lally, C., and Kelly, D., 2011. "Inelasticity of Human Carotid Atherosclerotic Plaque". Annals of Biomedical Engineering, 39(16), pp. 2445–2455.
- [5] Brinjikji, W., Huston, J., Rabinstein, A., Kim, G.-M., Lerman, A., and Lanzino, G., 2015. "Contemporary carotid imaging: from degree of stenosis to plaque vulnerability". *Journal of Neurosurgery*, **124**, pp. 1–16.
- [6] Lopes, D., Puga, H., Teixeira, J., and Lima, R., 2020. "Blood flow simulations in patient-specific geometries of the carotid artery: A systematic review". *Journal of Biomechanics*, **111**, pp. 1–17.
- [7] Ku, D., Giddens, D., Zarins, C., and Glagov, S., 1985. "Pulsatile Flow and Atherosclerosis in the Human Carotid Bifurcation: Positive Correlation between Plaque Location and Low and Oscillating Shear Stress". Arteriosclerosis, Thrombosis, and Vascular Biology, 5, pp. 295–302.
- [8] Hyun, S., Kleinstreuer, C., and Archie, J., 2000. "Computer Simulation and Geometric Design of Endarterectomized Carotid Artery Bifurcations". *Critical Reviews in Biomedical Engineering*, 28(1-2), pp. 53–59.
- [9] Younis, H., Kaazempur-Mofrad, M., Chan, R., Isasi, A., Hinton, D., Chau, A., Kim, L., and Kamm, R., 2004. "Hemodynamics and wall mechanics in human carotid bifurcation and its consequences for atherogenesis: investigation of inter-individual variation". *Biomechanics and Modeling in Mechanobiology*, **3**(1), pp. 17–32.
- [10] Morbiducci, U., Gallo, D., Massai, D., Consolo, F., Ponzini, R., Antiga, L., Bignardi, C., Deriu, M., and Redaelli, A., 2010. "Outflow conditions for image-based hemodynamic models of the carotid bifurcation: Implications for indicators of abnormal flow". Journal of Biomechanical Engineering, 132(9), pp. 1–11.
- [11] Domanin, M., Gallo, D., Vergara, C., Biondetti, P., Forzenigo, L., and Morbiducci, U., 2019. "Prediction of long term restenosis risk after surgery in the carotid bifurcation by hemodynamic and geometric analysis". Annals of Biomedical Engineering, pp. 1129–1140.
- [12] Groen, H., Gijsen, F., Lugt, A., Ferguson, M., Hatsukami, T., van der Steen, A., Yuan, C., and J.Wentzel, 2007. "Plaque rupture in the carotid artery is localized at the high shear stress region: A case report". *Stroke*, **38**(1), pp. 2379–2381.

- [13] Ohayon, J., Finet, G., Gharib, A., Herzka, D., Tracqui, P., Heroux, J., Rioufol, G., Kotys, M., Elagha, A., and Pettigrew, R., 2008. "Necrotic Core Thickness and Positive Arterial Remodeling Index: Emergent Biomechanical Factors for Evaluating the Risk of Plaque Rupture". American journal of physiology. Heart and circulatory physiology, 295, pp. 717–727.
- [14] Teng, Z., Canton, G., Yuan, C., Ferguson, M., Yang, C., Huang, X., Zheng, J., Woodard, P., and Tang, D., 2010. "3D Critical Plaque Wall Stress Is a Better Predictor of Carotid Plaque Rupture Sites Than Flow Shear Stress: An In Vivo MRI-Based 3D FSI Study". Journal of Biomechanical Engineering, 132, pp. 1–21.
- [15] Groen, H., Simons, L., Bouwhuijsen, Q., Bosboom, E., Gijsen, F., van der Giessen, A., van de Vosse, F., Hofman, A., van der Steen, A., Witteman, J., Lugt, A., and Wentzel, J., 2010. "MRI based quantification of outflow boundary conditions for computational fluid dynamics of stenosed human carotid arteries. Journal of Biomechanics". Journal of Biomechanics, 43(12), pp. 2332–2338.
- [16] Lorenzini, G., and Casalena, E., 2008. "CFD analysis of pulsatile blood flow in an atherosclerotic human artery with eccentric plaques". *Journal of Biomechanics*, 41(9), pp. 1862–1870.
- [17] Jabbar, A., Ali, R., Parvez, K., and Niazi, U., 2012. "Three-Dimensional Numerical Analysis of Pulsatile Blood Flow around Different Plaque Shapes in Human Carotid Artery". *International Journal of Bioscience, Biochemistry and Bioinformatics*, pp. 305–308.
- [18] Zhou, H., Meng, L., Zhou, W., Xin, L., Xia, X., Li, S., Zheng, H., and Niu, L., 2017. "Computational and experimental assessment of influences of hemodynamic shear stress on carotid plaque". *BioMedical Engineering OnLine*, **16**(1), pp. 1–11.
- [19] Rossmann, J., Berger, S., and Saloner, D., 2002. "Numerical Analysis of Flow Through a Severely Stenotic Carotid Artery Bifurcation". *Journal of Biomechanical Engineering*, **124**(1), pp. 9–20.
- [20] Lee, S., Lee, S.-W., Fischer, P., Bassiouny, H., and Loth, F., 2008. "Direct numerical simulation of transitional flow in a stenosed carotid bifurcation". *Journal of biomechanics*, 41, pp. 2551–2561.
- [21] Sui, B., Gao, P., Lin, Y., Jing, L., Sun, S., and Qin, H., 2014. "Hemodynamic parameters distribution of upstream, stenosis center, and downstream sides of plaques in carotid artery with different stenosis: a MRI and CFD study". Acta radiologica, 56(3), pp. 347–354.

- [22] Compagne, K., Dilba, K., Postema, E., Es, A., Emmer, B., Majoie, C., Zwam, W., Dippel, D., Wentzel, J., Lugt, A., and Gijsen, F., 2019. "Flow Patterns in Carotid Webs: A Patient-Based Computational Fluid Dynamics Study". American Journal of Neuroradiology, 40(4), pp. 703–708.
- [23] Guerciotti, B., Vergara, C., Azzimonti, L., Forzenigo, L., Buora, A., Biondetti, P., and Domanin, M., 2015. "Computational study of the fluiddynamics in carotids before and after endarterectomy". *Journal of Biomechanics*, 49, pp. 26–38.
- [24] Tang, D., Yang, C., and Ku, D., 1999. "A 3-D thin-wall model with fluid-structure interactions for blood flow in carotid arteries with symmetric and asymmetric stenoses". *Computers & Structures*, **72**(1), pp. 357–377.
- [25] Tang, D., Yang, C., Huang, Y., and Ku, D., 1999. "Wall stress and strain analysis using a three-dimensional thick-wall model with fluid–structure interactions for blood flow in carotid arteries with stenoses". *Computers & Structures*, **72**(1), pp. 341–356.
- [26] Alegre-Martínez, C., Choi, K.-S., Tammisola, O., and McNally, D., 2019. "On the axial distribution of plaque stress: Influence of stenosis severity, lipid core stiffness, lipid core length and fibrous cap stiffness". *Medical Engineering & Physics*, 68, pp. 76–84.
- [27] Kock, S., Nygaard, V., Eldrup, N., Frund, E.-T., Klaerke, A., Paaske, W., Falk, E., and Kim, W., 2008. "Mechanical stresses in carotid plaques using MRI-based fluid-structure interaction models". *Journal of Biomechanics*, 41, pp. 1651–1658.
- [28] Thrysøe, S., Oikawa-Wakayama, M., Yuan, C., Eldrup, N., Klaerke, A., Paaske, W., Falk, E., Kim, W., and Nygaard, J. V., 2010. "Longitudinal Distribution of Mechanical Stresses in Carotid Plaques of Symptomatic Patients". *Stroke; a journal of cerebral circulation*, **41**, pp. 1041–1043.
- [29] Lee, S., Kang, S., Hur, N., and Jeong, S.-K., 2012. "A fluid-structure interaction analysis on hemodynamics in carotid artery based on patient-specific clinical data". *Journal of Mechanical Science and Technology*, 26(12), pp. 3821–3831.
- [30] Pozzi, S., Domanin, M., Forzenigo, L., Votta, E., Zunino, E., Redaelli, A., and Vergara, C., 2020. A data-driven surrogate model for fluid-structure interaction in carotid arteries with plaque. MOX-Report n. 13-2019, Dipartimento di Matematica, Politecnico di Milano, Italy.
- [31] Tao, X., Gao, P., Jing, L., Lin, Y., and Sui, B., 2015. "Subject-Specific Fully-Coupled and One-Way Fluid-Structure Interaction Models for Modeling of Carotid Atherosclerotic Plaques in Humans". *Med Sci Monit*, 21, pp. 3279–3290.

- [32] Gao, H., and Long, Q., 2008. "Effects of varied lipid core volume and fibrous cap thickness on stress distribution in carotid arterial plaques". *Journal of Biomechanics*, 41, pp. 3053–3059.
- [33] Gao, H., Long, Q., Graves, M., Gillard, J., and Li, Z., 2009. "Carotid arterial plaque stress analysis using fluid–structure interactive simulation based on in-vivo magnetic resonance images of four patients". *Journal of Biomechanics*, 42, pp. 1416–1423.
- [34] Tang, D., Teng, Z., Canton, G., Yang, C., Ferguson, M., Huang, X., Zheng, J., Woodard, P., and Yuan, C., 2009. "Sites of Rupture in Human Atherosclerotic Carotid Plaques Are Associated With High Structural Stresses An In Vivo MRI-Based 3D Fluid-Structure Interaction Study". *Stroke; a journal of cerebral circulation*, 40(10), pp. 3258–3263.
- [35] Tang, D., Yang, C., Huang, S., Mani, V., Zheng, J., Woodard, P., Robson, P., Teng, Z., Dweck, M., and Fayad, Z., 2016. "Cap inflammation leads to higher plaque cap strain and lower cap stress: An MRI-PET/CT-based FSI modeling approach". *Journal of Biomechanics*, **50**, pp. 121–129.
- [36] Hassan, N., and Mahmoud, A., 2019. "Three dimensional fluid structure interaction analysis of carotid artery models with different calcification patterns". Conference proceedings: Annual International Conference of the IEEE Engineering in Medicine and Biology Society, 2019, pp. 7019–7022.
- [37] Xu, K., Yu, L., Wan, J., Wang, S., and Lu, H., 2020. "The influence of the elastic modulus of the plaque in carotid artery on the computed results of FFR CT". Computer Methods in Biomechanics and Biomedical Engineering, 23(2), pp. 1–11.
- [38] Group, W., Naylor, R., Ricco, J.-b., Borst, G., Debus, S., Haro, J., Halliday, A., Hamilton, G., Kakisis, J., Kakkos, S., Lepidi, S., Markus, H., McCabe, D., Roy, J., Sillesen, H., van den Berg, J., Vermassen, F., Committee, E., Kolh, P., and Venermo, M., 2017. "Management of Atherosclerotic Carotid and Vertebral Artery Disease: 2017 Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS)". European Journal of Vascular and Endovascular Surgery, pp. 1–80.
- [39] Barnett, H., Taylor, D., Haynes, R., Sackett, D., Peerless, S., Ferguson, G., Fox, A., Rankin, R., Hachinski, V., Wiebers, D., and Eliasziw, M., 1991. "Beneficial Effect of Carotid Endarterectomy in Symptomatic Patients with High-Grade Carotid Stenosis". New England Journal of Medicine, 325(7), pp. 445–453.
- [40] Antiga, L., and Steinman, D., 2009. "The vascular modeling toolkit (vmtk), www.vmtk.org".

- [41] Harloff, A., Zech, T., Frydrychowicz, A., Schumacher, M., Schöllhorn, J., Hennig, J., Weiller, C., and Markl, M., 2009. "Carotid intima-media thickness and distensibility measured by MRI at 3T versus high-resolution ultrasound". *European radiology*, **19**(6), pp. 1470–1479.
- [42] Li, Z.-Y., Howarth, S. P., Tang, T., and Gillard, J. H., 2006. "How Critical Is Fibrous Cap Thickness to Carotid Plaque Stability ?". Stroke, 37(5), pp. 1195–1199.
- [43] Thrysoe, S., Stegmann, A., Eldrup, N., A. Klaerke, W. Paaske, W. K., and Nygaard, J., 2012. "The Effect of Carotid Plaque Morphology on Longitudinal Fibrous Cap Stress Levels". World Journal of Mechanics, 2(4), pp. 216 – 223.
- [44] Athanasiou, L. S., Fotiadis, D. I., and Michalis, L. K., 2017. "2 principles of coronary imaging techniques". In *Atherosclerotic Plaque Characterization Methods Based on Coronary Imaging*, L. S. Athanasiou, D. I. Fotiadis, and L. K. Michalis, eds. Academic Press, Oxford, pp. 23 – 47.
- [45] Friedrich, G. J., Moes, N. Y., Mühlberger, V. A., Gabl, C., Mikuz, G., Hausmann, D., Fitzgerald, P. J., and Yock, P. G., 1994. "Detection of intralesional calcium by intracoronary ultrasound depends on the histologic pattern". *American Heart Journal*, **128**(3), pp. 435 – 441.
- [46] Li, Z.-Y., Howarth, S., Tang, T., Graves, M., U-King-Im, J., and Gillard, J., 2007. "Does calcium deposition play a role in the stability of atheroma? location may be the key". *Cerebrovascular diseases (Basel, Switzerland)*, 24, pp. 452–459.
- [47] Kral, B., Becker, L., Vaidya, D., Yanek, L., Qayyum, R., Zimmerman, S., Dey, D., Berman, D., Moy, T., Fishman, E., and Becker, D., 2014. "Noncalcified Coronary Plaque Volumes in Healthy People With a Family History of Early Onset Coronary Artery Disease". *Circulation. Cardiovascular imaging*, 7, pp. 446–453.
- [48] Cilla, M., Monterde, D., Peña, E., and Martínez, M. ., 2013. "Does microcalcification increase the risk of rupture ?". Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine, 227(5), pp. 588–599.
- [49] Hirt, C., Amsden, A., and Cook, J., 1974. "An arbitrary Lagrangian-Eulerian computing method for all flow speeds". *Journal of Computational Physics*, 14(3), pp. 227–253.
- [50] Donea, J., Giuliani, S., and Halleux, J., 1982. "An arbitrary Lagrangian-Eulerian finite element method for transient dynamic fluid-structure interactions". Computer Methods in Applied Mechanics and Engineering, 33(1), pp. 689–723.

- [51] Finet, G., Ohayon, J., and Rioufol, G., 2004. "Biomechanical interaction between cap thickness, lipid core composition and blood pressure in vulnerable coronary plaque: Impact on stability or instability". *Coronary artery disease*, 15, pp. 13–20.
- [52] Williamson, S., 2003. "On the Sensitivity of Wall Stresses in Diseased Arteries to Variable Material Properties". *Journal of Biomechanical Engineering*, 125, pp. 147–155.
- [53] Donea, J., Huerta, A., Ponthot, J.-P., and Rodríguez-Ferran, A., 2004. Arbitrary Lagrangian-Eulerian Methods. American Cancer Society, ch. 14, pp. 413–437.
- [54] Formaggia, L., Quarteroni, A., and Veneziani, A., 2009. Cardiovascular Mathematics: Modeling and Simulation of the Circulatory System, Vol. 1.
- [55] Küttler, U., and Wall, W., 2008. "Fixed-point fluid-structure interaction solvers with dynamic relaxation". *Computational Mechanics*, **43**, pp. 61–72.
- [56] Nobile, F., and Vergara, C., 2012. "Partitioned Algorithms for Fluid-Structure Interaction Problems in Haemodynamics". *Milan Journal of Mathematics*, 80, pp. 443–467.
- [57] Quarteroni, A., Manzoni, A., and Vergara, C., 2017. "The cardiovascular system: Mathematical modelling, numerical algorithms and clinical applications". Acta Numerica, 26, pp. 365–590.
- [58] Tezduyar, T., 1992. "Stabilized Finite Element Formulations for Incompressible Flow Computations". Advances in Applied Mechanics, 28, pp. 1– 44.
- [59] Forti, D., and Dede, L., 2015. "Semi-implicit BDF time discretization of the Navier–Stokes equations with VMS–LES modeling in a High Performance Computing framework". *Computers & Fluids*, **117**, pp. 168–182.
- [60] Crosetto, P., Deparis, S., Fourestey, G., and Quarteroni, A., 2011. "Parallel Algorithms for Fluid-Structure Interaction Problems in Haemodynamics". *SIAM Journal on Scientific Computing*, 33, pp. 1598–1622.
- [61] Westerhof, N., Lankhaar, J.-W., and Westerhof, B., 2008. "The arterial Windkessel". Medical & biological engineering & computing, 47, pp. 131– 41.
- [62] Quarteroni, A., Veneziani, A., and Vergara, C., 2016. "Geometric multiscale modeling of the cardiovascular system, between theory and practice". *Computer Methods in Applied Mechanics and Engineering*, **302**, pp. 193– 252.

- [63] Nobile, F., and Vergara, C., 2008. "An Effective Fluid-Structure Interaction Formulation for Vascular Dynamics by Generalized Robin Conditions". *SIAM J. Scientific Computing*, **30**, pp. 731–763.
- [64] Moireau, P., Xiao, N., Astorino, M., Figueroa, C., Chapelle, D., Taylor, C., and Gerbeau, J.-F., 2011. "External tissue support and fluid-structure simulation in blood flows". *Biomechanics and modeling in mechanobiology*, 11, pp. 1–18.
- [65] Tang, D., Yang, C., Zheng, J., Woodard, P., Sicard, G., Faffitz, J., and Chun, Y., 2004. "3D MRi-based Muticomponent FSI Models for Atherosclerotic Plaques". Annals of Biomedical Engineering, 32(7), pp. 947–960.
- [66] O'Reilly, B. L., Hynes, N., Sultan, S., McHugh, P. E., and McGarry, J. P., 2020. "An experimental and computational investigation of the material behaviour of discrete homogenous iliofemoral and carotid atherosclerotic plaque constituents". *Journal of Biomechanics*, **106**, pp. 1–9.
- [67] Mofidi, R., Powell, T., Crotty, T., Sheehan, S., Mehigan, D., MacErlaine, D., and Keaveny, T., 2005. "Increased Internal Carotid Artery Peak Systolic Velocity Is Associated with Presence of Significant Atherosclerotic Plaque Instability Independent of Degree of ICA Stenosis". International Journal of Angiology, 14, pp. 74–80.
- [68] Bang, J., Dahl, T., Bruinsma, A., Kaspersen, J., Hernes, T., and Myhre, H., 2003. "A new method for analysis of motion of carotid plaques from RF ultrasound images". Ultrasound in medicine & biology, 29, pp. 967–976.
- [69] Pedrigi, R. M., de Silva, R., Bovens, S. M., Mehta, V. V., Petretto, E., and Krams, R., 2014. "Thin-Cap Fibroatheroma Rupture Is Associated With a Fine Interplay of Shear and Wall Stress". Arteriosclerosis, Thrombosis, and Vascular Biology, 34(10), pp. 2224–2231.
- [70] Leach, J., Rayz, V., Soares, B., Wintermark, M., Mofrad, M. R. K., and Saloner, D., 2010. "Carotid Atheroma Rupture Observed In Vivo and FSI-Predicted Stress Distribution Based on Pre-rupture Imaging". Annals of Biomedical Engineering, 38, pp. 2748–2765.
- [71] Richardson, P., 2002. "Biomechanics of Plaque Rupture: Progress, Problems, and New Frontiers". Annals of Biomedical Engineering, 30, pp. 524– 536.
- [72] Arroyo, L. H., and Lee, R. T., 1999. "Mechanisms of plaque rupture: mechanical and biologic interactions". *Cardiovascular Research*, 41(2), pp. 369–375.

- [73] Van der Wal, A. C., and Becker, A. E., 1999. "Atherosclerotic plaque rupture – pathologic basis of plaque stability and instability". *Cardiovascular Research*, 41(2), pp. 334–344.
- [74] Huang, H., Virmani, R., Younis, H., Burke, A. P., Kamm, R. D., and Lee, R. T., 2001. "The Impact of Calcification on the Biomechanical Stability of Atherosclerotic Plaques". *Circulation*, **103**(8), pp. 1051–1056.
- [75] Brott, T., Halperin, J., Abbara, S., Bacharach, J., Barr, J., Bush, R., Cates, C., Creager, M., Fowler, S., Friday, G., Hertzberg, V., McIff, E., Moore, W., Panagos, P., Riles, T., Rosenwasser, R., and Taylor, A., 2011. "2011 ASA/ ACCF/ AHA/ AANN/ AANS/ ACR/ ASNR/ CNS/ SAIP/ SCAI/ SIR/ SNIS/ SVM/ SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: executive summary. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, C". Circulation, 124, pp. 489–532.
- [76] Takaya, N., Yuan, C., Chu, B., Saam, T., Underhill, H., Cai, J., Tran, N., Polissar, N., Isaac, C., Ferguson, M., Garden, G., Cramer, S., Maravilla, K., Hashimoto, B., and Hatsukami, T., 2006. "Association Between Carotid Plaque Characteristics and Subsequent Ischemic Cerebrovascular Events: A Prospective Assessment With MRI–Initial Results". Stroke; a journal of cerebral circulation, **37**, pp. 818–823.
- [77] Seeger, J. M., and Klingman, N., 1987. "The relationship between carotid plaque composition and neurologic symptoms". *Journal of Surgical Re*search, 43(1), pp. 78–85.
- [78] Zhao, X.-Q., and Hatsukami, T. S., 2018. "Risk Factors for Development of Carotid Plaque Components". JACC: Cardiovascular Imaging, 11(2), pp. 193–195.
- [79] Carr, S., Farb, A., Pearce, W. H., Virmani, R., and Yao, J. S., 1996.
 "Atherosclerotic plaque rupture in symptomatic carotid artery stenosis". Journal of Vascular Surgery, 23(5), pp. 755–766.
- [80] Nicolaides, A., Kakkos, S., Kyriacou, E., Griffin, M., Sabetai, M., Thomas, D., Tegos, T., Geroulakos, G., Labropoulos, N., Dor, C., Morris, T., Naylor, R., Abbott, A., Adovasio, R., Ziani, B., Alò, F., Cicilioni, C., Ambrosio, G., Andreev, A., and Wilkinson, A., 2010. "Asymptomatic internal carotid artery stenosis and cerebrovascular risk stratification". *Journal of Vascular Surgery*, **52**, pp. 1486–1496.

- [81] Redgrave, J., Lovett, J., and Rothwell, P., 2010. "Histological Features of Symptomatic Carotid Plaques in Relation to Age and Smoking The Oxford Plaque Study". Stroke; a journal of cerebral circulation, 41, pp. 2288–2294.
- [82] Altaf, N., Goode, S., Beech, A., Gladman, J., Morgan, P., Macsweeney, S., and Auer, D., 2011. "Plaque hemorrhage is a marker of thromboembolic activity in patients with symptomatic carotid disease.". *Radiology*, 258, pp. 538–545.
- [83] Ku, D., 1997. "Blood flow in arteries". Annual Review of Fluid Mechanics, 29(1), pp. 399–434.
- [84] Lancellotti, R. M., Vergara, C., Valdettaro, L., Bose, S., and Quarteroni, A., 2017. "Large Eddy Simulations for blood dynamics in realistic stenotic carotids". Int. J. Numer. Meth. Biomed. Eng., 33(11), pp. 1–25.

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