MECHANICS OF ANGIOPLASTY:
WALL, BALLOON AND STENT

Gerhard A. Holzapfel, Christian A.J. Schulze–Bauer and Michael Stadler

Graz University of Technology
Institute for Structural Analysis – Computational Biomechanics
Schiessstattgasse 14-B
A–8010 Graz, Austria

Appeared as Proceedings in
The American Society of Mechanical Engineers, Orlando, FL

TABLE OF CONTENTS

ABSTRACT
1 INTRODUCTION
2 MAGNETIC RESONANCE IMAGING (MRI) OF A STENOTIC HUMAN ARTERY
3 HISTOLOGY, IMAGE SEGMENTATION AND 3D MORPHOLOGICAL MODEL
4 MECHANICAL TESTING
5 ORIENTATION OF COLLAGEN FIBERS
6 CONSTITUTIVE MODEL
   6.1 Anisotropic Elastic Response
      6.1.1 Volumetric-isochoric Elastic Stress Response
   6.2 Anisotropic Inelastic Response
      6.2.1 Inelastic Stress Response and Plastic Dissipation
   6.3 Data Fitting
7 MECHANISM OF ANGIOPLASTY
   ACKNOWLEDGEMENTS
   REFERENCES

\footnote{Financial support for this research was provided by the Austrian Science Foundation under START-Award Y74-TEC.}
MECHANICS OF ANGIOPLASTY:
WALL, BALLOON AND STENT

Gerhard A. Holzapfel
Christian A.J. Schulze-Bauer and Michael Stadler
Institute for Structural Analysis
Computational Biomechanics
Graz University of Technology
Schiesskattgasse 14-B, 8010 Graz, Austria

ABSTRACT
Studying the solid mechanics of angioplasty provides essential insight in the mechanics of angioplasty such as overstretching the disease-free tissue, plaque disruption or dissection, redistribution inside the wall and lipid extrusion etc. We describe our current understanding of the mechanics of angioplasty based on the example of a human iliac artery with an eccentric stenosis. We outline a new approach which has the potential to improve interventional treatment planning, to predict the balloon and stent-induced wall stresses as well as the dilation success. In particular, we use MRI to obtain accurate geometrical data for the vessel wall and plaque architecture and to identify their different types of soft (biological) tissues and calcifications. One issue is to characterize the quasistatic stress-strain response of these components in both axial and circumferential directions. We present new experimental results showing strong nonlinearity and anisotropy. Another issue is to identify predominant directions of each component by analyzing orientations of cellular nuclei. The morphological and mechanical information is used for the elastoplastic constitutive model designed to capture the finite strains of the stenotic artery during angioplasty. The three-dimensional model is fitted to the experimental data. Associated material parameters, corresponding to the different tissues of the stenosis, are presented. The numerical part outlines briefly the concept of the finite element model and, based on a computational structural analysis, discusses the mechanism of angioplasty for the considered type of stenosis.

INTRODUCTION
Percutaneous Transluminal Angioplasty (PTA) with or without stenting is a well-established interventional method to reduce the severity of atherosclerotic stenoses. It represents a mechanical solution for a clinical problem and is the most frequent therapeutic intervention world wide (Fleisch and Meier, 1999) with great and steadily growing medical, socioeconomic and scientific interest (American Heart Association, 2000). The primary success rate of PTA is 90-95%; however, secondary success is not satisfactory. At the coronary site, restenosis (i.e. renarrowing of the dilated stenotic segment in the following months) occurs in about 40% of lesions within 6 months from the procedure (Fleisch and Meier, 1999, and Macaya et al., 1996). The deployment of a stent improves the primary success rate, the
long-term patency and clinical outcomes compared with PTA (Serruys et al., 1994, and Fischman et al., 1994). A better understanding of the mechanical factors involved in the underlying process might result in new strategies to prevent or reduce restenosis. For example, the effect of balloon-induced stresses on vascular smooth muscle cells may be an important mechanical factor of restenosis (Cheng et al., 1996). Therefore, the development of an appropriate histomechanical model of the diseased artery that may help to better understand the mechanism of angioplasty is a rewarding task.

This task requires a multidisciplinary approach. Mechanical assessment of PTA (with or without stenting) depends predominantly on the availability of a comprehensive data-set of the considered human atherosclerotic stenosis. Only the interplay of (i) plaque architecture, (ii) knowledge of mechanical responses of the different tissue components of the wall and (iii) mechanical properties of balloon catheters and stents may provide a complete description of interventional procedures. To yield clinically meaningful results it is necessary to ascertain all these data from the same human stenosis.

One of the most promising noninvasive techniques for obtaining accurate geometrical data of the plaque architecture is Magnetic Resonance Imaging (MRI). Changes in geometry of the individual tissue can be monitored without dissecting the artery. The mechanical response of each individual tissue is highly nonlinear, (visco)elastic and, due to its histological structure, also anisotropic. For loadings beyond the physiological range, which happens during PTA, the deformation process of an arterial component may be associated with inelastic effects (elastoplastic and/or damage mechanisms).

To the authors’ knowledge this paper tries for the first time to combine all these aspects. In particular, we consider one human atherosclerotic artery and use MRI to distinguish between different components. Histological analysis is necessary to identify the underlying tissue type and the morphological structure of each individual component. The goal on the experimental side is to provide a mechanically representative data-set of the stenotic artery. The fundamental basis of the constitutive model presented is nonlinear continuum mechanics. The three-dimensional elastoplastic model considers the histological structure of the involved tissues, i.e., an isotropic ground substance (modeled as a neo-Hookean material) and two families of collagen fibers symmetrically disposed with respect to the axis (modeled as an exponential energy function). The constitutive theory is based on multisurface plasticity. It is able to capture all features of biological soft tissues when loaded beyond the physiological range of deformation. Based on this information the goal on the numerical side is to create a finite element model which serves as a working tool for studying the mechanism of angioplasty.

**MAGNETIC RESONANCE IMAGING (MRI) OF A DISEASED HUMAN ARTERY**

A necessary prerequisite of a meaningful PTA-computation is the identification of the three-dimensional vessel wall and plaque architecture.

High resolution Magnetic Resonance Imaging (hrMRI) is the appropriate noninvasive method that provides non-destructively cross-sectional organ images with high contrasts and high spatial resolution by means of the electromagnetic tissue response to strong magnetic fields. This new and rapidly developing method is proven to be effective in characterizing human vessel walls and atherosclerotic plaque components (Pohost and Fuisz, 1998, Shinhar et al., 1999, and Coulson et al., 2000). It discriminates the biochemical constituents (plaque architecture) with high resolution and is sensitive to the heterogeneous components such as the adventitia, media, intima, lipid pool, collagenous cap, and calcification in vivo (Toussaint et al., 1995). hrMRI also allows in vivo identifications of the extent and distribution of the lipid pool and collagenous cap (Toussaint et al., 1996) and may allow better assessment of the gross behavior of atherosclerotic lesions during interventional procedures such as angioplasty and atherectomy (Toussaint et al., 1998). The morphological identification of these atherosclerotic components is one inevitable prerequisite for the histomechanical constitutive model to predict the three-dimensional plaque response to angioplasty on a numerical basis.
For our study we excised an external iliac artery (male, 68 years, primary disease: myocardial infarction; cause of death: cardiac tamponade) with an eccentric stenosis from a corpse during autopsy within 24 hrs after death. Loose connective tissue was removed. Axial *in situ* pre-stretch (defined as *in situ* length/*ex situ* length) was 1.03. The *ex situ* length was measured by means of a pair of compasses after 1 hr of equilibration in 37°C physiological salt solution. The artery was tethered with superficial surgical sutures to a grid of nylon threads fixed in a Perspex frame. The frame was placed in a Perspex container with the specimen hanging 5mm above the bottom in physiological salt solution at 37°C.

The three-dimensional geometry and composition of the stenotic artery was determined within 24 hrs after autopsy. The artery was scanned over 20mm axial length, on a 1.5T system (Philips ACS-NT) routinely used for clinical diagnostics. The in-plane resolution was 0.3mm with a slice thickness of 1mm. Figure 1(b) shows a typical MRI slice. The nylon threads were clearly seen on the hrMRI images and used as markers for subsequent histological correlations. Histological analysis is necessary since although hrMRI can distinguish between different components due to high signal contrasts it can not directly identify the underlying tissue type.

Afterwards the vessel wall was marked for histology by injecting black ink at a nylon thread crossing. The artery was cut through transversely in two halves. The section with ink marks was used for histopathological analysis and could be correlated with the corresponding hrMRI image, while the other half was used for mechanical testing.

**HISTOLOGY, IMAGE SEGMENTATION AND 3D MORPHOLOGICAL MODEL**

The ink-marked half of the vessel segment was fixed in 8% buffered formaldehyde solution (pH 7.4), decalcified with EDTA, sectioned at 5μm, and stained with Elastika van Gieson and hematoxylin & eosin. The histological section at the marked position was segmented by a pathologist, who drew the border of the different tissues on the microphotograph. Eight different tissue types were considered: the
adventitia A, the non-diseased media M-nos (nos stands for non otherwise specified), the non-diseased intima I-nos, the diseased fibrotic media M-f and the atherosclerotic plaque, which shows a highly characteristic architecture of a fibrous part at the luminal border I-f1 (collagenous cap), a central core of extracellular lipids and debris I-Ip (fluid-like lipid pool), a fibrous part at the medial border I-fm, and calcification I-c. This classification results in a separation of the diseased vessel wall that is (solid) mechanically representable and that covers the gross histological composition of the stenosis (see, for example, Stary et al., 1995). This separation is also physically feasible using surgical instruments.

Figure 1(a) gives an example of a segmented section. Comparison with the corresponding hrMRI cross-section, i.e., the image slice as illustrated in Fig. 1(b), allowed correlation of the histological tissue type with the hrMRI appearance. Based on the classification scheme described above, a three-dimensional morphological model of the considered stenosis was generated using interpolation between the 21 serial hrMRI slices.

MECHANICAL TESTING

Mechanical tests were performed with a high-precision tensile testing machine (Messphysik, μ-Strain Instrument ME-30-1, Fürstenfeld, Austria) designed for small biological specimens. It is equipped with a container filled with physiological salt solution maintained at 37°C by a heater-circulator unit (Lauda, Model E 200, Lauda-Königshofen, Germany). Gauge length and width are measured optically using a PC-based CCD-camera videocytometer that allows automatic gauge mark and edge recognition. Dimensional measurements are performed with a total resolution of 17bit with regard to the camera’s field of view.

The calciﬁcations, labeled as I-c, and the lipid pools, labeled as I-Ip, were excluded from mechanical testing and considered as rigid bodies and incompressible fluids, respectively. For the determination of the passive, quasistatic stress-stretch response of the remaining tissues, the stenosis was dissected in its components according to the tissue classiﬁcation mentioned above.

From the resulting patches rectangular strips (7-17 mm in length) were cut out in both axial and circumferential directions. However, preparation failed in the case of the axial strips for the diseased media M-f and for the intimal fibrous parts I-fm at the medial border. Squares of polishing paper were attached to the ends of the strips to widen them for clamping. Two black colored straw caps were glued transversely in parallel onto the middle part of the strips to act as gauge markers for the axial deformation measurements. The strips were allowed to equilibrate for 30 min in physiological salt solution at 37°C. Then they underwent cyclic uniaxial extension tests with continuous recording of tensile force, width and gauge length at a constant crosshead speed of 1 mm/min. Preconditioning was achieved by executing five successive loading cycles in each test.

For the non-diseased media strip (M-nos) in the circumferential direction the protocol was extended to loading beyond the elastic physiological range of deformation (Fig. 2(d)). Therefore, the maximum strain was increased incrementally until fracture occurred. At each new strain level two loading cycles were performed. All tests were finished within 36 hrs after autopsy.

Cauchy stresses were calculated assuming incompressibility and the stress-stretch plots were smoothed out using a linear regression ﬁlter. The mechanical responses of the different tissues show strong nonlinearity and anisotropy, as illustrated in Fig. 2 (the dots in Figs 2(a)-(d) indicate the ‘best-ﬁt’ curves of the constitutive model for the circumferential direction, as explained later in the text).

As seen in Figs 2(a)-(c), the intima is the stiffest layer, the media the softest and the adventitia shows the most pronounced stiffening behavior in larger strain regions. The loading-unloading paths showed small hystereses not indicated in the associated ﬁgures. Remarkably, the axial strip of the non-diseased intima (I-nos) is the stiffest. At the I-nos strip, an analysis of the fiber orientations indicated
Figure 2. Experimental stress-stretch response of different tissues (solid lines). For the least square regression data of the axial strips were considered up to strains of 15%. Best-fit curves of circumferential strips are indicated by dots (best-fit curves of axial strips are not illustrated here).

not only a more or less circumferential orientation of fiber bundles, but also an additional (weaker) predominant orientation, which is close to the axial direction. This histostuctural observation may be one explanation for the relatively stiff i-nos tissue. Circumferential strips of the diseased media M-f and of the intimal fibrous parts I-fm at the medial border exhibited similar mechanical responses, thus suggesting that these two thin adjacent layers behave functionally as one layer. In general axial strips were stiffer than circumferential ones. However, for the plaque cap this was not true, which underlines its special biological role.

The extended protocol for the non-diseased media strip (M-nos) shows that the deformation process is associated with inelastic effects (elastoplastic and/or damage mechanisms) leading to significant changes in the mechanical behavior (Fig. 2(d)). The overstrecthing due to the first loading cycle involved dissipation with large hystereses compared with the elastic domain. A subsequent second loading cycle shows a small hysteresis and (relatively large) non-vanishing strains at the unstressed state (up to 6%), these being responsible for the permanent change of shape of the strip. The strip is probably not preconditioned sufficiently after the second loading cycle; however, for the sake of practicality, the protocol was restricted to two loading cycles.

To specify the pressure-deformation behavior of a selected angioplasty balloon catheter (Cordis Opta 1r, balloon length 20mm, balloon diameter 10mm, shank diameter 1.65mm, total length 800mm), length gauge marks were attached on the balloon surface. The videoeextensometer was used for bi-
dimensional recordings. Balloon inflation was maintained by a 10ml standard inflation syringe and inflation pressure was measured with a pressure gauge (Schneider), both routinely used in balloon angioplasty.

**ORIENTATION OF COLLAGEN FIBERS**

All biological soft tissues may be treated as highly deformable, fiber-reinforced composites showing a nonlinear stress-strain response with a typical (exponential) stiffening effect at higher loads. This stiffening effect is based on the recruitment of the embedded wavy collagen fibrils, a biochemical constituent which renders the material properties anisotropic, or cylindrically orthotropic for the case of arteries (see, for example, Roach and Burton, 1957, Patel and Fry, 1969, and Nichols and O'Rourke, 1998, Chapter 4). The resistance to stretch at high pressures is almost entirely due to collagen fibers. Hence, it seems to be essential to incorporate this morphological information into the constitutive (and finite element) model. In particular, this means that statistical information about the alignment of collagen fibers is required.

Preferred directions in biological soft tissues are well specified by the orientation of prolate cell nuclei which can be identified in microphotographs of appropriately stained histological sections. By visual inspection a high directional correlation between smooth muscle cells and collagen fibers may be observed. We developed a software tool that allows a fully automatic detection of preferred directions in soft tissues by means of recognition of the cell nuclei arrangement in microphotographs. A detailed description of the automatic technique to specify the fiber orientations is given in Holzapfel et al. (2000a), with more references therein.

After mechanical testing the strips were fixed in 8% buffered formaldehyde solution (pH 7.4), embedded in paraffin, sectioned tangentially at 5µm, and stained with hematoxylin & eosin. Digital microphotographs were taken to obtain (statistically relevant) data about the orientation of nuclei by means of the developed software tool. Mean values of the predominant orientations of fiber bundles (nuclei) obtained from the axial and circumferential strips were used to specify the tissues. In arterial layers, typically, there are two preferred fiber directions observed, which we characterize by the fiber angles δ₁ and δ₂. The geometrical situation of the fiber location in a specific arterial layer is illustrated in Fig. 3. Typically, the fibers are arranged symmetrically with respect to the circumferential direction of the arterial layer (δ₁ = δ₂). They cause the locally orthotropic mechanical behavior of the vessel wall. Table 1 summarizes the mean values of the fiber angles for each individual tissue.

<table>
<thead>
<tr>
<th></th>
<th>Adventitia</th>
<th>Media</th>
<th>Media</th>
<th>Intima</th>
<th>Intima</th>
<th>Intima</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>M-nos</td>
<td>M-f</td>
<td>I-nos</td>
<td>I-fib</td>
<td>I-fib</td>
</tr>
<tr>
<td>Predominant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>orientation δ₁ = δ₂</td>
<td>49°</td>
<td>7°</td>
<td>5°</td>
<td>5°</td>
<td>0°</td>
<td>0°</td>
</tr>
</tbody>
</table>

**CONSTITUTIVE MODEL**

By applying loads far beyond the physiological range, as is the case during angioplasty, one might assume the load-carrying fibers of the tissue slip on each other so that plastic deformation takes place. To describe this phenomenon we adopt the non-associative rate-independent elastoplastic constitutive
model for biological soft tissues recently proposed by Gasser and Holzapfel (2000). This paper also includes a detailed description of a finite element implementation. The constitutive framework is based on multisurface plasticity and reviewed briefly in this section. The notation used is mainly adopted from computational plasticity (Simo and Hughes, 1998, and Simo, 1998).

Anisotropic Elastic Response

In order to describe the anisotropic elastic response of the different biological tissues, we use a Helmholtz free-energy function $\Psi$ in the decoupled form

$$\Psi(F^e, a^1_0, a^2_0, A) = \Psi_{macro}(F^e, a^1_0, a^2_0) + \Psi_{micro}(A),$$

where $\Psi_{macro}$ characterizes the macroscopic anisotropic response and $\Psi_{micro}$ is the energy stored in the microstructure due to hardening effects and depends on the hardening (scalar) variable $A$. In assumption (1) we used the multiplicative split of the deformation gradient $F = F^e F^p$ into an elastic part $F^e$ and a plastic part $F^p$. The fiber directions are characterized by the set $\{a^\alpha_0; \alpha = 1, 2\}$ of unit vectors. The vector $a^\alpha_0(X)$ at referential position $X$ describes the orientation of the $\alpha$-th family of fibers in the undeformed configuration of a tissue (see Fig. 3). Furthermore, we decompose $F$ into spherical and unimodular parts and use the expressions

$$F = J^{1/3} F^p, \quad J = \det F^e = \det F > 0,$$

with the volume ratio $J > 0$. We assumed that there is no volume change due to plastic flow, as in metal plasticity.

Using standard arguments, from the Clausius-Planck inequality (Holzapfel, 2000) we may derive expressions for the (non-symmetric) Mandel stress tensor $\Sigma$ and the plastic dissipation $\varphi^p$ (per unit reference volume). Thus,

$$\Sigma = F^{e T} \frac{\partial \Psi}{\partial F^e} = F^{e T} (g \Sigma) F^{e T}, \quad \varphi^p = \Sigma : L^p - B \dot{A} \geq 0,$$

147
where the superposed dot denotes the material time derivative and \( g \) and \( \tau \) denote the Eulerian metric and the symmetric (spatial) Kirchhoff stress tensor, respectively. Here we have introduced the micro-stress \( B = \partial \psi_{\text{macro}} / \partial A \) (Miehe, 1996), work conjugate to \( A \), and the plastic kinematic quantity \( L^p = \dot{E}^p \Phi \).\(^1\)

The macroscopic free-energy function \( \psi_{\text{macro}} \) is assumed to be based on the concept of fiber-reinforced composites proposed by Spencer (1984). We choose the specific form

\[
\psi_{\text{macro}}(F^e, a_i^g, a_j^g) = U(J) + \overline{\psi}_{gs}(\overline{I}_1) + \sum_{\alpha \in \mathcal{B}} \overline{\psi}^\alpha_f(\overline{I}_4)
\]  (4)

(see also Holzapfel, 2000, Holzapfel et al., 2000b, and Holzapfel and Gasser, 2001), with the particularization

\[
U(J) = \frac{\kappa}{2} (J - 1)^2, \quad \overline{\psi}_{gs}(\overline{I}_1) = \frac{\mu}{2} (\overline{I}_1 - 3),
\]  (5)

\[
\overline{\psi}^\alpha_f(\overline{I}_4) = \frac{k_1}{2k_2} \left\{ \exp \left[ k_2 (\overline{I}_4 - 1)^{\frac{1}{2}} \right] - 1 \right\}, \quad \alpha = 1, 2
\]  (6)

of the volumetric contribution \( U \) (which characterizes the energy stored due to elastic volume changes of the tissue) and the isochoric contributions \( \overline{\psi}_{gs} \), \( \overline{\psi}^\alpha_f \). To model the (isotropic) ground substance (‘elastin’ contribution) we may apply any Ogden-type elastic material (Ogden, 1997), in particular, we use the neo-Hookean potential \( \overline{\psi}_{gs} \). The exponential function \( \overline{\psi}^\alpha_f \) describes the energy stored in the \( \alpha \)-th family of fibers (‘collagen’ contribution).

In (4) \( \overline{I}_1 = \text{tr} F^e \) denotes the first invariant of the modified elastic right Cauchy-Green tensor \( F^e = F^e + \Phi \), while \( \overline{I}_4 = \text{tr} \overline{C}^e : a_i^g \otimes a_j^g, \alpha = 1, 2, \) are additional invariants of \( \overline{C}^e \) and \( a_i^g \otimes a_j^g \) are structural tensors. We assume that the fibers do not carry any compressive load, which is expressed by the set \( \mathcal{B} = \{ \alpha \in 1, 2 : \overline{I}_4 > 1 \} \) for active fibers which are stretched. Only the fibers which are active contribute to the free-energy function \( \psi_{\text{macro}} \). The introduced material parameters \( \kappa > 0 \) and \( \mu > 0 \) describe the isotropic response, while \( k_1 > 0 \) and \( k_2 > 0 \) are associated with the anisotropic material behavior. We assume that each family of fibers has the same mechanical response, which implies that \( k_1 \) and \( k_2 \) are the same for each fiber family.

The energy functions (5), (6) are well suited for the description of the typical anisotropic mechanical behavior of tissues during (physiological) loading conditions. They do not incorporate coupling phenomena occurring between the two fiber families (for a more general constitutive approach see Holzapfel and Gasser, 2001).

**Volumetric-isochoric Elastic Stress Response.** From the macroscopic free-energy function (4) the Kirchhoff stress tensor \( \tau \) may be derived in a standard way. Its decoupled representation is given by

\[
\tau = 2 \frac{\partial \psi_{\text{macro}}(F^e, a_i^g, a_j^g)}{\partial g} = \tau_{\text{vol}} + \tau_{\text{gs}}, \quad \tau = \overline{\tau}_{gs} + \sum_{\alpha \in \mathcal{B}} \overline{\psi}^\alpha_f(\overline{I}_4)
\]  (7)

with the expressions \( \tau_{\text{vol}} = 2 \partial U(J) / \partial g \) for the volumetric Kirchhoff stress tensor and \( \overline{\tau}_{gs} = 2 \partial \overline{\psi}_{gs}(\overline{I}_1) / \partial g \), \( \overline{\tau}^\alpha_f = 2 \partial \overline{\psi}^\alpha_f(\overline{I}_4) / \partial g \), \( \alpha = 1, 2 \), for the isochoric Kirchhoff stress tensor.

148
By use of the specified free-energy functions \( (5), (6) \) and by successive application of the chain rule, we find after some kinematic tensor manipulations that the volumetric-isochoric elastic stress response is governed by the three contributions

\[
\tau_{cd} = 2 \frac{\partial U(J)}{\partial J} \frac{\partial J}{\partial C} : \frac{\partial C^c}{\partial \varrho} = p \mathbf{I}, \quad \tau_{g0} = 2 \frac{\partial \Psi_g(J)}{\partial C} : \frac{\partial C^c}{\partial \varrho} = \mu \text{dev}\mathbf{B}^s, \tag{8}
\]

\[
\tau_i^\alpha = 2 \frac{\partial \Psi_i^\alpha (J)}{\partial C} : \frac{\partial C^c}{\partial \varrho} = 2 \psi^\alpha \text{dev}(a^\alpha \otimes a^\alpha), \quad \alpha = 1, 2, \tag{9}
\]

with the specified expressions

\[
p = \frac{\partial U(J)}{\partial J} = \kappa (J - 1), \quad \psi^\alpha = \frac{\partial \Psi_i^\alpha (J)}{\partial J} = k_1 (\bar{\rho}_s - 1) \exp \left[ k_2 (\bar{\rho}_s - 1)^2 \right], \quad \alpha = 1, 2 \tag{10}
\]

for the hydrostatic pressure \( p \) and the stress functions \( \psi^\alpha, \alpha = 1, 2 \). Additionally, we have introduced the deviatoric operator

\[
\text{dev}(\bullet) = (\bullet) - \frac{1}{3} \left( (\bullet) : \mathbf{I} \right) \mathbf{I} \tag{11}
\]

in the Eulerian description and the modified elastic left Cauchy-Green tensor \( \mathbf{B}^s = \mathbf{F}^s \mathbf{F}^{sT} \). In (9) we have defined the set \( \{ a^\alpha; \alpha = 1, 2 \} \) of Eulerian vectors \( a^\alpha \) as a map of the structural measures \( a^\alpha_s \) via the unimodular elastic part \( \mathbf{F}^0 \) of the deformation gradient. Thus,

\[
a^\alpha = \mathbf{F}^s a^\alpha_s, \quad \alpha = 1, 2. \tag{12}
\]

The (symmetric) Cauchy stress tensor \( \sigma \) is simply given by the relation \( \sigma = J^{-1} \tau \). In order to specify the Mandel stress tensor \( \Sigma \) we use expressions (7)-(9), the definition (12) of the Eulerian vectors and \( \mathbf{C}^s = \mathbf{F}^s \mathbf{F}^{sT}, \mathbf{B}^s = \mathbf{F}^{sT} \mathbf{F}^s \). Then, from relation (3), we find that

\[
\Sigma = p \mathbf{I} + \mu \text{dev}\mathbf{C}^s + 2 \sum_{\beta \neq \alpha} \psi^\beta \text{dev}(\mathbf{C}^s a^\beta \otimes a^\beta). \tag{13}
\]

For a more explicit derivation of the elastic stress response the reader is referred to Gasser and Holzapfel (2000).

**Anisotropic Inelastic Response**

Here we briefly outline the set of equations necessary to describe the anisotropic inelastic response of the different biological tissues. The continuum mechanical concept is set up by the introduction of a set \( \mathbb{E} \) assumed to be associated only with the *isochoric* stress response of the material. The interior of
$\mathcal{E}$ is defined as $\text{int}(\mathcal{E}) = \{(\text{dev} \Sigma, \mathbf{a}_0^1, \mathbf{a}_0^2, B) \mid \hat{\Phi}^\alpha < 0 \}, \alpha = 1, 2$. The set $\mathcal{E}$ is bounded by a convex but non-smooth yield surface $\partial \mathcal{E}$, defined as

$$\partial \mathcal{E} = \{(\text{dev} \Sigma, \mathbf{a}_0^1, \mathbf{a}_0^2, B) \mid \hat{\Phi}^\alpha = 0 \}, \quad \alpha = 1, 2,$$

with the two independent yield conditions $\hat{\Phi}^\alpha$, $\alpha = 1, 2$, defined as

$$\hat{\Phi}^\alpha = \Phi_{\text{macro}}^\alpha (\text{dev} \Sigma, \mathbf{a}_0^1, \mathbf{a}_0^2) - \Phi_{\text{micro}} (B), \quad \alpha = 1, 2.$$  \hfill (15)

To determine the isochoric plastic deformation of the different biological tissues we introduce a flow rule which is motivated by the histology of the tissue and characterized by the same set $\{\mathbf{a}_0^\alpha; \alpha = 1, 2\}$ of unit vectors, which already determine the anisotropic elastic behavior of the tissue. We postulate the flow rule

$$\mathbf{L} = \sum_{\alpha \in \mathcal{A}} \gamma^\alpha \text{dev} (\mathbf{a}_0^\alpha \otimes \mathbf{a}_0^\alpha)$$

(similar to crystal plasticity; Kahn and Huang, 1995), where $\gamma^\alpha \geq 0$, $\alpha = 1, 2$, are consistency parameters with initial conditions $\gamma^\alpha |_{t=0} = 0$. In (16), $\mathcal{A} = \{\alpha \in 1, 2 \mid \hat{\Phi}^\alpha = 0\}$ denotes the active working set. If $\mathcal{A} > \{0\}$ the flow rule determines the way in which plastic deformations evolve; otherwise the deformation is elastic.

In order to describe the evolution of the hardening variable $A$, we postulate the rate equation

$$\dot{A} = \sum_{\alpha \in \mathcal{A}} \gamma^\alpha, \quad A|_{t=0} = 0$$

(similar to the evolution of $A$ in crystal plasticity; compare with Miehe, 1996). The irreversible nature of the isochoric plastic deformation is enforced by the Kuhn-Tucker loading/unloading conditions.

Now we particularize the macro-stress dependent functions as

$$\Phi_{\text{macro}}^\alpha (\text{dev} \Sigma, \mathbf{a}_0^1, \mathbf{a}_0^2) = \ddot{\tau}^\alpha = \text{dev} \Sigma : \mathbf{a}_0^\alpha \otimes \mathbf{a}_0^\alpha,$$

with the new functions $\ddot{\tau}^\alpha$, $\alpha = 1, 2$. This approach is similar to that used in crystal plasticity (see, for example, Lubliner, 1990, and Kahn and Huang, 1995). We omit coupling effects between the different slip systems.

Based on isotropic Taylor hardening (Malvern, 1969), the micro-stress dependent function may be decomposed additively into an initial yield stress $\tau_0$ and a micro-stress $B$. We use the two parameter model

$$\Phi_{\text{micro}} (B) = \tau_0 + B, \quad B = hA,$$

where hardening is described by the linear hardening parameter $h$. Using equations (18) and (19), the yield criteria (15) lead to the specified form $\hat{\Phi}^\alpha = \ddot{\tau}^\alpha - (\tau_0 + B) = 0$, $\alpha = 1, 2$. 

150
Inelastic Stress Response and Plastic Dissipation. Before proceeding to examine the scalar measures \( \tau^\alpha \) of the stress state, we introduce the two symmetric \( n \times n \) matrices \( A^{\alpha\beta} = a^\alpha \cdot a^\beta \) and \( A^{\alpha\beta} = a^\alpha \cdot a^\beta \) via the dot products of the vectors \( a^\alpha \) and \( a^\beta \). Then, we substitute the stress relation (13) into (18) and take advantage of property (11). Using the definitions of the invariants \( \bar{I}_i, \bar{P}_i, \alpha = 1, 2 \), and the properties \( I: a^\alpha \otimes a^\alpha = 1 \) and \( \mathcal{A}^a a^\alpha \otimes a^\alpha \cdot a^\alpha \otimes a^\alpha = A^{\alpha\beta} a^\alpha \), we find the scalar measures

\[
\tau^\alpha = \mu \left( \frac{\tau^\alpha}{I^\alpha} - \frac{1}{3} I_1 \right) + 2 \sum_{\beta \in \mathcal{A}} \psi^\beta \left( A^{\alpha\beta} a^\alpha - \frac{1}{3} \bar{P}_i \right), \quad \alpha = 1, 2. \tag{20}
\]

With these scalar measures and the stress relation (13), flow rule (16), rate equation (17) and specified yield criteria \( \tau^\alpha - (\tau_0 + B) = 0 \), we are able to rewrite the plastic dissipation (3) in the remarkably simple form \( \mathcal{Q}^\alpha = \tau_0 \dot{A} \geq 0 \). We conclude from (17) and conditions \( \dot{\mathcal{Q}}^\alpha \geq 0 \) that the time derivative \( \dot{\mathcal{A}} \geq 0 \) of the hardening parameter is non-negative. Hence, the non-negative plastic dissipation \( \mathcal{Q}^\alpha \) in the proposed model is ensured.

Data Fitting

The aim is now to fit the constitutive model presented above to the experimental data (see Fig. 2) obtained for the different biological soft tissues. In particular, we are interested in an optimal choice of the material parameters (i.e. \( \mu \) and \( k_1, k_2 \) as introduced in (8) and (10), and \( \tau_0, h \) as used in (19)) in order to reproduce the experimental material response by theoretical means.

Consider now the uniaxial extension tests of the strips and compute the axial Cauchy stress, \( \sigma_{\text{exp}} \) say. Knowing that the reference width \( W \), reference thickness \( T \), axial load \( F \) and axial stretch \( \lambda \) are given (experimental) data, we may simply deduce that \( \sigma_{\text{exp}} = \lambda F / (WT) \).

Hence, the axial Cauchy stress determined from the constitutive model to be fitted, \( \sigma_{\text{mod}} \) say, and \( \sigma_{\text{exp}} \) were used to compute ‘best-fit’ values of the material parameters in question. For such nonlinear least square regression the Levenberg-Marquardt method is used to minimize the function \( \chi^2 = \sum (\sigma_{\text{mod}} - \sigma_{\text{exp}})^2 \). For each individual type of tissue we used 15 data points from the axial strip experiment and 15 from the circumferential strip experiment. In fitting the data emphasis was placed on the circumferential direction, which is the main loading direction in balloon angioplasty. Hence, experimental stress-stretch data of axial strips were considered only up to strains of 15% (axial strains larger than 15% are unlikely to occur in vessel dilation). The resulting material parameters are listed in Table 2 and the associated stress-stretch plots illustrated in Figs 2(a)-(c) (the ‘best-fit’ curves of circumferential strips are indicated by dots).

Experimental studies (Castaneda-Zuniga et al., 1980, and Zollikofer et al., 1984) on balloon angioplasty in cadaver arteries suggest that inelastic wall overstretch is governed by histostructural changes in the media. Our experiments showed that the healthy intima behaves elastically up to an ultimate tensile stress at which it ruptures abruptly. The diseased tissues such as the calcified parts (I-c), collagenous cap (I-II), I-fm and M-f behave relatively stiffly compared with non-diseased tissues and showed high ultimate tensile strengths. Consequently, we only modeled the non-diseased media M-nos as an inelastic material according to our experimental data (see Fig. 2(d)). The second loading cycles of the strain level series were used for fitting. The resulting material parameters associated with the inelastic response are \( \tau_0 = 70.0 \, \text{kPa} \) and \( h = 2500.0 \, \text{kPa} \), and the associated stress-stretch plot, Fig. 2(d), is illustrated by thick dots indicating the engineering response of the material.

We are assuming that the individual tissues are incompressible so that the parameter \( \kappa \), as introduced in (5), has no physical relevance. In addition, the present elastic constitutive model was fitted to bi-dimensional experimental data of the selected angioplasty balloon catheter (Cordis Opta Ir). However,
Table 2. Material parameters of different tissues describing the anisotropic response.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adventitia A</th>
<th>Media M-nos non-diseased</th>
<th>Media M-f diseased</th>
<th>Intima I-nos non-diseased</th>
<th>Intima I-fl fibrous</th>
<th>Intima I-fbn fibrous</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu$ [kPa]</td>
<td>1.75</td>
<td>15.0</td>
<td>16.2</td>
<td>31.0</td>
<td>78.9</td>
<td>30.8</td>
</tr>
<tr>
<td>$k_1$ [kPa]</td>
<td>65.6</td>
<td>4.0</td>
<td>98.1</td>
<td>51.0</td>
<td>23.7</td>
<td>45.0</td>
</tr>
<tr>
<td>$k_2$ [-]</td>
<td>61.8</td>
<td>2.3</td>
<td>10.0</td>
<td>1.10</td>
<td>26.3</td>
<td>9.8</td>
</tr>
<tr>
<td>$\tau_0$ [kPa]</td>
<td>-</td>
<td>70.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$h$ [kPa]</td>
<td>2500.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

This approach is purely phenomenological. The data are $\mu = 7.67$ [kPa], $k_1 = 6.01$ [kPa], $k_2 = 12.2$ [-] and $\delta_1 = \delta_2 = 26.7^\circ$.

**MECHANISM OF ANGIOPLASTY**

Because of the complex geometry and material properties of the stenosis, the Finite Element Method (FEM) is the only computational tool suitable for solving the highly nonlinear boundary-value problem of the balloon-stenosis interaction. The FEM is well suited for computing the distribution of stresses (and strains) in the atherosclerotic plaque components, for predicting areas of maximum stresses and for studying and understanding the mechanism of angioplasty. However, the aim of this section is not to present detailed numerical results. This will be done in subsequent papers. The aim is rather to outline briefly the concept of the numerical model and to discuss findings related to the mechanism of angioplasty.

Based on the histomechanical constitutive model described above we generated a three-dimensional FEM mesh of the considered stenosis using 3828 eight-node brick elements. Figure 1(c) gives an example of a typical discretized section corresponding to the hrMRI cross-section (Fig. 1(b)). Grey tones indicate different materials. Appropriate interpolation between 21 discretized sections gives the 3D FEM mesh (see Fig. 5(a)). Each element in space models the corresponding type of tissue (according to the classification scheme M-nos, M-f, I-nos, I-fl, I-fbn) with predominant fiber orientation presented in Table 1 and material parameters as given in Table 2. The calcifications I-c were modeled as stiff (rigid) components and the lipid pool I-lp as an incompressible fluid. The lipid pool is a less stiff component (Loree et al., 1994) which is not able to sustain shear stress (Richardson et al., 1989). Since we are only interested in the isochoric response (we assumed the tissues to be incompressible) the parameter $\kappa$ degenerates to a penalty parameter without physical meaning. Hence, the numerical model is composed of eight clusters of finite elements which are characterized by their corresponding material parameters, as shown in Fig. 4.

Furthermore, the numerical model assumed a long cylindrical balloon (discretized by eight-node brick elements) with pressure loading in the balloon. The contact between balloon surface and stenosis was assumed to be frictionless. Incremental pressure loads were used to control the large deformation of the stenosis and balloon inflation during analysis, performed with the software package ABAQUS, Version 5.8, in which the constitutive developments were implemented.

The nonlinear numerical analysis showed that for this type of stenosis, with the presence of a complete collagenous cap, the disease-free segments of the vessel wall were overstretched, i.e. loaded beyond the elastic limit, while the plaque region was relatively unstretched. This (over)stretch leads to gains of the cross-sectional lumen area (see the load-free configuration in Fig. 5(b)), which turns out to
be one major mechanism of angioplasty for this type of stenosis. This mechanism was also suggested by Hjemdal-Monsen et al. (1990). Several other scientists documented that lumen enlargement by angioplasty were achieved primarily through arterial stretch (see, for example, The et al., 1992, Virmani et al., 1994, Braden et al., 1994, and Baptista et al., 1996). In addition, a recent study of the mechanical behavior of human atherosclerotic plaque components after in vitro angioplasty performed by Tousaint et al. (1998) showed that on lesions with a complete collagenous cap the atherosclerotic plaque
structure did not change after radial compression, while the opposite disease-free side of the wall was stretched in the circumferential direction. Due to the high stiffness of the cap the strain response of the underlying atheroma is small in comparison with that of the disease-free wall. Acute wall stretching due to angioplasty causes late luminal loss, as was shown by, for example, Kakuta et al. (1994) in a rabbit artery model.

Our numerical analysis, which we do not present explicitly here, has further shown that the mechanical properties of the lipid pool cause (circumferential) stress concentrations in the collagenous cap, particularly at the junctions between cap and healthy intima. This finding is supported by the computational structural analysis before in vitro angioplasty performed by Lee et al. (1993). However, in real (clinical) angioplasty, these high stress concentrations would lead additionally to plaque disruption or dissection and to lumen area gain (Block et al., 1981), which is identified as a frequent mechanism of successful dilation (Waller et al., 1992, and Di Mario, 1995). In the numerical analysis we have not considered plaque rupture.

In the late 1990s the majority of coronary angioplasty was performed with stents. Nowadays, a broad variety of different stent designs is available (Popma, 1996). Endovascular stent placement yields larger gain of the lumen area than conventional balloon angioplasty (see the studies by Fischman et al., 1994, Macaya et al., 1996, and Rogers et al., 1999). We performed a finite element analysis for which an angioplasty balloon was used to dilate a stent to the same lumen diameter as before. We discretized a Palmaz-Schatz stent, which consists of a slotted tube (304 stainless steel). Figure 5(c) indicates the gain of lumen area due to stenting.

Despite the advantages, stents provoke greater absolute, but not relatively late loss of the lumen area than angioplasty (Kuntz et al., 1993, and Serruys et al., 1994). Clinicians have to cope with a restenosis rate of about 25-30% (Fischman et al., 1994, and Macaya et al., 1996). This complex biological process is initiated by the mechanical trauma due to acute vessel dilation and the ongoing interaction between stent and vessel wall. Thus, the proposed approach might be helpful in defining optimal procedural strategies in determining optimal stent designs with regard to luminal gain, tissue protection and restenosis prevention.

ACKNOWLEDGEMENTS

The authors are indebted to C. T. Gasser and E. Pemkopf for their contributions to this work and for valuable discussions. We also would like to thank Professor R. Stollberger from the Institute of Magnetic Resonance at the School of Medicine in Graz for his cooperation in developing appropriate MR sequences for high resolution plaque imaging. Thanks also go to P. Regitnig, MD from the Institute of Pathology for his support in harvesting autopsy specimens and preparing and analyzing the histological sections. Financial support for this research was provided by the Austrian Science Foundation under START-Award Y74-TEC. This support is gratefully acknowledged.

REFERENCES

American Heart Association, 1999, 2000 Heart and Stroke Statistical Update, American Heart Association, Dallas, Texas.


Chapter 4, pp. 73–97.