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Constitutive Modelling of Endothelium Denudation for Finite Element Simulation of Angioplasty

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Abstract. This study aims at characterizing and modelling the effect of mechanical factors on endothelial denudation during angioplasty, such as normal force between balloon and artery, stretching of arterial walls, and relative displacement between contacting surfaces. Friction damage was applied to porcine aorta samples with different contact forces, relative displacements, and biplanar stretching conditions. After the tests, endothelium denudation was quantified by isolating and counting the remaining endothelial cells. Using multiple-regression analysis, a constitutive model is proposed for integration in finite element software. This model will help optimize balloon and stent deployment conditions to minimize the amount of damage to the endothelium, and eventually to reduce the occurrence of restenosis.

Keywords: angioplasty, restenosis, endothelium, stretch, friction, pressure.

1 Introduction

Intravascular interventions trigger a cascade of cellular and biochemical events often leading to restenosis, a common complication of balloon angioplasty occurring within 6 months of treatment. In cases where stents are implanted, neointimal hyperplasia is the main contributor to a 15 to 20% rate of in-stent restenosis [1],[2].

Neointimal thickness has been shown clinically to be correlated with the aggressiveness of the angioplasty technique, in terms of balloon size and inflation pressure [3], or in terms of vessel wall stretch [4]. It has been shown histologically to be correlated with deepness of vessel injury [5], and with acute luminal stretching [6].

Despite considerable research efforts deployed at trying to inhibit neointimal hyperplasia through systemic or local drug delivery, little effort has been spent on understanding the vessel injury from a mechanical perspective. In vivo animal studies have concluded that denudation of the endothelium alone or in combination with medial injury triggered neointimal hyperplasia [7],[8], but that medial injury alone does not lead to intimal proliferation [9].

Rogers et al. [10] have observed that after the implantation of balloon-deployed stents in rabbit arteries, the endothelium was denuded not only under the stent struts, but also between the so-called stent “cells” (open region between stent struts) because of the balloon protrusion through the stent cells and against the arterial wall. They have not identified whether this denudation was due to friction or contact with the balloon.

Objective. The present study aims at characterizing and modelling the combined effect on the level of endothelium denudation, of the following mechanical parameters: 1) arterial wall stretch, 2) transmural pressure, and 3) friction of the balloon against the arterial wall during its deployment from the folded configuration.

2 Methods

2.1 Experimental Procedure

Descending aortas were harvested from pigs within 8 hours of death. The aortas were cut open longitudinally and cruciform-shaped samples were cut out from each aorta (Fig. 1a). The circumferential and axial directions of the artery were marked on the samples. A total of 51 samples were prepared. All the samples were kept in 0.9% isotonic solution, until the mechanical tests were performed.

Fig. 1. Experimental setup for friction testing: a) cruciform sample shape and dimensions in mm (gripping areas in grey); b) specimen holder, including grip clamps (1), stretch ratio adjustment screws (2), and knurled plate assembly (3); c) overall view and d) close-up view of friction testing apparatus, including heated bath (4), linear actuator (5), transmurial pressure adjustment screw (6) and load cell (7), and specimen holder (8)

Friction tests between polyethylene terephthalate (PET) samples, the material used in many angioplasty balloons, and aorta samples were performed on a custom-designed friction testing apparatus (Fig. 1c, d), using electromagnetic actuators (Bose ElectroForce Systems Group, Eden Prairie, MN). In each test, an aorta sample was mounted with four grip clamps on a specimen holder (Fig. 1b) and a biplanar stretch was applied. To prevent local planar deformation of the sample during the friction test, a cruciform plate assembly was placed over the sample. The plate assembly had a knurled 0.5 mm diamond-shaped pattern on its contact surface to minimize slip between the plate and the artery sample. Plate assemblies of various sizes were designed to exactly fit between the four grip clamps at the selected stretch ratios, to eliminate relative motion between the specimen holder and the assembly.

The specimen holder was then connected to actuators so that endothelial side of the artery was both immersed in saline solution maintained at body temperature and in contact with a PET specimen. The specimen holder had indexed recesses to allow repeatable positioning at predefined orientations. A compressive force was applied over the sample and was maintained constant while the specimen holder was pulled horizontally over a specific distance.

A design of experiment (DOE) was used to investigate the effect of stretch ratio, transmural pressure and friction on the denudation of the endothelium. A 5-factor 3-level Box-Behnken DOE was used to investigate the effect of the following independent variables: applied normal force (F_n ; values of 5, 62.5, and 120 N), stretch ratio¹ in the circumferential direction (λ_c ; values of 1.00, 1.25, and 1.50), stretch ratio in the axial direction (λ_a ; values of 1.00, 1.25, and 1.50), displacement in the circumferential direction (d_c ; values of 0.0, 2.25 and 4.5 mm), and displacement in the axial direction (d_a ; values of 0.0, 2.25 and 4.5 mm). Vector combinations of axial and circumferential displacements were accomplished by attaching the sample holder to the actuator at different orientations. The contact area was either 15-by-15 mm or 20-by-20 mm depending on the displacement vector. A total of 46 samples were tested, and 5 samples were used as controls.

At the end of each experiment, the endothelial cells (EC) that had detached from the intima were in the saline solution of the heated bath. The aorta sample was taken out of the grips and gently rinsed with saline. A round sample (6 or 10 mm diameter, depending on applied displacements) was punched out of the sample area in contact with the PET and placed on a Petri dish with the luminal side downwards. The intima layer was incubated for 30 min in Phosphate Buffered Saline (PBS) with collagenase (1 mg/ml), in order to detach the remaining EC from the endothelium after the friction tests. The EC were then removed by gently scraping the intimal surface using a plastic cell scraper. The collagenase was eliminated by pelleting the EC at 170 g (1000 rpm) for 5 min. The cell pellet was resuspended in PBS. The EC were stained with antibody anti-Human von Willebrand Factor (vWF). The remaining EC were counted under a microscope with a hemacytometer. The same process was also performed on the control samples. The cell density was obtained by dividing the number of cells counted on a sample by the surface area of the sample. The coverage percentage of EC after a friction test (e_{remain}) was obtained by dividing the cell density on the tested sample by the average cell density on the control samples.

2.2 Shear Deformation Artefact

Preliminary tests have shown that the friction force in the proposed DOE can be high enough to create non-negligible shear deformation of a sample across its thickness, as illustrated in Fig. 2a. To obtain a better estimate of the relative displacement between the two contacting surfaces, the shear deformation was calculated and subtracted from the applied displacement vector (Fig. 2b). The tissue is assumed to be incompressible. Therefore, the following relationship applies to the stretch ratios in the axial, circumferential, and thickness directions (Fig. 2c):

$$\lambda_a \lambda_c \lambda_t = 1 \quad (1)$$

¹ The stretch ratio is calculated by dividing the final length of the sample by its initial length.

Fig. 2. Shear deformation artefact: a) shear deformation due to friction force; b) three-dimensional stretch on sample; c) vector sum of applied displacement d and shear deformation d_{shear}

Biaxial stretching of the sample reduces its thickness t down to

$$t = \lambda_t t_0 = \frac{1}{\lambda_a \lambda_c} t_0, \quad (2)$$

where t_0 is the initial thickness of the sample. Assuming that the Amonton-Coulomb's law of friction applies, the friction force F_f can be written as a function of the normal force F_n :

$$F_f = \mu F_n, \quad (3)$$

where μ is the dynamic friction coefficient. The shear stress τ is given by

$$\tau = \frac{F_f}{A} = \mu \frac{F_n}{A}. \quad (4)$$

where A is the contact area. The shear stress can also be expressed in terms of the shear angular deformation γ

$$\tau = G\gamma, \quad (5)$$

where G is the shear modulus. The shear deformation is defined by

$$d_{shear} = \gamma t. \quad (6)$$

Substituting equations 2, 4 and 5 into 6 gives

$$d_{shear} = \frac{\mu t_0}{G} \times \frac{F_n}{\lambda_a \lambda_c} \times \frac{1}{A}, \quad (7)$$

where $G = 17\text{kPa}$ and $\mu = 0.02$ according to published results [11].

2.3 Statistical Analysis and Modelling

A multiple regression was calculated using NCSS statistical software to model the dependent variable as a function of independent variables. The dependent variable was the percentage of denuded endothelium on the sample, given by

$$e_{denuded} = 1 - e_{remain} \quad . \quad (8)$$

Given that the values of the dependent variable y and of the independent variables x_i can be represented in matrix forms by

$$\mathbf{Y} = \begin{bmatrix} y_1 \\ \vdots \\ y_j \\ \vdots \\ y_N \end{bmatrix}, \quad \mathbf{X} = \begin{bmatrix} 1 & x_{11} & \cdots & x_{p1} \\ \vdots & \vdots & \cdots & \vdots \\ 1 & x_{1j} & \cdots & x_{pj} \\ \vdots & \vdots & \cdots & \vdots \\ 1 & x_{1N} & \cdots & x_{pN} \end{bmatrix}, \quad (9)$$

where N is the number of observations and p is the number of independent variables, as described in [12]. The predicted values of the dependent variables are given by

$$\hat{\mathbf{Y}} = \mathbf{b}'\mathbf{X} \quad . \quad (10)$$

where $\mathbf{b}$ is the coefficient vector calculated by

$$\mathbf{b} = \begin{bmatrix} b_0 \\ b_1 \\ \vdots \\ b_p \end{bmatrix} = (\mathbf{X}'\mathbf{X})^{-1} \mathbf{X}'\mathbf{Y} \quad . \quad (11)$$

3 Results

The following model was calculated using only linear terms involving the five independent parameters (d_a , d_c , F_n , λ_a , λ_c):

$$e_{denuded} = -0.020d_a - 0.046d_c + 5.0 \times 10^{-3} F_n + 0.087\lambda_a + 0.063\lambda_c \quad , \quad (12)$$

where d_a and d_c are expressed in millimetres, F_n is expressed in Newtons, and λ_a and λ_c are dimensionless. The coefficient of determination (R^2) was 0.9523.

For integration in finite element software, a different model is proposed using the following independent variables: the transmural pressure (P), the friction work (W_f), and the sum of biplanar stretch ratios (λ_{1+2}). These independent variables were calculated from the factors of the DOE using the following equations:

$$P = \frac{F_n}{A} \quad , \quad (13)$$

$$W_f = \mu F_n d \quad , \quad (14)$$

$$\lambda_{1+2} = \lambda_1 + \lambda_2 = \lambda_a + \lambda_c \quad , \quad (15)$$

where d is the length of the displacement vector. Despite the fact that the DOE was not generated with these 3 new independent variables, correlation between the independent variables was low (<0.375). The range of values used in the DOE becomes 0.12 atm (90 mm Hg) to 5.26 atm (4000 mm Hg) for P , 0 to 18.6 mJ for W_f , and 2 to 3 for λ_{1+2} (see Table 1). The following model is proposed to predict endothelium denudation

$$e_{denuded} = 5.5 \times 10^{-4} P + 0.077 \lambda_{1+2} + 0.023 W_f \quad , \quad (16)$$

where P is expressed in kPa and W_f is in mJ. The coefficient of determination was 0.9317. Fig. 3 shows the predicted values using model in equation 13 as a function of the observed values for the dependent variable.

Table 1. Values of the independent variables and the observed dependent variable for each experiment

Exp.	λ_{1+2}	P (kPa)	W_f (mJ)	$e_{denuded}$	Exp.	λ_{1+2}	P (kPa)	W_f (mJ)	$e_{denuded}$
1	2.5	13	0.440	0.000	24	2.5	278	13.243	0.569
2	2.25	156	3.750	0.380	25	2.5	156	6.455	0.496
3	2.25	278	2.292	0.457	26	2.5	156	6.455	0.535
4	2.5	156	9.750	0.535	27	2.5	156	6.455	0.535
5	2.75	156	4.375	0.535	28	3	156	6.913	0.677
6	2.75	156	4.375	0.574	29	2.25	533	2.986	0.462
7	2.5	300	5.270	0.612	30	2.25	533	2.986	0.457
8	2.5	13	0.997	0.070	31	2.75	300	10.666	0.729
9	2.25	278	9.245	0.354	32	2.75	300	10.666	0.690
10	2.25	278	9.245	0.380	33	2.5	13	0.997	0.070
11	2.75	156	11.328	0.569	34	2.25	278	9.245	0.354
12	2.75	156	11.328	0.677	35	2.25	278	9.245	0.354
13	2.5	300	18.620	0.690	36	2.75	156	11.328	0.569
14	2.25	22	0.615	0.070	37	2.75	156	11.328	0.569
15	2.25	22	0.615	0.031	38	2.5	300	18.620	0.651
16	2.75	13	0.628	0.109	39	2.5	13	0.440	0.109
17	2.75	13	0.628	0.031	40	2.25	278	2.292	0.341
18	2	278	3.788	0.302	41	2.25	156	3.750	0.457
19	2.5	278	5.177	0.419	42	2.5	156	9.750	0.612
20	2.5	278	5.177	0.419	43	2.75	156	4.375	0.457
21	2.5	156	6.455	0.457	44	2.75	156	4.375	0.574
22	2.5	156	6.455	0.574	45	2.5	300	5.270	0.612
23	2.5	156	6.455	0.535	46	2.5	156	0.000	0.496

Fig. 3. Predicted vs. observed $e_{denuded}$ using model in equation 13

4 Discussion

In the present study, a constitutive model is proposed for prediction of endothelium denudation. The model is based on in vitro experiments using porcine artery samples. Porcine, rat and rabbit arteries have been used as a model to better understand the mechanical behaviour of arteries and their response to injuries [5],[7],[8],[9], including endothelium denudation, but whether the results of the present study are applicable to humans remains to be demonstrated.

The experiments involved contact between arterial tissue and PET samples. Although care was taken to reproduce in vivo conditions of angioplasty balloon in contact with an artery, it is possible that 1) the surface condition of the balloon might change as the balloon membrane stretches; and that 2) the use of saline solution might create different friction conditions than in an artery filled with blood.

In this study, the speed of relative displacement between the artery and the PET sample was not considered as an independent variable. Slow balloon inflation has been recently shown to reduce neointimal thickening [13],[14]. Whether this effect is due to a reduction of endothelium denudation is unknown. However, recent findings on the effect of strain rate on the mechanical behaviour of the arterial wall [15] rather suggest a relationship between strain rate and overstretch injury.

The experimental method was designed to minimize experimental artefacts. Nevertheless, the biggest artefact appears to be due to the shear deformation of the sample due to the friction force. The magnitude of the artefact was estimated and displacements were corrected accordingly. However, this estimation depends on parameters such as friction coefficient and shear modulus that were obtained from published data rather than being measured on the samples used in the present study. Moreover, the shear modulus was assumed to be constant, although it is possible that the shear modulus varies with the level of stretch of the artery, especially since the stress-strain curve of the artery is nonlinear at the level of stretch used in this study. These simplifying assumptions might impair the accuracy of the model.

Despite the above-mentioned experimental limitation, the selected values for the independent variables generated a wide distribution for the dependent variable, spanning almost the whole range of 0 (intact endothelium) to 1 (no endothelium left), as shown in Fig. 3. This maximizes the range of application of the model.

During an angioplasty and stent implantation, balloon inflation is a combination of two possibly overlapping phases: 1) deployment of the balloon flaps, and 2) stretching of the balloon membrane. During the first phase, friction between the balloon and endothelium can occur if the balloon contacts the arterial wall before the deployment of the balloon flaps is completed. During the second phase, friction between the balloon and endothelium can also occur if the wall does not stretch as uniformly as the balloon. Knowledge of the exact sequence of event requires numerical simulation of the intervention using patient-specific artery shape and mechanical properties.

The proposed constitutive model is expressed as a function of variables that can be calculated in finite element software. Since endothelium denudation is irreversible, at least during balloon deployment, the model must be formulated to take into account the history of the tissue. This is obvious for the friction work, which can never decrease over time. However, it is debatable whether the model should only consider the instantaneous values for the stretch and the pressure or should consider the history of stretch and pressure. It was observed from pilot experiments that pressure alone, without displacement or stretch, causes denudation. Also, when a regression analysis was performed including interactions, first order stretch was a significant factor. So it is proposed that at each load step or iteration of the finite element calculation, the instantaneous values of stretch and pressure and the cumulative values of friction work be used in the calculation of the endothelium denudation. However, in order for the denudation never to decrease, the maximum historical value of the endothelium denudation would always override the instantaneous value, as in

$$e_{denuded}(t) = \max \left[5.5 \times 10^{-4} P(t) + 0.077 \lambda_{1+2}(t) + 0.023 W_f(t) \right]_0^t, \quad (17)$$

where $P(t)$ and $\lambda_{1+2}(t)$ are instantaneous values, and $W_f(t)$ is a cumulative value given by

$$W_f(t) = \mu \int_{\tau=0}^t F_n(\tau) d(\tau) d\tau. \quad (18)$$

Solid mechanics simulation software with multi-body contact algorithms is currently being developed and used to study the mechanics of balloon-stent-artery interaction [16]. The proposed constitutive model of endothelium damage will be implemented in the software to take into account the complexity of balloon-stent-artery interaction in the patient-specific prediction of endothelium denudation.

5 Conclusion

In this study, a model is proposed to predict endothelium denudation as a function of mechanical variables describing the interaction between balloon and arterial wall. This is the first step towards prediction of arterial damage and biological response of the artery. Other experimental work is underway to develop a model predicting neointimal thickness as a function of stretch, intramural pressure and friction work. Used in finite element analysis of balloon angioplasty and stenting, such models will help clinicians select for a specific patient the balloon size and inflation pressure, not only that maximizes the lumen patency, but also that minimizes arterial injury and long-term lumen loss.

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References

1. Kiemeneij, F., Serruys, P.W., Macaya, C., et al.: Continued benefit of coronary stenting versus balloon angioplasty: five-year clinical follow-up of Benestent-I trial. *J. Am. Coll. Cardiol.* 37, 1598–1603 (2001)
2. Serruys, P.W., Luijten, H.E., Beatt, K.J., et al.: Incidence of restenosis after successful coronary angioplasty: a time-related phenomenon. A quantitative angiographic study in 342 consecutive patients at 1, 2, 3, and 4 months. *Circulation* 77, 361–371 (1988)
3. Hoffmann, R., Mintz, G.S., Mehran, R., et al.: Tissue proliferation within and surrounding Palmaz-Schatz stents is dependent on the aggressiveness of stent implantation technique. *Am. J. Cardiol.* 83, 1170–1174 (1999)
4. Koyama, J., Owa, M., Sakurai, S., et al.: Relation between vascular morphologic changes during stent implantation and the magnitude of in-stent neointimal hyperplasia. *Am. J. Cardiol.* 86, 753–758 (2000)
5. Schwartz, R.S., Huber, K.C., Murphy, J.G., et al.: Restenosis and the proportional neointimal response to coronary artery injury: results in a porcine model. *J. Am. Coll. Cardiol.* 19, 267–274 (1992)
6. Kuntz, R.E., Safian, R.D., Carrozza, J.P., et al.: The importance of acute luminal diameter in determining restenosis after coronary atherectomy or stenting. *Circ.* 86, 1827–1835 (1992)
7. Capron, L., Bruneval, P.: Influence of applied stress on mitotic response of arteries to injury with a balloon catheter: quantitative study in rat thoracic aorta. *Cardiovasc. Res.* 23, 941–948 (1989)
8. Olson, N.E., Chao, S., Lindner, V., Reidy, M.A.: Intimal smooth muscle cell proliferation after balloon catheter injury. The role of basic fibroblast growth factor. *Am. J. Pathol.* 140, 1017–1023 (1992)
9. Jamal, A., Bendeck, M., Langille, B.L.: Structural changes and recovery of function after arterial injury. *Arterioscler. Thromb. Vasc. Biol.* 12, 307–317 (1992)
10. Rogers, C., Tseng, D.Y., Squire, J.C., Edelman, E.R.: Balloon-artery interactions during stent placement: a finite element analysis approach to pressure, compliance, and stent design as contributors to vascular injury. *Circ. Res.* 84, 378–383 (1999)
11. Caldwell, R.A., Woodell, J.E., Ho, S.P., et al.: In vitro evaluation of phosphonylated low-density polyethylene for vascular applications. *J. Biomed. Mater. Res.* 62, 514–524 (2002)
12. Multiple Regression. In: NCSS User's Guide, pp. 305-1–305-98 (2007)
13. Umeda, H., Iwase, M., Kanda, H.: Promising efficacy of primary gradual and prolonged balloon angioplasty in small coronary arteries: A randomized comparison with cutting balloon angioplasty and conventional balloon angioplasty. *Am. Heart J.* 147, 1–8 (2004)
14. Weiss, T., Leibovitz, D., Katz, I., Danenberg, C., Varshitsky, B., Lotan, C.: The value of computerized angioplasty in patients undergoing coronary stenting: a prospective, randomized trial. *Am. J. Cardiol.* 100, 118 (2007)
15. Virues Delgadillo, J.O., Delorme, S., DiRaddo, R., Hatzikiriakos, S.: Stiffness of porcine aortas decreases with strain-rate. *Simulation in Healthcare* 2, 156 (2007)
16. Laroche, D., Delorme, S., Anderson, T., DiRaddo, R.: Computer prediction of friction in balloon angioplasty and stent implantation. In: Harders, M., Székely, G. (eds.) *ISBMS 2006. LNCS*, vol. 4072, pp. 1–8. Springer, Heidelberg (2006)