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INFLUENCE OF PLAQUE PROPERTIES AND CONSTITUTIVE MODELING APPROACH ON THE SIMULATION OF PERCUTANEOUS ANGIOPLASTY OF CHRONIC TOTAL OCCLUSIONS

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Abstract. *Clinical treatment of Chronic Total Occlusion (CTO) of an artery often involves percutaneous procedures, like sub-intimal balloon angioplasty, in which the controlled inflation of a balloon restores the lumen by compression of atherosclerotic plaque. Realistic simulations of these challenging techniques could provide valuable information for clinician, but characterization of CTO in human studies is problematic. Reported data are highly variable and the few published models employed different approaches to fit (apparently) the same experimental tests. Moreover, atherosclerotic plaques are commonly assumed as elastic and incompressible, but in angioplasty procedures they may be subjected to large and not physiological overstretch. Permanent plaque damage after balloon inflation is expected, suggesting that some form of inelastic behavior should be considered. Thus, the goal of the present work is to investigate the influence of changing plaque properties and constitutive modeling assumptions, on the predicted outcomes of a simulation of CTO percutaneous angioplasty. To this aim, a finite element model of the compression of a total occlusion inside an artery was implemented. Different forms of hyperelastic constitutive laws proposed in literature were compared in presence of the complex stress state resulting from sub-intimal angioplasty. The degree of compressibility and the threshold for a permanent damage, introduced in the form of a plastic yield limit, were varied. Overall, results demonstrated that the choice of different data sets or constitutive modeling approaches for plaque has a primary influence. Some common assumptions for plaque modeling may lead to highly variable or even unrealistic predictions for the extreme case of total occlusion treatment. In this sense, more specific experimental investigations on the properties of plaque constituents as a function of heterogeneous CTO composition, are necessary in order to exploit the potential usefulness of the method as a patient-specific predictive tool.*

1 INTRODUCTION

Peripheral artery disease (PAD), also known as stenosis, is a clinical condition in which blood flow to the surrounding tissues is limited or disrupted by the narrowing of arteries. Progressive development of the disease may eventually lead to complete blockage, known as chronic total occlusion (CTO). Thus, by definition, a CTO is an almost complete obstruction of the artery and its percutaneous revascularization is much more difficult when compared to partially occluded artery. In fact, before inflating the balloon to mechanically widen the occlusion, a path through it for the catheter must be created to place it correctly. To this aim, different techniques for the CTO treatment were developed [1, 2]. The main difference between various solutions is the working space used to cross the occlusion by means of the dedicated devices, which can be either intra-luminal or extra-luminal with respect to the true lumen of the vessel. Extra-luminal techniques consist in intentionally bypassing the site of the occlusion via a sub-intimal path [3], where the angioplasty balloon can be placed and inflated. Sub-intimal angioplasty represents a technical challenge, which requires great operator skill for the manipulation of wires and devices through a CTO. Balloon inflation may locally cause the dissection of the intima from the media, with risks to collateral vessels entering distal to the occlusion, arterial perforation, presence of an eccentric post-dilation arterial lumen and the so-called barotraumas associated after angioplasty [4].

Finite Element Method (FEM) may potentially help the physician to get additional information on feasibility of the procedure and its possible outcomes and risks. While several examples of FEM analyses have been reported concerning partially occluded arteries [5-8], to the best of authors' knowledge, for CTO this type of approach has not yet been explored.

The development of a finite element model for sub-intimal treatment of CTO presents several challenges, including initially folded configuration of the balloon and creation of a space for inflation from an eccentric position. Characterization of CTO in human studies is also problematic and a systematic investigation regarding the mechanical behavior and failure properties of peripheral CTOs is still lacking. For modeling purposes, it is necessary to rely on a limited number of literature data, mostly concerning partial occlusions from different vascular districts and highly variable. Moreover, during sub-intimal angioplasty a CTO may experience complex stress states, not necessarily similar to those used for tissue characterization in the laboratories. Therefore, the choice of different constitutive laws to fit test data may potentially lead to different results for (apparently) the same material. Atherosclerotic plaques are commonly assumed to be elastic and incompressible in the physiological loading range, but in angioplasty plaque constituents may be subjected to a large and not physiological overstretch. In order to reproduce such severe deformation hyperelastic laws are typically required, but a key role is played by compressibility parameters [9]. Moreover, to account for permanent plaque damage after balloon inflation, inelastic behavior should be considered. To this aim, as an example, the introduction of plastic response beyond a given stress threshold has been proposed [10, 11]. The definition of a plastic yield stress value or the degree of compressibility are of course critical aspects of the simulation that may substantially influence the results in terms of lumen restoration after the procedure.

It can be concluded that to gain information of clinical relevance, or potentially useful for development or optimization of dedicated devices for CTO sub-intimal angioplasty, there is a need to develop more specific predictive models, using data as close as possible to what could be expected in a peripheral occlusion. On the other hand, the influence of constitutive modeling approach and assumptions must be evaluated carefully. To this aim, in the present work we developed a finite element model of CTO compression, focusing on the identification of main CTO morphological features and mechanical properties for FEM modeling. In particular, we evaluated the influence of different properties, modeling approaches and assumptions on the treatment of a CTO by compression from an eccentric position. Results obtained will help identifying a more realistic CTO model, to be used in future simulations, currently under development, in which the complete sub-intimal angioplasty procedure is virtually reproduced.

2 MATERIALS AND METHODS

2.1 CTO mechanical properties

CTOs exhibit a complex spatial organization, with presence of different types of constituents. From a pathobiology standpoint, three specific regions [12, 13] are usually identified in a CTO: proximal fibrous cap (PFC), distal fibrous cap (DFC) and main body of CTO. Each region has different constituent and properties, and most of the times the plaque has a high level of calcification, depending on CTO age.

For numerical simulations, treating CTO as a heterogeneous body to include local variations of the properties is extremely complex, since it is very difficult to assess in-vivo the spatial distribution of various constituents [14]. Furthermore, composition and geometry are highly variable between subjects and change during the development of the pathology. On the other hand, even for partial occlusions, in the context of complex simulations of balloon angioplasty procedure, it is not uncommon that the plaque is assumed as a homogeneous part with an equivalent uniform mechanical response. Correspondingly, equivalent properties for the whole plaque are often obtained from mechanical testing (i.e. tensile, compression or indentation tests), classifying plaques in terms of degree of calcification or prevalent type of tissue. Unfortunately, experimental data available are limited, highly scattered and often referring to specific arterial districts.

A set of data frequently used in balloon angioplasty simulations, is the one reported in [15], referring to tensile tests on aortic plaques. In this case, plaques were classified histologically as either cellular, hypo-cellular or calcified. It is interesting to note that since their publication these data have been fitted by various research groups, using different types of hyperelastic constitutive laws. In [16] Pericevic et al. used a Mooney-Rivlin law with incompressible behavior, as per eq. 1:

$$W = C_{10}(I_1 - 3) + C_{01}(I_2 - 3) + C_{20}(I_1 - 3)^2 + C_{11}(I_1 - 3)(I_2 - 3) + C_{30}(I_1 - 3)^3 \tag{1}$$

In [10] Gastaldi et al. adopted a constitutive law (nearly incompressible form) based on a sixth-order reduced polynomial strain energy density function to simulate a cellular plaque (eq.2):

$$\begin{aligned} W = {} & C_{10}(\overline{I_1} - 3) + C_{20}(\overline{I_1} - 3)^2 + C_{30}(\overline{I_1} - 3)^3 + C_{40}(\overline{I_1} - 3)^4 \\ & + C_{50}(\overline{I_1} - 3)^5 + C_{60}(\overline{I_1} - 3)^6 \end{aligned} \tag{2}$$

In [17] Schiavone et al. used the same approach for cellular plaques, whereas Ogden hyperelastic model (eq.3) was used to describe the constitutive behavior of the hypocellular and calcified plaques:

$$W = \sum_{i=1}^{3} \frac{2\mu_i}{\alpha_i^2}\left(\lambda_1^{\alpha i} + \lambda_2^{\alpha i} + \lambda_3^{\alpha i} - 3\right) + \sum_{i=1}^{3} \frac{1}{D_i}(J - 1)^{2i} \tag{3}$$

In this case, for the compressibility parameter D_1 infinitesimal value was assumed, whereas others compressibility parameters were set to zero.

In [18] Karimi et al. reproduced instead the same data with a Neo-Hookean law, with nearly incompressible behavior (eq. 4):

$$W = \frac{\mu}{2}(\bar{I_1} - 3) + \frac{1}{D}(J-1)^2 \tag{4}$$

Finally, in [19] Cunnane et al. introduced a Yeoh hyper-elastic law (eq.5):

$$W = \sum_{i=1}^{3} C_{i0}(I_1 - 3)^i \tag{5}$$

As shown in Figure 1, by running a simple simulation with the evaluate function available in Abaqus © code for previously mentioned hyperelastic models, it is clear that predicted behaviors can be quite different, especially when large deformation, compressive stress or not uniaxial stress states are considered.

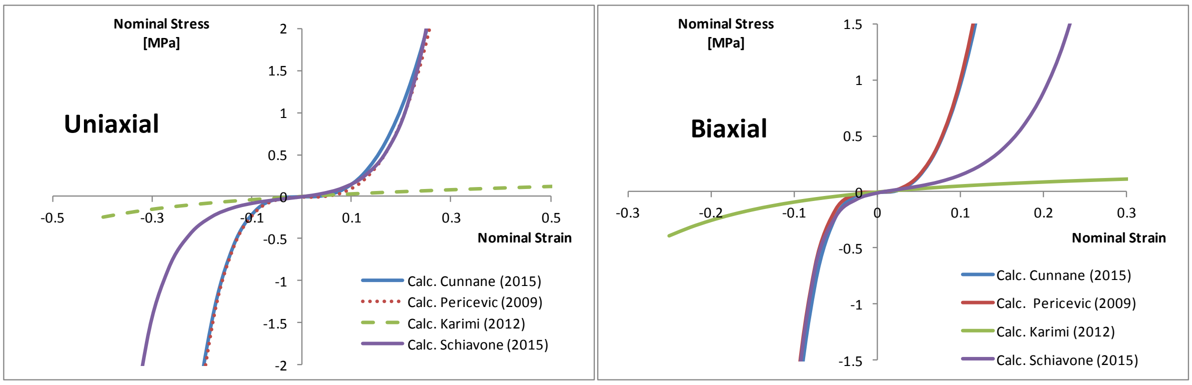

Figure 1: Uniaxial and Biaxial Stress-Strain curve for plaque constitutive laws fitted on the same data set.

A further relevant set of test data for plaques in peripheral arteries has been provided in [19, 20]. In this study, human atherosclerotic femoral plaques were classified as lightly, moderately or heavily calcified, using as a metric the ratio Calcium/Lipid content. The average response for the different groups was fitted with an isotropic hyperelastic law (Yeoh type) as per eq. (5). In [21] Maher et al., employed a polynomial strain energy similar to eq. (1) but with a different order of the equation and with parameters obtained by fitting compression tests. Finally, a Neo-Hookean law was adopted also in [9] by Badel et al., for an idealized atherosclerotic plaque. In this case coefficients were derived assuming a shear modulus G of 20 kPa. In this work plaque compressibility was varied in the range of 15-180 kPa.

Overall, it can be observed that different test data have been used and the same data were fitted with different hyper-elastic model or assumptions on compressibility. Since the CTO may experience complex stress states during angioplasty, with extreme squeezing in a confined space, significant differences on simulation outcome can be expected.

2.2 CTO model

In order to compare the influence of plaque material properties and modeling assumptions on the simulation of an atherosclerotic plaque subjected to the angioplasty, a FEM model was developed. The model consisted of a blood vessel occluded by a plaque, which is compressed from an eccentric position. Fig. 2 displays the whole assembly. In order to reduce the computational effort the model represents only half of the vessel, assuming symmetry of the problem.

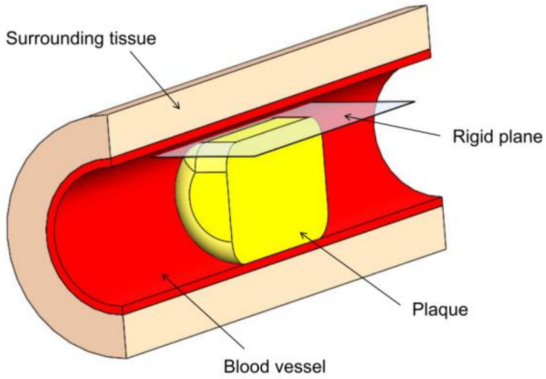

Figure 2: CTO Model

The plaque is represented as a cylinder of 4 mm in diameter and 6 mm length. Since a chronic total occlusion is often highly calcified, the plaque is here considered as globally calcified. Material parameters for compared model are reported in Table 1, in which the asterisk indicate models fitted on data reported in [15].

Model	Coefficients [kPa]
Cunnane 2015 [20]	C_{10}=46.2 C_{20}=-14.7 C_{30}= 4.95
Cunnane* 2015 [20]	C_{10}=1.41 C_{20}=4730 C_{30}=851
Karimi* 2012 [18]	$\mu/2$=57
Maher 2009 [21]	C_{10}=1.14 C_{01}=19.3 C_{11}=71.4 C_{20}=139 C_{02}=19.7
Pericevic* 2009 [16]	C_{10}=-492 C_{01}=506 C_{11}=1193 C_{20}=3637 C_{30}=4737
Schiavone* 2015 [17]	μ_1=84 α_1=20.82

Table 1: Strain energy coefficients for models considered.

The vessel is modeled as a hollow cylinder of 4 mm inner diameter, 0.25 mm thickness and 20 mm length. The plaque is positioned concentrically inside it, at equivalent distance from the sides. The vessel has to contain the plaque even during the compression phase and can itself undergo some deformation. An isotropic, nearly incompressible hyperelastic model is assigned to the vessel in the form of polynomial strain energy function [22]. Plaque and artery are embedded into a cylinder, with a thickness of 1.25 mm around the vessel, representing the soft tissues around the artery. This is modeled as a hyperelastic material with a stiffness lower than the vessel. The strain energy is taken as Neo-Hookean. The external surface of this component is completely fixed, constraining all the assembly.

Contact interaction properties were defined for contact pairs vessel/plaque (friction coefficients between 0.1 and 0.3) and plaque/rigid plane (friction coefficients 0.1).

The mesh of vessel and surrounding tissues consisted of 2400 linear hexahedral element, the plaque is meshed with 39860 linear hexahedral elements (type C3D8R for each component). Sensitivity analyses on mesh size and friction coefficient values were carried out.

In order to simulate the action determined by balloon inflation, the plaque is compressed by means of a rigid plane. The plane is initially in contact with a small upper planar surface created on the plaque, to reproduce the sub-intimal path. During the simulation a 2.5 mm displacement is imposed to the plane. In a first series of simulations, hyperelastic laws previously described were compared in terms of plaque percentage reduction and applied force. However, because of balloon inflation, the occlusion undergoes extreme deformation, which necessarily must result in some form of permanent damage; otherwise, the arterial lumen would not be restored, even partially, at the end of procedure.

To this aim, a (perfectly) plastic behavior was introduced, considering three different levels of yield stress (i.e. 0.3, 0.1 and 0.05 MPa). When plasticity was considered residual deformation after rigid plane complete retraction was compared.

3 RESULTS

3.1 Influence of compressibility

Before proceeding with comparison of hyperelastic laws, a preliminary investigation on the sensitivity of model predictions to the value assumed for bulk modulus K, was carried out. For each law, a simulation with 1 mm rigid plane motion was conducted, considering values of compressibility parameter (D = 2/K) of 0.1, 1 and 5 [MPa^{-1}] respectively. Results are summarized in Table 2.

Compression force [N]						
Compressibility [MPa^{-1}]	Cunnane 2015 [20]	Cunnane* 2015 [20]	Karimi* 2012 [18]	Maher 2009 [21]	Pericevic* 2009 [16]	Schiavone* 2015 [17]
5	1.15	2.78	1.36	1.73	2.81	1.65
1	1.42	5.40	1.87	2.82	5.54	2.87
0.1	1.50	-	2.03	3.38	7.75	3.58
Compression force increment						
from 5 to 1	23.4%	94.2%	37.5%	63.0%	97.1%	73.9%
from 1 to 0.1	5.63%	-	8.55%	19.8%	39.8%	24.7%

Table 2: Compression force and percentage increment as a function of compressibility.

Moving from compressibility 1 to 0.1 [MPa^{-1}] the increment of force is quite variable, (range 5.63-40%, average 19%), but generally lower that what observed when comparing results passing from 5 to 1 [MPa^{-1}], (range 23.4-97.1%, average 64%). For some of the models simulations were also run considering a further reduction to value of 0.01 [MPa^{-1}], which does not lead to significant differences from the previous results at 0.1. Overall, the force necessary for the compression depends on the bulk modulus value of the material. For this type of simulation, to reproduce the behaviour of an incompressible material a compressibility of 0.1 seems sufficient, further reduction does not lead to significant changes. However, it should be noted that different constitutive models were significantly differently sensitive to the changes of their compressibility, and that in some cases its reduction was associated with convergence problems. Considering the comparative nature of the present study, a compressibility equal to 1 [MPa^{-1}] was considered for subsequent investigated models.

3.2 Influence of constitutive law

Figure 3 displays the results obtained by the implementation of six different strain energy functions (see Table 1) for the plaque model. Considering models based on data reported in [15], it is clear that models by Pericevic and Cunnane predict the same behavior, as well that they both predict a higher value of compression force compared to the other models.

This difference is an example of the possible consequences of using strain energy functions fitted on uniaxial tensile test data to simulate a loading condition in which compressed plaque may experience a different and more complex stress state. This highlights the need for testing protocols in which multiple types of stress state are considered.

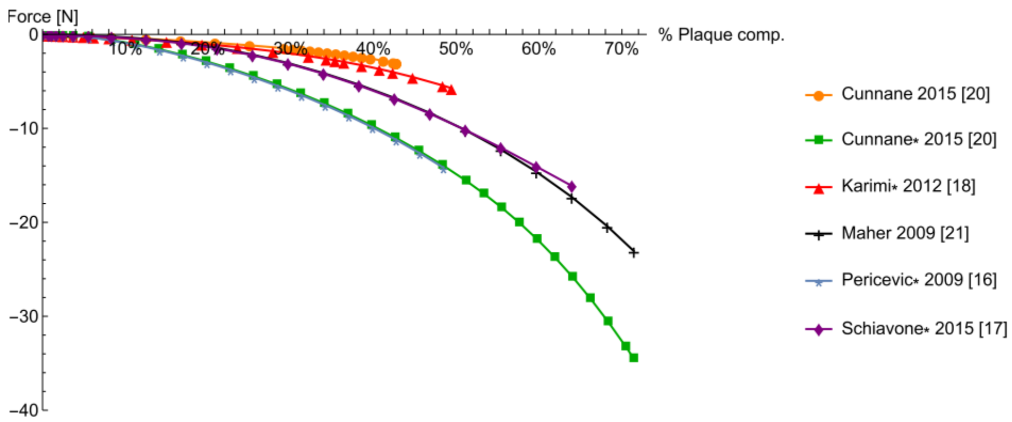

Figure 3: Plaque reduction as a function of plaque properties and models

On the other hand, comparison of results for hyperelastic models fitted on different set of data [19-21] also showed a significant difference on plaque percentage reduction. Even considering the scattering of test data available and the inherent difficulty of this type of test, results suggest the need to look for investigation methods capable to provide more patient specific data.

3.3 Influence of plastic behavior

An example of progressive and residual deformation of the occlusion when plasticity is associated with hyperelastic behavior is reported in Figure 4, for the case of Maher's law and yield stress 0.1 N/mm^2. Results showed that associating plasticity and hyperelastic behavior could be a relatively simple but effective way to induce a permanent damage.

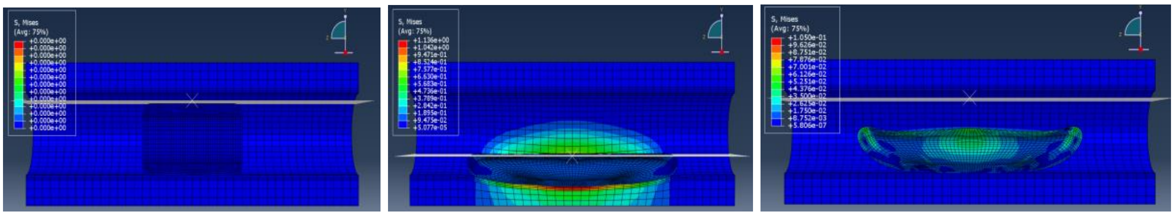

Figure 4: Example of plaque reduction with hyper-elastic model and plasticity (Yield stress 0.1 N/mm^2)

In Figure 5 the different strain energy functions under investigation are compared for the same yield stress of 0.1 MPa. In comparison with elastic-only models, the force needed to compress the plaque is generally lower and, at least in this case, for the compression phase the differences between the models is less apparent. When considering permanent residual plastic deformation some differences could instead be noticed.

In general, with a higher value of plastic limit, a higher variability of results was obtained in terms of residual deformation at the end of the procedure simulation. On the other hand, with a lower yield limit all the strain energy functions show more or less the same trend since the beginning because more plastic deformation takes place. This behavior is probably caused by a lower contribution of elastic response, due to the presence of large plasticized regions.

In Figure 6, taking again Maher's law as a reference, it is possible to appreciate the influence of changing the yield stress limit. By decreasing the yield stress, the plaque is more deformable and therefore lower force is necessary to reach the same deformation.

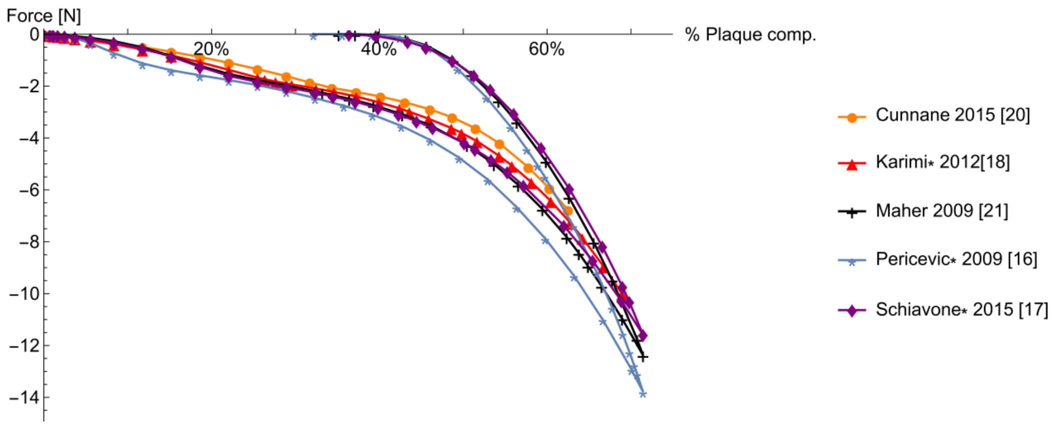

Figure 5: Plaque reduction with hyperelastic model and plasticity (Yield stress 0.1 N/mm^2)

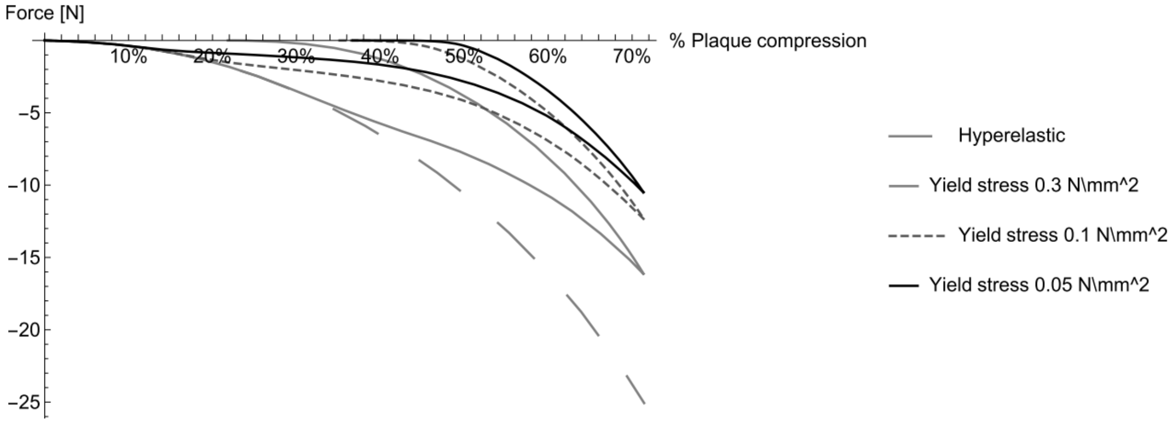

Figure 6: Comparison yield stress level (Maher's model)

Differences between models in terms of permanent percentage reduction of plaque thickness as a function of assumed yield stress value are instead summarized in Table 3.

Yield stress [N/mm^2]	Maher 2009 [21]	Pericevic* 2009 [16]	Schiavone* 2015 [17]
0.05	39%	33%	-
0.1	37%	35%	36%
0.3	22%	32%	16%

Table 3: Plaque reduction as a function of yield stress and models

The greater residual plaque compression obtained is about 39%, that corresponds to a reduction of 1.35 mm in height of the plaque, originally 3.5 mm high. For some models, a yield limit of 0.3 N/mm^2, resulted in limited plastic deformation, indicating that a lower yield limit needs to be imposed to obtain more realistic results, if CTO is treated as a homogeneous body. On the other hand, reducing the yield stress below 0.1 N/mm^2 did not lead to a significant increment in the residual deformation, suggesting that in order to simulate more extreme plaque compression, other ways of permanent damage have to be developed in the simulations.

4 DISCUSSION

The set up of FEM model for simulation of sub-intimal balloon angioplasty is really complex. In particular, a complete model of the procedure, including positioning of folded balloon in eccentric position, inflation, deflation and retraction can be computationally intensive and difficult to handle. As a consequence, some simplifying assumptions on plaque and surrounding artery behavior may be necessary. The goal of the present study was to investigate the potential impact of some of these assumptions in the specific context of CTO percutaneous angioplasty. To this aim, aspects related to artery layered structure were not considered and anisotropy was not included, both for artery or plaque regions that may exhibit such behavior. Similarly, aspects related to intima dissection phenomena caused by balloon expansion were not included and left for future (fundamental) investigations. Despite these limitations, results of the present study provided some interesting insight on the consequences of considering different types of homogeneous response.

In particular, the comparison of results obtained for different sets of material data, clearly showed that careful evaluation of equivalent plaque mechanical properties is needed, since the predicted outcome can change significantly. As remarked in [19,20], this suggest that in order to increase the accuracy of model prediction, it is important to use test data pertinent to the arterial district considered, limiting the use, often forced by the lack of data, of general plaque properties. A further aspect that has to be underlined is the importance of choosing constitutive laws and fitting material parameters basing on different types of experimental tests. Results clearly indicate that different fitting of the same data may lead to largely incoherent predictions of plaque reduction, when material models are employed far from the range and type of stress within they were tested. Actually, this is typically the case of balloon angioplasty procedures. Similar reasoning applies for assumptions related to compressibility and choice of plastic yield limit, which are often influenced by convergence issues or guessed from the few works where this aspect is considered.

Overall, in order to exploit the potential usefulness of the method as a patient-specific predictive tool, more specific experimental investigations on the properties of plaque constituents are necessary. Information concerning mechanical properties for different types of plaques constituents (i.e. fibrous or partially calcified tissues, hematoma, lipid core or calcification) can be found in literature for partial occlusions [23]. For CTO this kind of investigation is still difficult to perform, especially in-vivo. An interesting attempt to get more specific information is reported in [24], in which case CTO ex-vivo properties were determined from retrieved peripheral arteries. Of course, the composition of CTO is highly variable and ideally, material properties should be assigned by taking into account such local modifications. However, basing on this kind of data, a possible approach to account for these variations at least at a macroscopical scale, could be to subdivide the CTO into regions with different sets of associated homogeneous properties. An interesting example in this direction was reported in [25] for partial occlusions, considering a heterogeneous atherosclerotic plaque with 80% of stenosis in presence of diseased artery.

5 CONCLUSIONS

In the present work, the influence of plaque properties and modelling assumptions on the simulation of percutaneous angioplasty of chronic total occlusion has been investigated. This study was motivated by the very limited experimental data available and the lack of literature references for simulation of this type of CTO treatment. In order to evaluate the possibility to use modelling approach similar to those adopted in the context of partial occlusion angioplasty models, several hyperelastic laws were compared, including compressibility and plastic behavior. Some common assumptions for plaque modeling may lead to highly variable or even unrealistic predictions for the extreme case of total occlusion treatment. In this sense, results suggest that in order to exploit the potential usefulness of the method as a patient-specific predictive tool, more specific experimental investigations on the properties of plaque constituents as a function of heterogeneous CTO composition are necessary.

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