Zuned Hajiali

COMPUTATIONAL MODELING OF STENTED CORONARY ARTERIES

Thesis for the degree of Doctor of Science (Technology) to be presented with due permission for public examination and criticism in the Auditorium 1381 at Lappeenranta University of Technology, Lappeenranta, Finland on the 26th of November, 2014, at noon.

Acta Universitatis Lappeenrantaensis 592
Supervisors

Associate Professor Payman Jalali
LUT Energy
LUT School of Technology
Lappeenranta University of Technology
Finland

Doctor Mahsa Dabaghmeshin
LUT Energy
LUT School of Technology
Lappeenranta University of Technology
Finland

Reviewers

Professor Fumihiko Kajiya
Department of Medical Engineering
Kawasaki University of Medical Welfare
Japan

Professor Dr.-Ing habil. Dieter Liepsch
Laboratory of Fluid Mechanics
Faculty of Engineering (Faculty 05)
Munich University of Applied Sciences
Germany

Opponent

Professor Francesco Migliavacca
Laboratory of Biological Structure Mechanics
Department of Chemistry, Materials and Chemical Engineering
Polytechnic University of Milan
Italy

ISSN-L 1456-4491
ISSN 1456-4491

Lappeenrannan teknillinen yliopisto
Yliopistopaino 2014
Abstract

Zuned Hajiali
Computational modeling of stented coronary arteries

Lappeenranta 2014
98 pages
Acta Universitatis Lappeenrantaensis 592
Diss. Lappeenranta University of Technology

The application of computational fluid dynamics (CFD) and finite element analysis (FEA) has been growing rapidly in the various fields of science and technology. One of the areas of interest is in biomedical engineering. The altered hemodynamics inside the blood vessels plays a key role in the development of the arterial disease called atherosclerosis, which is the major cause of human death worldwide. Atherosclerosis is often treated with the stenting procedure to restore the normal blood flow. A stent is a tubular, flexible structure, usually made of metals, which is driven and expanded in the blocked arteries. Despite the success rate of the stenting procedure, it is often associated with the restenosis (re-narrowing of the artery) process. The presence of non-biological device in the artery causes inflammation or re-growth of atherosclerotic lesions in the treated vessels. Several factors including the design of stents, type of stent expansion, expansion pressure, morphology and composition of vessel wall influence the restenosis process. Therefore, the role of computational studies is crucial in the investigation and optimisation of the factors that influence post-stenting complications.

This thesis focuses on the stent-vessel wall interactions followed by the blood flow in the post-stenting stage of stenosed human coronary artery. Hemodynamic and mechanical stresses were analysed in three separate stent-plaque-artery models. Plaque was modeled as a multi-layer (fibrous cap (FC), necrotic core (NC), and fibrosis (F)) and the arterial wall as a single layer domain. CFD/FEA simulations were performed using commercial software packages in several models mimicking the various stages and morphologies of atherosclerosis. The tissue prolapse (TP) of stented vessel wall, the distribution of von Mises stress (VMS) inside various layers of vessel wall, and the wall shear stress (WSS) along the luminal surface of the deformed vessel wall were measured and evaluated.

The results revealed the role of the stenosis size, thickness of each layer of atherosclerotic wall, thickness of stent strut, pressure applied for stenosis expansion, and the flow condition in the distribution of stresses. The thicknesses of FC, and NC and the total thickness of plaque are critical in controlling the stresses inside the tissue. A small change in morphology of artery wall can significantly affect the distribution of stresses. In particular, FC is the most sensitive layer to TP and stresses, which could determine plaque’s vulnerability to rupture. The WSS is highly influenced by the deflection of artery, which in
turn is dependent on the structural composition of arterial wall layers. Together with the stenosis size, their roles could play a decisive role in controlling the low values of WSS (<0.5 Pa) prone to restenosis. Moreover, the time dependent flow altered the percentage of luminal area with WSS values less than 0.5 Pa at different time instants. The non-Newtonian viscosity model of the blood properties significantly affects the prediction of WSS magnitude. The outcomes of this investigation will help to better understand the roles of the individual layers of atherosclerotic vessels and their risk to provoke restenosis at the post-stenting stage. As a consequence, the implementation of such an approach to assess the post-stented stresses will assist the engineers and clinicians in optimizing the stenting techniques to minimize the occurrence of restenosis.

Keywords: atherosclerosis, stenting, restenosis, computational fluid dynamics, multilayer plaque

UDC 616.13/.14:51.001.57:004.94
Acknowledgements

This study was carried out at the Laboratory of Thermodynamics, LUT Energy, Lappeenranta University of Technology, Finland during 2010-2014. The research conducted in this study was supported and funded by the Finnish Graduate School of Computational Fluid Dynamics and Academy of Finland (Grant No. 123938).

First of all, I express my sincere gratitude to my supervisors Dr Payman Jalali and Dr Mahsa Dabaghmeshin for all their valuable guidance and support provided during this entire period of study. It all began when I was first inducted by Dr Payman Jalali into the area of CFD in biomedical engineering as a Master’s thesis student. I am thankful to him for giving me this opportunity and teaching me all technical skills that made me to step in the world of research. The encouragement and enthusiasm received from him were priceless. I am grateful to Dr Mahsa Dabagh for all her guidance, comments and advices that have helped me to grow. I also thank Dr Tero Tynjälä for all his friendly help and administrative support.

I am thankful to preliminary examiners Professor Fumihiko Kajiya and Professor Dieter Liepsch for their detailed review and comments that helped to make the work of the thesis more valuable. The stent geometry used in one of the chapters was provided by bioMMeda group, Ghent University, Belgium. I would like to thank Professor Patrick Segers and Dr Matthieu De Beule for letting me visit their laboratory and introducing me to the stent geometries. I thank CSC–IT Center for Science, Finland for allowing access to the software that was used in one of the chapters.

I thank my friends Ashvin and Paritosh who have been the best companion throughout the study, fun times and in all other matters. I thank Arjun, and Markku for their ever ready support and upliftments. I also thank Hetal and Bhavna for their homemade delicious foods. I thank my childhood friends Mohsin and Priyanka for their warm and encouraging talks during the study. Special thanks to my dear friend Hemal for motivating me in hard times and believing in my work. I thank all others for their direct/indirect contributions.

Finally, this would not have been possible without constant support of my family. I am forever grateful to my loving parents Hajiali and Zulekha Mansuri for all their sacrifices that were made to raise and educate me. I take this opportunity to devote this to my mother who has always dreamed to achieve higher education. I express my love and gratitude to my siblings (Shahid, Asif, Farzana, and Safiya) who have always stood by my side. My fiancée Tamanna deserves special thanks for her love, understanding, and patience. Above all, I thank almighty Allah for many showers of blessings on my life so far and may it continue in future, Ameen...

Zuned Hajiali
November 2014, Lappeenranta
To my family
# Contents

Abstract ......................................................... 3
Acknowledgments ........................................ 5
Contents ......................................................... 9
List of publications .......................................... 11
Nomenclature .................................................. 13

1 Introduction .................................................. 17
  1.1 Atherosclerosis and its classifications ................ 17
  1.2 Treatment of atherosclerosis ............................ 20
    1.2.1 Coronary stent .................................... 20
    1.2.2 Post stenting complications ....................... 21
  1.3 Clinical importance of the study ....................... 21
  1.4 Literature review and motivation ....................... 22
  1.5 Author’s contribution ................................ 24
  1.6 Outline of the thesis .................................. 25

2 Idealized 2D axisymmetric model of stent-plaque-artery 27
  2.1 Geometric model ....................................... 27
    2.1.1 Stent strut profile ................................ 29
  2.2 Material properties ................................... 30
  2.3 Artery expansion schemes ................................ 30
    2.3.1 Scheme 1: Under pressurization to achieve the diameter of a
            healthy artery .................................... 30
    2.3.2 Scheme 2: Under a fixed pressurization ............ 31
  2.4 Computational method ................................... 32
    2.4.1 Mesh grid ......................................... 34
  2.5 Results and discussion ................................ 34
    2.5.1 Scheme 1 .......................................... 37
      2.5.1.1 Wall shear stress distribution ............... 38
      2.5.1.2 von Mises stress distribution .............. 40
    2.5.2 Scheme 2 .......................................... 41
      2.5.2.1 Wall shear stress distribution ............... 42
      2.5.2.2 von Mises stress distribution .............. 42
  2.6 Summary ................................................ 43

3 Idealized 3D model of stent-plaque-artery ................. 45
  3.1 Geometric model ....................................... 45
    3.1.1 Stent cell geometry .............................. 45
List of publications

The presented work in this monograph contains unpublished material. During the course of study, the following articles were published in which the candidate is the main author or co-author.

**Published Journal Articles:**


**Submitted Journal Articles:**


III. Hajiali Z., Dabagh, M., Jalali, P (2014). Influence of plaque morphology and tissue prolapse on wall shear stress distribution in the lumen of 3D stented coronary artery. *(To be submitted)*

**Conference Articles:**


**Author’s contribution**

The numerical simulations and post-processing of the results in Publication I, Publication II, Publication III, Publication IV and Publication V were carried out by the candidate. The CAD part of the stent geometry in Publication II was conducted by M.Sc. Nic Debusschere. The manuscripts of Publication I, Publication II, Publication III were written by the candidate with Dr Mahsa Dabagh and Dr Payman Jalali. The manuscripts of Publication IV and Publication V were written by the candidate. The image processing and CAD operations in Publication V and Publication VI were performed by the candidate with Dr Paritosh Vasava.
# Nomenclature

## Latin alphabet

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>$a_i$</td>
<td>constants of the polynomial fitting velocity waveform</td>
<td>–</td>
</tr>
<tr>
<td>$a_{ii}$</td>
<td>material constants</td>
<td>–</td>
</tr>
<tr>
<td>$A$</td>
<td>surface area of face</td>
<td>mm</td>
</tr>
<tr>
<td>$b_i$</td>
<td>constants of the polynomial fitting velocity waveform</td>
<td>–</td>
</tr>
<tr>
<td>$c_i$</td>
<td>constants of the polynomial fitting velocity waveform</td>
<td>–</td>
</tr>
<tr>
<td>$d_i$</td>
<td>constants of the polynomial fitting velocity waveform</td>
<td>–</td>
</tr>
<tr>
<td>$D$</td>
<td>diameter of the flow domain</td>
<td>mm</td>
</tr>
<tr>
<td>$E$</td>
<td>combined (plaque and AW) Young’s modulus</td>
<td>kPa</td>
</tr>
<tr>
<td>$E_{NC}$</td>
<td>Young’s modulus of the NC</td>
<td>kPa</td>
</tr>
<tr>
<td>$G_{AW}$</td>
<td>shear modulus of the AW</td>
<td>kPa</td>
</tr>
<tr>
<td>$G_F$</td>
<td>shear modulus of the F</td>
<td>kPa</td>
</tr>
<tr>
<td>$G_{FC}$</td>
<td>shear modulus of the FC</td>
<td>kPa</td>
</tr>
<tr>
<td>$G_{NC}$</td>
<td>shear modulus of the NC</td>
<td>kPa</td>
</tr>
<tr>
<td>$h$</td>
<td>total thickness of the vessel wall</td>
<td>mm</td>
</tr>
<tr>
<td>$I$</td>
<td>invariants</td>
<td>–</td>
</tr>
<tr>
<td>$K_{AW}$</td>
<td>bulk modulus of the AW</td>
<td>Pa</td>
</tr>
<tr>
<td>$l_d$</td>
<td>expanded diameter of the lumen</td>
<td>mm</td>
</tr>
<tr>
<td>$n$</td>
<td>total number of the elements</td>
<td>–</td>
</tr>
<tr>
<td>$p$</td>
<td>pressure</td>
<td>Pa</td>
</tr>
<tr>
<td>$p_i - p_0$</td>
<td>transmural pressure</td>
<td>Pa</td>
</tr>
<tr>
<td>$r$</td>
<td>radial coordinate</td>
<td>mm</td>
</tr>
<tr>
<td>$r_{in}$</td>
<td>radius at the inlet</td>
<td>mm</td>
</tr>
<tr>
<td>$R$</td>
<td>reference radius of the vessel wall</td>
<td>mm</td>
</tr>
<tr>
<td>$s_{df}$</td>
<td>expanded diameter of the stent</td>
<td>mm</td>
</tr>
<tr>
<td>$s_{di}$</td>
<td>unexpanded diameter of the stent</td>
<td>mm</td>
</tr>
<tr>
<td>$s_{li}$</td>
<td>axial length of the stent</td>
<td>mm</td>
</tr>
<tr>
<td>$t$</td>
<td>time</td>
<td>s</td>
</tr>
<tr>
<td>$t_1$</td>
<td>thickness of the rectangular strut</td>
<td>mm</td>
</tr>
<tr>
<td>$t_2$</td>
<td>thickness of the circular strut</td>
<td>mm</td>
</tr>
<tr>
<td>$u$</td>
<td>velocity vector</td>
<td>m/s</td>
</tr>
<tr>
<td>$u_{max}$</td>
<td>maximum velocity at the inlet</td>
<td>m/s</td>
</tr>
<tr>
<td>$w_1$</td>
<td>width of the rectangular strut</td>
<td>mm</td>
</tr>
<tr>
<td>$w_2$</td>
<td>width of the circular strut</td>
<td>mm</td>
</tr>
<tr>
<td>$W$</td>
<td>strain energy density function</td>
<td>–</td>
</tr>
<tr>
<td>$WSS_{avg}$</td>
<td>area-weighted average WSS</td>
<td>Pa</td>
</tr>
<tr>
<td>$z$</td>
<td>coordinate axis</td>
<td>mm</td>
</tr>
</tbody>
</table>

## Greek alphabet

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\delta V$</td>
<td>volume of the mesh element</td>
<td>mm$^3$</td>
</tr>
<tr>
<td>$\delta_l$</td>
<td>thickness of FC layer</td>
<td>mm</td>
</tr>
</tbody>
</table>
\[ \delta_2 \text{ thickness of NC layer mm} \]
\[ \delta_3 \text{ thickness of F layer mm} \]
\[ \delta_4 \text{ thickness of AW layer mm} \]
\[ \eta \text{ dynamic viscosity of the blood } \text{Pa⋅s} \]
\[ \nu \text{ Poisson’s ratio } \]
\[ \rho \text{ density of the blood kg·m}^{-3} \]
\[ \rho_{\text{plaque}} \text{ density of the plaque kg·m}^{-3} \]
\[ \rho_{\text{AW}} \text{ density of the AW kg·m}^{-3} \]
\[ \rho_{\text{NC}} \text{ density of the NC kg·m}^{-3} \]
\[ \sigma \text{ VMS in a element Pa} \]
\[ \tau_i \text{ face-averaged WSS Pa} \]

**Dimensionless numbers**

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re</td>
<td>Reynolds number</td>
</tr>
</tbody>
</table>

**Subscripts**

- \( i \) general index

**Abbreviations**

- 2D two dimensional
- 3D three dimensional
- AHA American Health Association
- AR aspect ratios
- AW arterial wall
- BMS bare metal stent
- CAD coronary artery disease
- CFD computational fluid dynamics
- CT computed tomography
- CVD cardiovascular disease
- DES drug eluting stent
- F fibrosis
- FC fibrous cap
- FCT fibrous cap thickness
- FEA finite element analysis
- FEM finite element method
- IVUS intravascular ultrasound
- LD lumen diameter
- LDL low density lipoprotein
- MRI magnetic resonance imaging
- NC necrotic core
- OCT optical coherence tomography
- OSI oscillatory shear index
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCSA</td>
<td>plaque cross-sectional area</td>
</tr>
<tr>
<td>PTCA</td>
<td>percutaneous coronary transluminal angioplasty</td>
</tr>
<tr>
<td>TP</td>
<td>tissue prolapse</td>
</tr>
<tr>
<td>VMS</td>
<td>von Mises stress</td>
</tr>
<tr>
<td>WHO</td>
<td>world health organization</td>
</tr>
<tr>
<td>WSS</td>
<td>wall shear stress</td>
</tr>
<tr>
<td>WSSG</td>
<td>wall shear stress gradient</td>
</tr>
</tbody>
</table>
1 Introduction

Cardiovascular diseases (CVDs) are the leading cause of deaths worldwide. According to the World Health Organization (WHO), approximately 17.3 million people died from CVDs in 2008, representing 30% of all deaths globally. By 2030, it is estimated that more than 23.3 million people will die annually from CVDs. A recent statistical report from the American Heart Association (AHA) shows that the rates of the death attributable to CVD have declined, but the burden of the disease still remains high (Go et al., 2013). The most important risk factors of CVDs are unhealthy diet and obesity, physical inactivity, harmful use of tobacco and alcohol, high blood pressure, diabetes, and raised lipids. The burden of CVD can be kept in control by routine checks of the factors influencing the risk level. In acute conditions, surgical interventions are required to treat CVDs, for example by coronary artery bypass, balloon angioplasty, valve repair and replacement, heart transplantation, and artificial heart operations.

Atherosclerosis is the most common cause of CVDs. On the other hand, coronary artery disease (CAD) is the most common type of CVDs causing approximately 13% of deaths every year. Coronary stenting is a widely practiced medical treatment for the stenosed and narrowed arteries. Stents are tubular scaffolds that keep the blocked artery open and restore the normal blood flow. However, the risk of restenosis occurrence (re-narrowing of the artery) is high. As a conclusion, the treatment of CAD motivates clinicians and engineers to investigate the optimized techniques for the best possible outcomes.

1.1 Atherosclerosis and its classifications

Atherosclerosis is caused by the gradual build-up of lipids, fatty materials, and cholesterol in the inner layers of the arterial wall, known as plaque. Over time, the plaque grows hardening the walls and narrowing down the lumen of artery. The reduced amount of flow through the coronary artery limits the supply of fresh oxygenated blood to the heart resulting in heart strokes.

Arterial walls, with the exception of small blood vessels (arterioles, capillaries, and veins), consist of three layers: tunica intima, tunica media, and tunica adventitia as shown in Fig. 1.1(a). The tunica intima is the innermost layer of the artery lined by a thin layer of endothelium. It is made up of endothelial cells, which are in direct contact with the luminal blood flow. It plays a vital role in preventing the adhesion of blood cells to the arterial wall and the occurrence of thrombosis. The intermediate layer, tunica media, is made up of smooth muscle cells and elastic tissues. It contracts to regulate the pressure of blood flow and provides elasticity to the wall. The outermost layer of the arterial wall is tunica adventitia, which is covering the artery. It is composed of connective tissues as well as collagen and elastic fibers. These fibers allow the artery to stretch and prevent the over expansion due to the pressure exerted on the wall.
The mechanism of atherosclerosis is not yet fully understood. However, it has been widely accepted that atherosclerosis develops when the endothelium is damaged. The low density lipoprotein (LDL) present in blood enters the intima through the damaged endothelium. The LDL is the transport medium of cholesterol and necessary for the metabolism of smooth muscle cells in the tunica media layer. Over a period of time, the LDL along with the accumulated cholesterol and macrophage white blood cells undergoes complex biological reactions, and plaque is formed in the arterial wall. Initially, the arterial wall tries to compensate the presence of plaque by growing outwards without narrowing the lumen (Glagov et al., 1987). Nevertheless, in advanced atherosclerosis stages, narrowing of lumen is found and it is referred to as stenosis.

The pathology of atherosclerotic lesions is defined based on the autopsy observations,
1.1 Atherosclerosis and its classifications

which are based on static images (Garcia-Garcia et al., 2009). The types of atherosclerotic lesions are comprehensively classified in a report from AHA (Stary et al., 1995). Figure 1.1(b) shows the sequential phases in the progression of atherosclerosis. The initial (Type I) lesion has isolated macrophage foam cells. In the subsequent lesion types, more changes are observed in the location of arteries at the adaptive intimal thickening (adaptive thickenings are present at constant locations in everyone from birth, they do not obstruct the lumen and represent the adaptations to mechanical forces). In the following stage (Type II), the lesion grows by the accumulation of intracellular lipid and forms a layer of macrophage foam cells. Type I and Type II lesions are early and non-atherosclerotic lesions. Type III (preatheroma) lesion is the intermediate stage between Type II and Type IV containing small scattered pools of extracellular lipids. This type of plaque has a pathological intimal thickening, but it does not disturb the luminal blood flow until the lesion occupies up to 40% of the potential lumen area. The extracellular lipid found in Type III is the immediate precursor of a larger, confluent, and more disruptive core of the extracellular lipid that characterizes Type IV lesions.

Type IV lesions are known as atheroma where a characteristic necrotic core (NC) appears to develop from small isolated pools of extracellular lipids. In atheroma lesion, a distinctive layer of tissue begins to cover completely the NC. In other words, it is the distance between the lumen and NC layer defined as the fibrous cap (FC) (shown in Fig. 1.2). In the atheroma stage, the lesion may have a thick or thin FC overlying the NC. A FC having a thickness of <65 µm is defined as thin fibrous cap atheroma, and NC is usually large in such plaques (Virmani et al., 2000). Type IV lesions are found at same locations as the adaptive thickenings of the eccentric type. Thus, atheroma is at least initially an eccentric lesion.

Figure 1.2: Cross-section of a typical eccentric (atheroma) plaque.

Type V lesions are defined as lesions in which new fibrous connective tissue has been formed. This type of morphology is also referred to as fibroatheroma in which the NC and other parts of the lesions are fibrotic or calcified. Type V lesions may also have
a minimal amount of NC and sometimes the lipid core is absent. Type V lesion may be clinically silent or overt depending upon the degree of stenosis (lumen blockage). The last stage in the classification is Type VI referred to as a complicated lesion. In Type VI, the disruptions of lesion surface, hematoma, and thrombotic deposits have developed. Clinically, the lesions of Type VI have a higher rate of stenosis and are often very obstructive to the blood flow.

1.2 Treatment of atherosclerosis

Coronary arteries play an important role in the circulation of blood. Just like any other muscle, the proper functioning of the heart muscle requires regular supply of fresh blood delivered by coronary arteries. Any coronary artery disorder can have serious implications by reducing the blood supply to the heart muscle, which may lead to heart attacks. Because of their physical location, the walls of coronaries are always under high blood pressure flowing from the aorta. A continuous exposure to hypertension in relatively narrow diameters can damage the endothelium making the coronary artery one of the highly vulnerable arteries to atherosclerosis.

Few decades ago, a minimally invasive technique called balloon angioplasty (percutaneous coronary intervention) was performed to treat CAD. This procedure involves the opening of balloon mounted over a catheter, which is positioned to the blocked site of the artery. Although this treatment had high clinical success rates, many patients were still found to redevelop the blockage. This re-narrowing due to elastic recoil of the artery called ‘restenosis’ is the principal limitation of balloon angioplasty. Restenosis following balloon angioplasty is observed in 30%–40% of treated patients (Fischman et al., 1994) and is attributed to three main responses: acute elastic recoil, negative wall modeling (reduction in the lumen area without a change in wall mass), and arterial wall thickening into the lumen (due to an increase in the number of cells within the arterial wall) (Murphy and Boyle, 2010). To overcome this problem, stents were introduced which could act like a scaffold and prevent the re-narrowing of the artery. Stents are tubular mesh like endovascular devices usually made of metals. Commercially, several types of stents are available. They are used depending on the features of the blockage. An interventional cardiologist will use angiography technique to assess the location and size of the stenosis. This information is used to decide whether a stent is to be placed to treat the stenosis, and of what kind and size.

1.2.1 Coronary stent

Coronary stents are either balloon-expandable or self-expanding. The procedure of the balloon-expandable scheme is schematically presented in Fig. 1.3. In this procedure, the stent is initially crimped and loaded upon a balloon catheter. Subsequently, when the balloon is inflated by applying pressure, the plaque compresses against the arterial wall, and the stent is opened up to the desired lumen through plastic deformation (Schatz et al., 1991). As the stent scaffolds the artery, the balloon is deflated and the catheter is removed.
1.3 Clinical importance of the study

In the self-expanding type, the stent is retracted inside a delivery catheter. The gradual removal of catheter sheath allows the stent to expand by itself and keeps the artery open (Stoeckel et al., 2004).

1.2.2 Post stenting complications

In the short term, stenting prevents the elastic recoil of the artery and overcomes the limitation of balloon angioplasty. However, in the long term, the intima cells begin to proliferate due to the injury caused to the arterial wall. Excessive neointimal hyperplasia results in in-stent restenosis, which is a drawback to the stenting procedure. Although the use of bare metal stents has reduced the incidences of restenosis, the problem of in-stent restenosis still occurs in 20%–30% (Fischman et al., 1994; Rajagopal and Rockson, 2003) of the stented vessels. In recent years, the introduction of drug eluting stents (DES) has declined the use of the former bare metal stents (BMS). Drug-eluting stents are coated with medicines to stop excessive tissue growth around the stent. Clinical trials have shown a reduction (∼10%) in the in-stent restenosis when a drug eluting stent is used (Moses et al., 2003; Morice et al., 2006). However, drug-eluting in-stent restenoses still occur in 3%–20% of the patients, depending on the patient and lesion characteristics and the drug-eluting stent type (Dangas et al., 2010). Furthermore, the delivery of the anti-proliferative drug is also significantly influenced by the stent design. Despite the advances in the treatment procedure, the problem of restenosis retains eventually.

1.3 Clinical importance of the study

The process of restenosis is combination of complex biological and physical interactions that occurs in response to the stent induced arterial wall damage. The excessive reaction to vascular injury causes restenosis in the form of neointimal hyperplasia (Kim and Dean,
The rupture of endothelium and the migration of smooth cells due to stretching are linked to the neointimal hyperplasia (Hoffmann and Mintz, 2000; Grewe et al., 2000). Coronary stent placement is traditionally used to treat restenosis following percutaneous transluminal coronary angioplasty (PTCA), the ideal revascularization strategy in patients who develop in-stent restenosis (Kim and Dean, 2011). In the case of either using the BMS or DES, the occurrences of restenosis does not completely vanish.

Clinical studies have well shown the morphological characteristics of the plaque (Naghavi et al., 2003; Virmani et al., 2006; Fleg et al., 2012). These studies have identified the plaque composition and morphology as key predictors of vulnerability and likelihood of rupture (Shah, 1998). Such vulnerable plaque can be detected by various techniques including intravascular ultrasound (IVUS), optical coherence tomography (OCT), computed tomography (CT) and magnetic resonance imaging (MRI) (Fayad et al., 2002; Jang et al., 2002; Carlier and Tanaka, 2006; Briley-Saeb and et al., 2007). However, identifying lesions vulnerable to plaque rupture and characterizing them as such remains a major issue (Ohayon et al., 2014). Advanced biomechanical studies have largely overcome the limitation of clinical studies to define the morphological factors of vulnerable plaque and their stability (Cardoso and Weinbaum, 2014; Ohayon et al., 2014). The key predictor, stress, has been widely considered as a parameter that estimates the risk of biological structure by combining its geometric, material and load characteristics (Dolla et al., 2012).

On the other hand, the regeneration of endothelial reduces neointimal hyperplasia which in fact is influenced by the blood flow (Asahara et al., 1995; Steinmetz et al., 2010). The remodeling of atherosclerotic plaques is also greatly associated with local wall shear stress distribution (Glagov et al., 1987; Samady et al., 2011; Wentzel et al., 2012). Moreover, Tahir et al. (2011) suggested that the growth of restenotic lesion is strongly dependent on stent struts configuration. As WSS is proportional to the gradient of blood flow velocity over the endothelium, it is necessary to derive precise knowledge of hemodynamics (Rikhtegar et al., 2013). Clinically, it is extremely hard to achieve the required level of precision using phase-contrast magnetic resonance imaging, Doppler ultrasound, or other flow measurement techniques (Doriot et al., 2000; Fearon et al., 2003; Kaufmann and Camici, 2005; Hollnagel et al., 2009). Currently, there exist no clinical imaging modality that can give the precise definition of deployed stent with features sizes of orders of tens of microns (Wentzel et al., 2001; Samady et al., 2011; Chiastra et al., 2012). This opens the way for state-of-the-art computational methods to provide a missing link between clinical experiments and their optimized outcomes in healthcare practices.

1.4 Literature review and motivation

Stenting is a mechanical procedure, and hence its outcome depends on the pressure applied to the balloon; the geometries of the artery, plaque, stent, and balloon; and the mechanical properties of each vessel component (Colombo et al., 2002). Until now, stenting is the only widely accepted technique to treat stenosed arteries; however, the in-stent
restenosis is a recurrent incidence found to occur in 20%–30% of the stented vessels after the treatment (Fischman et al., 1994; Rajagopal and Rockson, 2003). Although new generation drug eluting stents have helped to reduce the rate of in-stent restenosis up to a certain extent, they have not yet been completely eliminated. Patients in such conditions will have to undergo more medical interventions. In the past years, numerous studies have been carried out with the aim to investigate the cause of restenosis and to optimize its occurrence. Factors influencing the progress of restenosis include the degree of damaged endothelium and the depth of the injury (Schwartz et al., 1992; Kornowski et al., 1998; Farb et al., 2002; König et al., 2002), the type of the stent expansion (balloon-expanding or self-expanding, (Grenacher et al., 2006)), the design of the stent (Rogers and Edelman, 1995; Kastrati et al., 2001; Ürgen Pache et al., 2003), the plaque shape and composition (Yutani et al., 1999), and the local hemodynamics (Wentzel et al., 2001; Sanmartín et al., 2006).

Computational methods have emerged as essential and widely adopted tools for the assessment and optimization in the field of biomedical engineering. They have not only helped to compensate the limitations of clinical and experimental research, but also to acquire high accuracy in the outcomes. Advances in numerical simulations have certainly provided versatility to perform various analyzes. This development has inspired researchers to be in hunt and contribute enormously in this field. In recent times, numerical modeling techniques like finite element analysis (FEA) and computational fluid dynamics (CFD) have been widely proven to investigate the biomechanical interaction between the stent-arterial wall and related arterial hemodynamics. The FEA provides an excellent means of investigating mechanical implications associated with the stenting procedure. CFD packages enable us to study the features of blood flow patterns in stented arteries with greater flexibility and easiness. These methodologies have been utilized as a pre-clinical testing tool for improving and developing novel stent designs for better clinical performances (Prendergast et al., 2003; Lally et al., 2005; LaDisa Jr et al., 2005; Sakurai et al., 2005; Balossino et al., 2008; Zahedmanesh and Lally, 2009).

It is speculated that the stresses induced during stenting procedure provoke the process of restenosis. Migliavacca et al. (2004) performed a computational study on stent-vessel wall interactions and compared the types of stent expansion schemes (self-expanding and balloon-expandable). Their comparison showed the difference in the level of stresses induced with both schemes. Lally et al. (2005) and Zahedmanesh and Lally (2009) carried out a FEA in stent-plaque-artery models. The effect of vessel wall composition and morphology were ignored in these studies. They reported the influence of the stent design parameter and related vessel stresses. These results supported the finding of the previous experimental and clinical studies to consider the stent geometry as a key determinant of restenosis rates (Schwartz et al., 1992; Carter et al., 1994; Farb et al., 1999; Kastrati et al., 2001; Ürgen Pache et al., 2003).

On the other hand, many studies relate the stent design to local hemodynamics in stented arteries (LaDisa Jr et al., 2005; Balossino et al., 2008; Jiménez and Davies, 2009; Pant
et al., 2010; Morlacchi et al., 2011). Parts of the stent strut protruding into the lumen promote blood flow separations and recirculation zones, which eventually affect the distribution of wall shear stress (WSS) patterns. Regions with low values of WSS are believed to be at the risk of developing plaque. A correlation exists between WSS values less than 0.5 Pa and sites of intimal thickenings, which appears to be a leading factor in the development of atherosclerosis (Ku, 1997; Henry, 2000). Clinically, the importance of the WSS’s role in plaque localization and plaque growth has been demonstrated in several studies (Wentzel et al., 2001, 2003; Sanmartín et al., 2006).

Moreover, the deflection of the tissue between the strut of the stents (called ‘tissue prolapse’ (TP)) has been used as a measure of the potential of stent to cause restenosis Pendergast et al. (2003). Prolapse refers to lumen loss due to the vessel wall protrusion. Pant et al. (2011) reported that the areas of recirculation zones are affected significantly in the cases with and without TP. The TP partly depends on the stent strut gaps and the morphology and composition of plaque/vessel wall (Farb et al., 2003). The influence of plaque composition on vessel wall stresses has been demonstrated by Pericevic et al. (2009). They showed that for a given inflation pressure, higher stresses are predicted in cellular plaque than in calcified plaque. Higher stresses in softer plaque can cause injury to the tissue and eventually lead to restenosis. This finding supports the clinical research reported by Sahara et al. (2004).

It has also been shown that in addition to vessel wall composition, the vessel wall morphology plays a vital role in determining the risk of plaque rupture. Kastrati et al. (1999); Imoto et al. (2005); Gu et al. (2010) analyzed in their studies the effect of plaque shape and size of stress distributions. Farb et al. (2002); Ohayon et al. (2008); Akyildiz et al. (2011) have demonstrated in their research the role of NC and FC as decisive predictors of the plaque vulnerability to rupture.

Altogether, the plaque composition and morphology of the vessel wall play a key role in local hemodynamics in stented arteries, besides the stent geometry. The aim of the present work was to study the interactions of stent-plaque-artery and blood flow with the help of CFD and FEA techniques. The results of the study will provide a deeper insight in the incidents of the post-stenting phase and thus will contribute to a better understanding and optimization of the restenosis.

1.5 Author’s contribution

Most of the stent-plaque-artery modeling have concentrated on stent design and arterial wall composition. Studies concentrating on stent expansion with different plaque constituents have not included flow dynamics. On the other hand, studies related to stent design with hemodynamics have ignored the presence of plaque and its constituents. All things considered, the effect of plaque structure and its morphology on stresses acting on and within the vessel wall on the local hemodynamics, and on the TP have not been
studied in post-stenting. The main objective of the thesis was to investigate this issue on stented coronary arteries. A multi-layered model of diseased arterial wall is applied to investigate how the morphology and the properties of plaque layers influence the in-stent restenosis in the post-stenting stage.

Firstly, a 2D axisymmetric model is implemented to evaluate the post-stenting stresses within the diseased wall of coronary artery. The stenosed coronary wall is composed of three-layer plaque and one layer vessel wall. The layers have different morphology and properties. This is an idealized model which predicts the wall stresses within different layers of vessel wall in stented coronaries. The findings of the study are in good agreement with previously reported data on in-stent restenosis. The novelty of the model is that it reveals the role of plaque severity and morphology on the in-stent restenosis. Secondly, FEA is performed in a repeated unit of a full 3D coronary stent. The multi-layered plaque and one layered arterial wall are considered as distinct layers with different mechanical properties and morphology. The evaluation of tissue prolapses demonstrates the significance of plaque morphology to predict the vulnerability of restenosis. Lastly, a 3D solid-fluid model is proposed to investigate the influence of realistic tissue prolapse on the luminal surface. The impact of plaque severity on these parameters are also studied. The model also explain the role of plaque morphology in elevating the stress magnitude. Moreover, the non-Newtonian viscosity models are applied to simulate the influence of blood property on the wall stresses in post-stenting phase.

In summary, the major contribution of the author in the current thesis was to investigate the parameter affecting the restenosis rate in the post-stenting stage. The author has focused on the wall layers of diseased coronary arteries to determine their influence on the local stresses which play a critical role in the process of restenosis. The knowledge provided computationally in this thesis will assist engineers and clinicians to improve the stenting techniques.

1.6 Outline of the thesis

The content of this thesis is divided into six chapters. The first chapter begins with the introduction of the arterial disease, atherosclerosis, and its brief histological classification followed by the treatment procedure and related complications. Then, a subsection discuss the clinical importance of the this study. It is continued by the previous studies in this topic and motivation to carry out this computational work. This chapter is concluded by the author’s contribution in the current scientific research followed by the organization of the thesis.

The following chapters (2, 3, and 4) discuss three separate models, which are the main core of the thesis, including a complete description of their modeling and simulation processes. Chapter 2 is based on the article from Hajiali et al. (2014) (Publication I). Chapter 2 begins with introducing the idealized 2D axisymmetric model of a stent-plaque-artery geometry with different stent strut profiles and material properties of atherosclerotic ves-
sel wall layers. It is followed by the description of two different expansion schemes for stenosed arteries. Then, the results of von Mises stress (VMS) and WSS over the vessel wall are presented. A brief summary of the model will come in the end of the chapter.

Chapter 3 is based on the unpublished article (Publication II). It begins with introducing the idealized 3D model of the stent-plaque-artery. It is followed by a detailed description of the modeling of atherosclerotic plaque layers. In the next sections, the material models, computational method, and validation of the model are discussed. This chapter presents the results of TP and VMS within the vessel layers in detail. This chapter ends with a brief summary of the presented model.

Chapter 4 is based on the unpublished article (Publication III). It starts with introducing the 3D expanded stent with a brief description of the vessel model in the subsection. It is followed by the section where material properties and the computational set up for solid (artery) and fluid (blood) domains are discussed. In the next section, a mesh sensitivity analysis is presented for solid and fluid domains. This chapter is concluded with the results from solid and fluid simulations and a brief summary of the model.

Chapter 5 summarizes the findings of the thesis. The significance and the importance of the research carried out by the author of the thesis are concluded in this chapter.

Chapter 6 lists the suggestions and possible extensions of work in the future.
2 Idealized 2D axisymmetric model of stent-plaque-artery

This chapter describes the implementation of a simple computational model for studying the effect of plaque severity and plaque structure on wall surface and internal stresses in stented coronary artery. Simulations are carried out in a small segment of locally straight human coronary artery around a single stent strut. Several axisymmetric models of stent-plaque-artery are generated representing the stented artery at various stages of atherosclerotic lesions. The results from the pressures of two different expansion schemes, stent strut structure, and static and transient flow conditions are discussed.

2.1 Geometric model

Human coronary artery is modeled as a cylindrical tube with a symmetrically located stenosis. The internal diameter of a healthy artery is 3.0 mm, the thickness of arterial wall (AW) is 0.4 mm (Mejia et al., 2009), and the length of the chosen segment is 1.25 mm (David Chua et al., 2004). Figure 2.1(a) show a schematic view of an expanded artery with a ring like stent, various layers of plaque, and AW. This model represents the idealized and simplified version of a stented artery. The model was reduced to 2D geometry because of the symmetrical shape. An axisymmetric plane AX shown in Fig. 2.1(a) cuts the artery and results as shown in Fig. 2.1(b).
2 Idealized 2D axisymmetric model of stent-plaque-artery

Figure 2.1: (a) Schematic representation of expanded stent strut with three distinct layers of plaque (fibrous cap (FC), necrotic core (NC), fibrosis (F)) and arterial wall (AW) (b) 2D axisymmetric plane representing the model geometry.

Table 2.1: Area fractions of NC to the total plaque area, lumen diameter (LD), and FCT (thin, medium, and thick) corresponding to their degrees of stenosis.

<table>
<thead>
<tr>
<th>Degree of stenosis (%)</th>
<th>Necrotic core (%)</th>
<th>Before expansion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>LD (mm)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>thin</td>
</tr>
<tr>
<td>20</td>
<td>12</td>
<td>2.68</td>
</tr>
<tr>
<td>40</td>
<td>22</td>
<td>2.32</td>
</tr>
<tr>
<td>60</td>
<td>32</td>
<td>1.90</td>
</tr>
<tr>
<td>80</td>
<td>42</td>
<td>1.34</td>
</tr>
</tbody>
</table>

The plaque is modeled as a multi-layered medium with three distinct layers: FC, soft NC, and fibrosis (F). Four different stenosis sizes representing 20%, 40%, 60%, and 80% blockages have the plaque thicknesses of 0.16 mm, 0.34 mm, 0.55 mm, and 0.83 mm, respectively. The increment in plaque size is followed by an increase in the NC (García-García et al., 2007). Virmani et al. (2006) showed the area fraction of NC in different
2.1 Geometric model

stages of atherosclerotic plaque in coronary arteries. Those values were associated with
the growing stenosis sizes in this study. Table 2.1 presents the area fraction of the NC sizes
for 20%, 40%, 60%, and 80% respectively. The fibrous cap thickness (FCT) is varied with
three different sizes: thin, medium, and thick. Their values (presented in Table 2.1) were
decided by the thicknesses with the aspect ratios of layers FC:F thin (0.5:1.5), medium
(1:1), and thick (1.5:0.5). The layer F is defined as the thickness that lies between NC and
AW.

2.1.1 Stent strut profile

The stent is assumed to be a ring-like structure placed in the cylindrical unit of stenosed
artery (Jiménez and Davies, 2009). The stent struts are assumed to repeat periodically,
and only one periodic unit is presented in the model (Jiménez and Davies, 2009). The
presence of multiple struts would not make significant changes in the WSS distribution
demonstrated in Section 2.5). This assumption will also save computational time. Stent
strut has a rectangular cross-section with the thickness of $t_1 = 0.1$ mm (Balossino et al.,
2008) and width of $w_1 = 0.15$ mm (Mejia et al., 2009). It is well accepted that the stent
strut configuration influences the local flow dynamics in the vicinity of stent strut (Jiménez
and Davies, 2009; Mejia et al., 2009; Pant et al., 2010). Two more thicknesses of strut ($t_1
= 0.5, 0.025$) with rectangular cross-sections are varied to study their effects such as the
aspect ratio (AR), the ratio of width to thickness, $w_1 : t_1$ is equal to 1.5:1, 3:1, and 6:1 as
shown in Fig. 2.2. A circular cross-section of the stent strut with the width of $w_2 = 0.2$
mm and thickness $t_2 = 0.1$ mm is also taken into account.

![Figure 2.2: Cross-sectional stent strut profiles with different aspect ratios (AR); width $w_1$
to thickness $t_1$ ($w_1 : t_1$) and width $w_2$ to thickness $t_2$ ($w_2 : t_2$).](image-url)

$AR=1.5:1$

$AR=3:1$

$AR=6:1$

$AR=2:1$

$w_2$

$w_1$

$w_2$

$t_1$

$t_2$
2.2 Material properties

Elastic material deforms under applied stress and quickly returns to its original shape once the stress is eliminated. A viscous material requires time to return to its initial state after stress is removed. Viscoelasticity is the property of the material that exhibits both viscous and elastic characteristics when undergoing deformation. Human arteries affected by atherosclerosis are characterized by altered viscoelastic properties (Balocco et al., 2010). Thus, the behaviour of arterial walls has been described as viscoelastic response (Holzapfel et al., 2002; Balocco et al., 2010).

The AW is modeled as a viscoelastic layer described by the generalized Maxwell model found in Comsol Multiphysics 3.5a. The shear modulus for AW is taken as $G_{AW} = 5.6$ kPa based on the Young’s modulus of coronary (phantom) walls described by Baldewsing et al. (2004). Since the deformation of arteries is volume-preserving within the physiological range of deformation, the arteries, like other biological tissue, may be regarded as incompressible materials (Holzapfel et al., 2002; Lally et al., 2005). Thus, AW layers are in the present study assumed to be of incompressible material (i.e., Poisson’s ratio = 0.49). Due to the material’s incompressibility, the bulk modulus of the wall, $K_{AW}$ tends towards infinity, taken as $10^{20}$ Pa. Three distinct layers of plaque in the model are also assumed to be incompressible and represented by the generalized Maxwell model. The shear moduli of FC and F layers are taken as $G_{FC}, G_F = 200$ kPa (stiffer material), while the soft NC has the shear modulus of $G_{NC} = 3.3$ kPa from an in vitro vessel phantom study (Le Floc’h et al., 2010). The density of AW and plaque layers is considered as $\rho_{plaque}, \rho_{AW} = 1000$ kg·m$^{-3}$ (Kim et al., 2010). The deformation of AW and plaque are taken into account in static condition in the model. Thus, the time parameter is ignored in the generalized Maxwell model, and the material response would be normal elastic behavior.

2.3 Artery expansion schemes

Angioplasty and stenting are mechanical procedures, and hence, their outcome depends on the pressure applied to the balloon, the geometry (artery, plaque, stent, and balloon), and the mechanical properties of each vessel component (Pericevic et al., 2009). In practice, clinicians apply a broad range of pressure (10 atm–17 atm) for stent expansion (Kastrati et al., 2001). The selection of expansion pressure is generally based on clinical experience, lesion type, and observed vessel dilation under fluoroscopy (Pericevic et al., 2009).

In this model study, two different expansion schemes are defined. In the first one, all the stenosed arteries are expanded to the lumen diameter of a healthy artery. In the second scheme, a fixed value of pressure is applied for the expansion of all degrees of stenosis.

2.3.1 Scheme 1: Under pressurization to achieve the diameter of a healthy artery

Initially, the stenosed arteries are expanded under various pressures to acquire the lumen diameter of a healthy coronary artery. During the expansion, the presence of stent and balloon is disregarded and the pressure is directly applied to the inner surface of arteries.
2.3 Artery expansion schemes

Under a small pressure of 100 mmHg, the 20% stenosed artery reaches a diameter greater than 3 mm. This violates the assumption of 3 mm as a lumen diameter of healthy coronary artery. Moreover, lumen area may remain virtually unchanged (due to compensatory positive remodeling) until a blockage occupies up to 40% of the potential area (Stary et al., 1995). Thus, any further discussion of artery with the 20% stenosis is discarded, and its initial lumen diameter (2.68 mm) is considered as the lumen diameter of a healthy coronary. Table 2.2 shows the pressure values applied for 40%, 60%, and 80% stenoses to achieve a lumen diameter of 2.68 mm.

In the following step, the stent strut is located in the place as shown in Fig. 2.1(b). The stent strut is fixed, and the plaque and AW are constrained in axial directions while allowed to deform in the radial direction. This condition prevents the tangential deformation of the stenosed artery (Gu et al., 2010) with no slip allowed between the strut and plaque face. The insertion of the stent naturally boosts internal stresses and external compression of the adjacent tissue. Due to the elastic nature of the arteries, the expanded tissue recoils creating a prolapse in the void spaces of stent struts. In this context, various factors are involved including the geometry and mechanical properties of stent and vessel wall, material properties of vessel wall, and blood pressure. In this model study, an external pressure is created over the outer surface of the artery due to the opening of the stent. The internal lumen pressure is decreased to the mean blood pressure of 100 mmHg. The external pressure is expressed relative to the internal luminal pressure of 100 mmHg so that the net pressure applied to the outer surface of the artery remains 15 mmHg. This value has been applied in all the cases to eliminate the effect of variations from the results. The plaque and AW are allowed to deform under this value of external pressure, noting that the stent strut is kept fixed.

Table 2.2: Pressure and FCT for 40%, 60%, and 80% stenoses (FCT is varied from thin, medium, and thick) when all arteries are opened to a lumen diameter of 2.68 mm.

<table>
<thead>
<tr>
<th>Degree of stenosis (%)</th>
<th>Displaced to healthy lumen diameter of 2.68 mm</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pressure (mmHg)</td>
<td>FCT (mm)</td>
<td>pressure (mmHg)</td>
<td>FCT (mm)</td>
</tr>
<tr>
<td>40</td>
<td>134</td>
<td>0.058</td>
<td>140</td>
<td>0.115</td>
</tr>
<tr>
<td>60</td>
<td>450</td>
<td>0.063</td>
<td>510</td>
<td>0.126</td>
</tr>
<tr>
<td>80</td>
<td>1255</td>
<td>0.027</td>
<td>1620</td>
<td>0.069</td>
</tr>
</tbody>
</table>

2.3.2 Scheme 2: Under a fixed pressurization

In this scheme, the stent strut is initially not placed and the stenosed arteries are expanded by applying a uniform pressure of 100 mmHg. During this phase, the diameter of the artery increased from 3.0 mm to 3.20 mm, 3.10 mm, and 3.04 mm for a stenosis of 40%,
60%, and 80%, respectively. The corresponding diameter of the plaque rose from 2.32 mm, 1.90 mm, and 1.34 mm to 2.58 mm, 2.06 mm, and 1.42 mm, respectively. Table 2.3 shows the lumen diameter (LD) and fibrous cap thickness (FCT) under the pressurization of 100 mmHg. Then, similar to the first scheme, the stent strut is located under the internal luminal pressure of 100 mmHg (mean blood pressure). The external pressure is adjusted with respect to the internal lumen pressure in such a way that the net pressure remains 15 mmHg. Then, static deformation of plaque and AW takes place under this pressure value.

<table>
<thead>
<tr>
<th>Degree of stenosis (%)</th>
<th>Displaced under fixed pressure of 100 mmHg LD (mm)</th>
<th>FCT (mm)</th>
<th>LD (mm)</th>
<th>FCT (mm)</th>
<th>LD (mm)</th>
<th>FCT (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>2.59</td>
<td>0.058</td>
<td>2.58</td>
<td>0.120</td>
<td>2.57</td>
<td>0.181</td>
</tr>
<tr>
<td>60</td>
<td>2.08</td>
<td>0.086</td>
<td>2.06</td>
<td>0.179</td>
<td>2.05</td>
<td>0.264</td>
</tr>
<tr>
<td>80</td>
<td>1.45</td>
<td>0.113</td>
<td>1.43</td>
<td>0.229</td>
<td>1.41</td>
<td>0.348</td>
</tr>
</tbody>
</table>

Table 2.3: LD and FCT for 40%, 60%, and 80% stenoses (FCT is varied from thin, medium, and thick) when all arteries are opened under a fixed pressure of 100 mmHg.

2.4 Computational method

The working fluid (blood) is modeled as a Newtonian incompressible fluid with a density of \( \rho = 1000 \text{ kg m}^{-3} \) and a dynamic viscosity of 0.0035 Pa \( \cdot \) s (Jimenez and Davies, 2009; Mejia et al., 2009). The Reynolds number for all stenosis sizes is below 300 given by Equation (2.1)

\[
Re = \frac{\rho u D}{\eta}
\]  

where \( u \) is the velocity of fluid, \( D \) is the diameter of flow domain, and \( \eta \) is the dynamic viscosity of the fluid. Because of the low value for Reynolds number, turbulence effect is not expected and a laminar flow model is applied to the simulation. Parabolic velocity profiles are applied at the inlet, for steady and transient flow conditions, as

\[
u_z = u_{\text{max}} \left( \frac{1 - r^2}{r_{\text{in}}^2} \right)
\]  

where \( r \) is the radial coordinate, \( r_{\text{in}} \) is the radius at the inlet, and \( u_{\text{max}} \) is the maximum velocity for the steady conditions as 0.35 m/s (Brandts et al., 2010). For transient flow simulations (\( u_{\text{max}} \) in Equation (2.2) is substituted by \( u_{\text{max}}(t) \) of Equation (2.3), a time dependent inlet velocity for one cardiac cycle is directly adopted from Jung et al. (2006). A set of polynomials representing the waveform is given by Equation (2.3) and the constants are given in Table 2.4.
2.4 Computational method

\[ u_{max}(t) = \begin{cases} (a_1 t + a_2), & 0 \leq t(s) \leq 0.054 \\ (b_1 t^4 + b_2 t^3 + b_3 t^2 + b_4 t + b_5), & 0.054 < t(s) \leq 0.341 \\ (c_1 t + c_2), & 0.341 < t(s) \leq 0.373 \\ (d_1 t^2 + d_2 t + d_3), & 0.373 < t(s) \leq 0.735 \end{cases} \] (2.3)

Table 2.4: Constant values of parameters in the polynomials representing the inlet velocity.

<table>
<thead>
<tr>
<th>parameter</th>
<th>constant value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( a_1 )</td>
<td>-0.143</td>
</tr>
<tr>
<td>( a_2 )</td>
<td>0.132</td>
</tr>
<tr>
<td>( b_1 )</td>
<td>-457.35</td>
</tr>
<tr>
<td>( b_2 )</td>
<td>397.71</td>
</tr>
<tr>
<td>( b_3 )</td>
<td>128.92</td>
</tr>
<tr>
<td>( b_4 )</td>
<td>17.69</td>
</tr>
<tr>
<td>( b_5 )</td>
<td>-0.505</td>
</tr>
<tr>
<td>( c_1 )</td>
<td>4.555</td>
</tr>
<tr>
<td>( c_2 )</td>
<td>-1.425</td>
</tr>
<tr>
<td>( d_1 )</td>
<td>0.690</td>
</tr>
<tr>
<td>( d_2 )</td>
<td>-1.148</td>
</tr>
<tr>
<td>( d_3 )</td>
<td>0.603</td>
</tr>
</tbody>
</table>

Transient simulations are performed for three cardiac cycles to guarantee a stable solution, where one cardiac cycle is 0.735 s. The results discussed in the following sections belong to the last cycle. At the outlet, a pressure value of 100 mmHg is specified. A no slip condition is imposed on the wall, which makes all velocity components equal to zero. The convergence criterion for continuity and momentum residuals was kept at \( 10^{-6} \). The deformed structure only served as a boundary where the flow simulations were carried out numerically in Comsol Multiphysics 3.5a by solving Navier-Stokes equations using finite element method, described by

\[
\rho \frac{\partial u}{\partial t} + \rho (u \cdot \nabla u) = \nabla \cdot \left[ -pI + \left( \nabla u + (\nabla u)^T \right) \right] \tag{2.4}
\]

and

\[
\nabla \cdot u = 0, \tag{2.5}
\]

where \( u \) is the velocity vector, \( \rho \) is the density, \( \eta \) is the dynamic viscosity of the blood, and \( p \) is the pressure. For steady simulations, the term \( \rho \partial u/\partial t \) in Equation (2.4) is equal to zero.
2.4.1 Mesh grid

The computational domain is discretized with the help of the default meshing tool available in Comsol Multiphysics 3.5a. A mesh sensitivity analysis was performed to assess the results independence from the grid. Five different meshes were generated with the number of nodes increasing from 1500 to 5400 in the whole domain. In the vicinity of strut and the walls of plaque and artery (regions of interest), sufficiently fine mesh was prescribed. The results of the WSS distribution and von Mises stress (VMS) over various meshes were compared. The patterns of the WSS distribution from the flow simulations did not show no significant differences for all the meshes, and the average magnitude of WSS varied by 2% among each mesh. The relative differences in the area weighted VMS for the combined solid layers (FC, NC, F, and AW) were less than 1.5%. These variations can be considered small enough in any numerical calculations and were ignored. Thus, the mesh with the finest mesh size was selected for all simulations that contained triangular elements. As the maximum value of VMS in the FC layer was found sensitive to mesh size changes, the mesh was additionally refined near the strut corners where the concentration of stress is high.

2.5 Results and discussion

Initially, it was tested whether the model with only a single strut would represent the actual WSS distribution. Thus, an extended model (Fig. 2.3(a)) with the total axial length of 7.5 mm in the presence of six stent struts was simulated. Figure 2.3(b) shows the WSS distribution after the insertion of stent with multiple struts. A periodic distribution of WSS is observed for 40%, 60%, and 80% stenosed coronary arteries. However, the WSS vary by 0.3 Pa from inlet to the first strut and 0.1 Pa from last strut to the exit of single and multiple strut models. In order to provide more evidence of periodicity, the velocity profiles are demonstrated at different locations along the multiple struts in Fig. 2.3(c). These indicates that the assumption of the single stent is justified and will also save the computational time for the rest of the model cases.

The effect of stent strut profiles on flow dynamics has been well reported by clinical and computational studies (Ürger Pache et al., 2003; Balossino et al., 2008; Zahedmanesh and Lally, 2009; Jiménez and Davies, 2009; Mejia et al., 2009). The thickness of rectangular strut was varied by defining AR as explained in Subsection 2.3.1. Figure 2.4 demonstrates the distribution of WSS on the stented arterial wall surface with various strut thicknesses. Figure 2.4(a), (b), and (c) demonstrate that the thinner struts increase the WSS magnitude. The extent of recirculation zones in the vicinity of the strut corners are affected by the strut thickness. Thus, the WSS magnitude reduces with the decreasing strut thickness for all the percentages of stenosis. These results are in agreement with those presented by Jiménez and Davies (2009).
Figure 2.3: (a) Schematic geometry with multiple struts, and (b) WSS distribution along the luminal side of the plaque surface. (c) Velocity profiles at the center of every two struts and on the middle of struts. The fibrous cap has medium thickness.
Figure 2.4: WSS distribution at the plaque surface with different thicknesses ($t_1 = 0.1$ mm, $0.05$ mm, $0.025$ mm) of strut for a) 40%, b) 60%, and c) 80% stenosed arteries.
2.5 Results and discussion

Figure 2.5 illustrates the effect of cross-sectional strut profiles on the distribution of WSS. For appropriate comparison, the thickness ($t_1$, $t_2 = 0.1$ mm) and width ($w_1$, $w_2 = 0.2$ mm) of circular and rectangular strut profiles respectively were assigned equal. The data presented in Figure 2.5 belongs to the 60% stenosis having the medium thickness of FC. The horizontal line $z = 0.525$ mm to $z = 0.725$ mm represents the location (width) of the stent strut. The comparison shows that the circular strut yields higher values of WSS magnitude than the rectangular strut throughout the luminal surface. In the vicinity of strut, the circular strut results a minimal region of flow re-circulation. In the downstream, the rectangular strut creates a significantly larger flow re-circulation zone. For a given aspect ratio of the strut, a streamlined design of the stent strut can avoid low values of WSS and reduce flow re-circulation zones. This is consistent with the earlier findings reported by Jiménez and Davies (2009). However, their work did not consider arterial wall deformation.

Prior to the pressurization of the arteries, the flow simulations were performed for arteries with 40%, 60%, and 80% stenoses, which resulted in the values of WSS of 2.1 Pa, 2.6 Pa, and 3.6 Pa, respectively. The main results and discussions are broken down into sub-sections as discussed in Section 2.3. For each section, two sets of results will be presented: one set reporting the WSS magnitude and the distribution with reference to the luminal side of the plaque surface, and the second set presenting the VMS for the AW and the plaque layers.

2.5.1 Scheme 1

The 40%, 60%, and 80% stenosed coronaries were pressurized to gain a fixed lumen diameter of 2.68 mm, corresponding to the lumen of a 20% stenosed artery that is considered
equivalent to a healthy lumen.

2.5.1.1 Wall shear stress distribution

Figure 2.6 shows the magnitude and distribution of WSS along the z (axial) direction of the stented coronaries in different stenoses. Figure 2.6 belongs to the stenosis with the medium thickness of FC. The WSSs are demonstrated at the surface of the plaque in the stented coronary arteries. The horizontal line from \( z = 0.55 \text{ mm} \) to \( z = 0.7 \text{ mm} \) represents the location of strut over which the WSS is not shown.

![Graph showing WSS distribution along the z (axial) direction for 40%, 60%, and 80% stenosed arteries. FC has the medium thickness.](image)

Figure 2.6 reveals that the WSS drops dramatically from its maximum at the inlet (the center of two consecutive struts) to values below 0.5 Pa near the upstream sides of the strut. The WSS value decreases more on the downstream side near the strut before it rises to a plateau at 1.25 Pa. It should be noted that slight discrepancy occurs between the WSS values for 40%, 60%, and 80% stenosis cases. This reveals that the stented coronaries lead to similar shear stresses on the wall surface when different percentages of stenosis are expanded to a fixed lumen diameter for a given stent. However, the variable stent strut profiles alter the WSS magnitude as presented in Fig. 2.5.

The time dependent flow simulation was performed to compare the shear stress between steady and transient flows. Figure 2.7 represents the histograms of the luminal surface area percentage with a WSS magnitude <0.5 Pa, in five time instants of the cardiac cycle. The threshold of 0.5 Pa indicates a critical WSS value to consider a region prone to restenosis (Balossino et al., 2008; Kim et al., 2010).
2.5 Results and discussion

Figure 2.7: a) Coronary inlet velocity pulse representing a cardiac cycle at five selected time instants. Histograms of the percentage of luminal wall with WSS area <0.5 Pa with thin, medium, and thick FC for stenoses sizes of b) 40%, c) 60%, and d) 80%.

Figure 2.7(b-d) demonstrate the area percentages with WSS values below 0.5 Pa for the 40%, 60%, and 80% plaque with thin, medium, and thick sizes of the FC. Results show that the percentage area of WSS<0.5 Pa decreases at systole time points, in 40%, 60%, and 80% stenosed arteries. The area below the critical value of WSS (0.5 Pa), unlike in the steady flow, is dependent on the instants taken in the cardiac cycle, which are shown in Fig. 2.7(a). The WSS magnitude elevates with increasing velocity values, and simultaneously, the luminal surface area under the critical WSS value declines. It is maximized when the blood velocity is at its minimum. These results are in good agreement with those presented by Balossino et al. (2008). Furthermore, the results also demonstrate that the WSS<0.5 Pa is higher in the 40% stenosis than the other stenosis percentages, particularly in the thinner FC. This may be explained by comparing the data of FCT given in Table 2.1 and Table 2.2 for different degrees of stenoses before and after stenting. Although the 80% stenosis has the thinnest FC, the whole plaque remains thicker in this case. In addition to FCT, the thickness of the remaining NC and F layers is critical in
determining the low values of WSS.

2.5.1.2 von Mises stress distribution

The maximum VMS values for plaque (FC, NC, and F) layers and AW of 40%, 60%, and 80% stenosed coronaries are represented in Fig. 2.8. Figure 2.8 reveals that the VMS is significantly elevated within the FC and F layers by the stent insertion, while it is less affected within the NC and AW layers. Figure 2.8 also takes into account the effect of FCT on VMS. Among all the layers, the maximum values of VMS are observed in the FC layers. Higher stress is predicted in the layers of thinner FC, while the thicker FC appears to play a protective role by reducing the levels of stresses within the next plaque layers and arterial tissue for a given inflation pressure (Pericevic et al., 2009).

The effect of stenosis severity on VMS through different layers can also be observed from the graphs demonstrated in Fig. 2.8. The maximum value of VMS is observed in the FC of the 80% stenosed coronary that is significantly larger than in the 40% and 60% stenoses. This suggests that higher degrees of stenosis that require a higher pressure to gain healthy lumen are also at a higher risk of vascular injury. The maximum value of VMS in the FC layer is one order higher than that of the other layers. The result also reveals that in all layers excluding the FC, the maximum VMS is higher in the 40% stenosis than those in the 60% and 80% stenoses. This can be associated with the effect of different thicknesses of plaque layers in the 40% stenosis that does not allow the stress to be uniformly distributed.

Within the 80% stenosis, the higher stresses in FC layers are observed among the thinner FC, with the only exception in the 40% stenosis where higher stress is observed in the medium FC than in the thin FC. It should also be noted that the high stresses and maximum value of VMS are observed in the FC layer in the vicinity of its contacts to the strut corners. The presented value in Fig. 2.8(a) is averaged within the neighbourhood around the two strut corners of the radius of 20, where high stress concentration occurs. Typically, the plaques with a thin FC (65 µm) have been well defined as plaques vulnerable to rupture (Ohayon et al., 2008). The thinnest FC applied in this study was 0.027 mm (27 µm) that belonged to the 80% stenosed artery. However, the maximum value of VMS in this case is lower than the reported critical stress value (300 kPa) for rupture. Nevertheless, the present results show the importance of stenosis severity and its component combination in causing the alteration of stress levels that play a vital role in determining the risk of plaque rupture.
2.5 Results and discussion

![Graphs showing VMS values for different layers: (a) Fibrous cap (FC), (b) Necrotic core (NC), (c) Fibrosis (F), and (d) Arterial wall (AW).]

Figure 2.8: Maximum VMS values against the varying FCT (thin, medium, and thick) for 40%, 60%, and 80% stenosed coronaries opened to a fixed lumen diameter on different layers: (a) Fibrous cap (FC), (b) Necrotic core (NC), (c) Fibrosis (F), and (d) Arterial wall (AW).

2.5.2 Scheme 2

In this scheme, the 40%, 60%, and 80% stenosed coronaries were all pressurized under the fixed pressure value of 100 mmHg. Therefore, the lumen diameters for all stenoses are different and are presented in Table 2.1.
2.5.2.1 Wall shear stress distribution

Figure 2.9 shows the WSS distribution along the z (axial) direction of the stented coronaries with the 40%, 60%, and 80% stenoses. In the presented results, the FC has the medium thickness. The horizontal line from \( z = 0.55 \text{ mm} \) to \( z = 0.7 \text{ mm} \) represents the location of the stent strut over which the WSS is not shown. Similar to Scheme 1, the WSS drops from its maximum at the inlet (center of two consecutive struts) to the low value of 0.5 Pa near the upstream side of the strut. On the downstream side near the strut, WSS value falls lower before it rises to a plateau of 1.25 Pa. However, Figure 2.9 reveals the effect of the stenosis severity on the WSS distribution if a uniform pressure is applied to all the sizes of stenosed arteries. The WSS magnitude differs considerably between the sides of the strut in the 80% stenosis creating an asymmetric hemodynamic condition around the strut. It is due to the large recirculation zones created behind the strut caused by the relatively smaller deformation of the arterial tissue.

![Figure 2.9: WSS distribution along the z (axial) direction at the luminal surface of 40%, 60%, and 80% stenosed arteries when opened under a fixed pressure of 100 mmHg.](image)

2.5.2.2 von Mises stress distribution

Figure 2.10 demonstrates the maximum VMS values in several layers of the 40%, 60%, and 80% stenosed coronaries taking into account the effect of FCT. Similar to Scheme 1, the results demonstrate that among all the layers, FC experiences the highest stresses. The AW experiences the least stresses compared to the plaque layers. In general, a plaque with the thinner FC has a higher value of maximum VMS than the thicker FC in all the layers. However, in the 40% stenosis, the thin FC has a lower value of the maximum VMS than the medium FC. In contrast to Scheme 1, the maximum VMS in the FC layer is higher in mild stenoses than in severe stenoses. This can be related to the thicknesses of
2.6 Summary

An idealized axisymmetric model was employed to assess the hemodynamic and mechanical stresses in the post-stenting stage of various stenosed coronary arteries. The level of FC (Table 2.2 and Table 2.3), which sufficiently becomes thin to elevate the level of stress.
stent-induced injury to the vessel depends upon the stent design, the opening pressure, the mechanical properties of plaque and AW, and the geometrical features of the artery. In this model, the influence of plaque severity and morphology on the stresses acting on or within the vessel wall is investigated.

The computational model of stenosed coronary arteries consists of a single layer of AW and multi-layer (FC, NC, F) plaque that represent the various stages of atherosclerosis by the percentage of stenosis. Simulations were performed locally around a single stent strut. The simulations were carried out in two steps: In the first step, stenosed arteries were expanded by applying a uniform pressure on the luminal side of the plaque surface. This was accomplished by defining two different expansion schemes. In Scheme 1, all the stenosed arteries were expanded to a healthy lumen diameter of coronary artery by using various pressures. In Scheme 2, a fixed pressure of 100 mm Hg was applied to expand all stenosed arteries. Then, under a fixed external pressure, the expanded arteries were allowed to deform around the strut in static condition. Blood flow was simulated with deformed structure of plaque and AW in static as well as in transient condition.

The results reveal that FCT has a significant influence on the stresses within the next plaque layers and AW. The thick FC layer appeared to play a protective role by reducing the level of stresses within NC, F, and AW, regardless of the stenosis size. However, VMS in the FC layers is highly dependent on the severity of the stenosis. Higher VMS was observed in the 80% stenosis when the lumen was expanded to its healthy diameter. This suggests that the higher pressures applied to the 80% plaque induce a higher risk of vascular injury. The thinnest FC in this study was 27 µm that belongs to the 80% stenosed artery with the thin FC. The WSS magnitude was significantly affected by the opening pressures in the post-stenting stage. Various stenoses sizes when expanded to a fixed lumen diameter resulted in a similar magnitude and distribution of WSS regardless of the stenosis size, whereas the WSS magnitude rises remarkably with the severity of stenosis when a fixed pressure value is applied to expand different stenosis sizes. Transient flow simulations revealed that the WSS distribution varies significantly through different time instants of a cardiac cycle. The finding of this study also confirms the influence of strut thickness and cross-sectional strut profiles on the rate of the risk of restenosis.

This study is limited to the simplified and axisymmetric assumptions of the plaque and artery. The pressures applied for the stenosis expansion do not represent the real values of clinical practices. The balloon expansion of stent was also not considered, and the initial stresses induced due to stent expansion have been ignored. However, it simply describes the role of plaque structure, severity of stenosis, influence of strut profile, and the flow conditions on the risk of restenosis and the level of VMS generated in the post-stenting stage. Nevertheless, this type of simulation model provides quick and useful information to improvements associated with stent design under various cases of plaque possibly found in patients.
3 Idealized 3D model of stent-plaque-artery

This chapter presents the FEA of a stent-plaque-artery model in a repeated unit of 3D full stent. In Chapter 2, the effect of tissue deflection on WSS has been comprehensively discussed. However, the domain in that model is short and limited around only one strut. The model in this chapter represents the repeated unit of a fully opened 3D coronary stent. For example, Prendergast et al. (2003) and Capelli et al. (2009) have studied the repeated units of an expanded stent. However, in their studies, the presence of plaque has been ignored. The stresses provoking neointimal hyperplasia and restenosis are suggested to be in those layers where damage is caused to the smooth muscle cells (Prendergast et al., 2003). During the process of intimal thickening, the smooth cells migrate from media to intima where the growth of atherosclerotic plaque occurs (Yutani et al., 1999). The aim in this work was to study the effect of plaque structure and its geometric variations on wall deformation and stresses induced inside vascular tissue after the stenting procedure. These characteristics are vital because they influence the local hemodynamics and progression of in-stent restenosis (Wentzel et al., 2012).

The chapter begins with the description of the stent cell model extracted from a fully expanded 3D stent. This includes the modeling of atherosclerotic plaque layers and their geometric properties. It is followed by a brief description of the mechanical properties of plaque and AW. Then, the applied boundary conditions and a mesh sensitivity analysis in the idealized 3D model are discussed. Before the Results and discussion section, the current model is verified with the existing model in the literature. The Results and discussions section comprises detailed discussions of tissue prolapse (TP) and distribution of VMS through several layers of plaque and AW. This chapter concludes with the summary of the idealized model of stent-plaque-artery in the repeated unit of a 3D stent.

3.1 Geometric model

3.1.1 Stent cell geometry

A typical coronary stent with the initial diameter $s_{di} = 1$ mm and the axial length $s_{li} = 10$ mm was chosen as shown in Fig. 3.1(a). The thickness, width, and dimensions of the rounded cross-section of the stent strut are also mentioned in Fig. 3.1. The geometry of stent was constructed with the help of an open source software ‘pyFormex’. The expansion of the stent was performed in the FEA program ‘Abaqus’. The coronary stent was uniformly expanded in the radial direction with no dogboning effects to reach a final diameter $s_{df} = 2.8$ mm (Fig. 3.1(b)). The final diameter of the expanded stent was in respect to the lumen diameter (3 mm) of a healthy coronary artery (Balossino et al., 2008; Capelli et al., 2009; Gu et al., 2010). This configuration of a fully expanded stent was provided by bioMMeda research group, Ghent University, Belgium.
Figure 3.1: (a) Initial (unexpanded) state (b) Final (expanded) state of a coronary stent presenting axial length, radius, stent strut thickness, and dimensions of the strut cross-section.
3.1 Geometric model

For constructing the stent cell model, the geometry of expanded stent was imported to DesignModeler of ANSYS Workbench 14.5. A cylinder representing the expanded lumen diameter of $d = 3\, \text{mm}$ was integrated with the geometry of expanded stent. The Boolean subtraction of the stent left the imprint of stent struts on the cylinder surface as shown in Fig. 3.2. The surface area between the stent strut is subjected to tissue deformation while the edges act as a scaffold by the stent struts. From the Fig. 3.2(a), it is clearly visible that the stent has repeated units in circumferential and axial directions. One such unit (highlighted in Fig. 3.2(a)) was extracted in the form of surface (Fig. 3.2(b)) representing the luminal side of vessel wall expanded to a lumen diameter of healthy coronary artery. This surface (stent cell geometry) was used as a base for reconstructing the atherosclerotic tissue layer over it. In the design program ANSYS Gambit 2.4.6, the stent cell geometry was extruded in the outward direction to create four volume sub-domains representing FC, NC, F, and AW, as shown in Fig. 3.2(c-d).

![Figure 3.2](image)

Figure 3.2: (a) The expanded coronary stent volume with the imprints of stent struts, (b) a single unit of stent cell (vessel tissue) surface in between the stent struts, (c) extruded cell surface in the outward direction to create plaque (FC, NC, F) layers, and (d) extruded outer plaque layer to create the AW layer. Thicknesses of all the layers are shown in the inset picture.
3 Idealized 3D model of stent-plaque-artery

3.1.2 Atherosclerotic plaque model

As discussed earlier in Section 1.1, the property of atherosclerotic plaque varies depending on the level of its progression. Lesions of Type I-II are initial stages where adaptive intimal thickening or positive remodeling (plaque growth in the outward direction) occurs. Type III (preatheroma) lesions are the intermediate plaques that have intimal thickening that narrows the luminal area. The plaques of Type IV lesions (atheroma) have well defined NC with thin or thick layer of FC. Type V lesions (fibroatheroma) consist of NC and the other part of lesions are fibrotic or calcified. Type VI is the final lesion with disruptions of the surface and thrombotic development.

Plaques are more often lying eccentrically in the stenosed coronary arteries. Two such eccentric plaques having initial degrees of stenoses of 51% (Plaque1) and 36% (Plaque2) were chosen. These plaques can be categorized as type fibroatheroma each having plaque burden greater than 40% (García-García et al., 2009; de Graaf et al., 2013). The percentage plaque burden was calculated as plaque cross-sectional area plus media cross-sectional area divided by the external elastic membrane (plaque+media+lumen area) multiplied by 100 (Fig. 3.3).

![Diagram showing cross-sectional area of lumen, plaque and media.](image)

Initial lumen diameter of the arteries with Plaque1 is 2.1 mm and with Plaque2 2.4 mm. After acquiring the lumen diameter of healthy coronaries (3 mm), the mean thicknesses of Plaque1 and Plaque2 at the location of stent cell model are 0.54 mm and 0.4 mm, respectively. García-García et al. (2007) categorized the relation of the plaque size to the proportion of NC into small, medium, and large based on the plaque cross-sectional area (PCSA) in three major coronary arteries. Their data has been related to Plaque1 (medium PCSA) with relative NC of 10% and 14% and Plaque2 (small PCSA) with relative NC of 8% and 11%. Finet et al. (2004) organized a range of size different values of FCs obtained from typical in-vivo intravascular ultrasound images of three fibro-atheromatous plaques. Their five values of FCs starting from 0.032 mm to 0.230 mm were directly adapted to represent varying FCs in Plaque1 and Plaque2. It has been reported that the NC underlying thin FCs is found usually large and vice versa (Virmani et al., 2006). Therefore, three thinner FC values are assigned to Plaque1 as it has a larger NC in proportion to Plaque2.
which is assigned with three thicker values of FC presented in Table 3.1 and Table 3.2. Altogether, 12 model cases representing different structural compositions of plaque layers were created.

Table 3.1: The thicknesses of plaque layers when the total thickness of Plaque1 is 0.54 mm. Six cases are generated with different NC and FC layers.

<table>
<thead>
<tr>
<th>Thickness of necrotic core, NC, $\delta_2$, (mm)</th>
<th>Thickness of fibrous cap, FC, $\delta_1$, (mm)</th>
<th>Case</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.096</td>
<td>0.032</td>
<td>1</td>
</tr>
<tr>
<td>0.134</td>
<td>0.070</td>
<td>2</td>
</tr>
<tr>
<td>0.134</td>
<td>0.118</td>
<td>3</td>
</tr>
<tr>
<td>0.096</td>
<td>0.032</td>
<td>4</td>
</tr>
<tr>
<td>0.134</td>
<td>0.070</td>
<td>5</td>
</tr>
<tr>
<td>0.134</td>
<td>0.118</td>
<td>6</td>
</tr>
</tbody>
</table>

Table 3.2: The thicknesses of plaque layers when the total thickness of Plaque2 is 0.40 mm. Six cases are generated with different NC and FC layers.

<table>
<thead>
<tr>
<th>Thickness of necrotic core, NC, $\delta_2$, (mm)</th>
<th>Thickness of fibrous cap, FC, $\delta_1$, (mm)</th>
<th>Case</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.056</td>
<td>0.118</td>
<td>7</td>
</tr>
<tr>
<td>0.080</td>
<td>0.205</td>
<td>8</td>
</tr>
<tr>
<td>0.080</td>
<td>0.230</td>
<td>9</td>
</tr>
<tr>
<td>0.056</td>
<td>0.118</td>
<td>10</td>
</tr>
<tr>
<td>0.080</td>
<td>0.205</td>
<td>11</td>
</tr>
<tr>
<td>0.080</td>
<td>0.230</td>
<td>12</td>
</tr>
</tbody>
</table>

3.2 Material properties

Plaques of fibroatheroma type have the growth of new fibrous connective tissue. In this type of lesions, the NC and other parts of the lesion are calcified. The NC tissue is assumed to be incompressible material with the density $\delta_{NC} = 1000$ kg·m$^{-3}$. Young’s modulus of NC is assigned as $E_{NC} = 50$ kPa, adapted from Baldewsing et al. (2004). $E_{NC} = 50$ kPa is defined as the mean value of 1, 0.5, 17.4, and 202 kPa (taken from Cheng et al., 1993; Lee et al., 1996; Veress et al., 2000; De Korte et al., 1999) that acts as the intermediate stiffness of NC. A very soft NC tissue ($E_{NC} = 1$ kPa) may not represent the actual mechanical stiffness of NC in the plaque of the fibroatheroma type.

The AW tissue, FC, and F layers are assumed to be incompressible materials, which are modeled using a 5-parameter third order Mooney-Rivlin hyperelastic constitutive equation. This has been widely used to characterize the non-linear stress-strain relationship of the elastic arterial tissue (Prendergast et al., 2003; Lally et al., 2005). The strain energy density function, $W = W(I_1, I_2, I_3)$ in terms of the strain invariants, given by Prendergast et al. (2003) for an isotropic hyperelastic material, is:

$$W = a_{10}(I_1 - 3) + a_{01}(I_2 - 3) + a_{20}(I_1 - 3)^2 + a_{11}(I_1 - 3)(I_2 - 3) + a_{30}(I_1 - 3)^3$$  (3.1)

where $I_1$, $I_2$, $I_3$ are invariants and $a_{10}$, $a_{01}$, $a_{20}$, $a_{11}$, $a_{30}$ are material constant parameters presented in Table 3.3.
Table 3.3: Hyperelastic constants used to describe the non-linear elastic behaviour of AW, F, and FC layers

<table>
<thead>
<tr>
<th></th>
<th>AW tissue (kPa)</th>
<th>Plaque (FC,F) tissue (kPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( a_{10} )</td>
<td>18.90</td>
<td>-495.96</td>
</tr>
<tr>
<td>( a_{01} )</td>
<td>2.75</td>
<td>506.61</td>
</tr>
<tr>
<td>( a_{20} )</td>
<td>590.32</td>
<td>1193.53</td>
</tr>
<tr>
<td>( a_{11} )</td>
<td>85.72</td>
<td>3637.80</td>
</tr>
<tr>
<td>( a_{30} )</td>
<td>0</td>
<td>4747.25</td>
</tr>
</tbody>
</table>

The constants for plaque (FC, F) tissue are obtained by fitting a curve to the data points obtained from the stress-strain relation of human calcified plaque (Loree et al., 1994; Lally et al., 2005). Human femoral arterial tissue properties were used to define the hyperelastic model for AW (Prendergast et al., 2003; Lally et al., 2005).

### 3.3 Computational set up

The present model describes the condition when the geometry (stent, plaque, AW) is in the final expanded state. The stent expansion procedure pushes the vessel wall back and stimulates the internal stresses in the arterial tissue. Due to the elastic nature of hyperelastic arterial tissue, the vessel contracts around the stent with the stent behaving as scaffold within the vessel.

Using the law of Laplace, Tambaca et al. (2011) defined a relation to estimate the exterior pressure loads applied on the stent. This law relates the displacement of the vessel wall tissue with the transmural pressure generated within the vessel wall during the expansion of the stent. The formula is given by Equation 3.2.

\[
p_i - p_0 = \frac{Eh}{(1 - \nu^2)R^2}u
\]

where \( p_i - p_0 \) the transmural pressure, \( E \) is the combined (plaque and AW) Young’s modulus of the vessel wall, \( h \) is the total thickness of the vessel wall, \( R \) is the (reference) vessel radius (3 mm), and \( \nu \) is the Poisson’s ratio.

It has been suggested that a maximum pressure which the stent is expected to sustain in vivo is approximately 60 kPa (~450 mmHg) (Beyar and Serruys, 1998; Prendergast et al., 2003). A pressure value of 60 kPa is used (in Equation 3.2) for one of the thicker plaques (Plaque1) to estimate the transmural pressure for the remaining geometry cases as given in Table 3.4. An internal pressure of 13.3 kPa (~100 mmHg) representing the mean blood flow is applied to the luminal surface of the vessel wall. The exterior side of the vessel wall is imposed by a pressure load (representing the force by which an expanded artery acts on a stent) such that the transmural pressure within the vessel wall for several model
3.3 Computational set up

remains as presented in Table 3.4.

Three dimensional models of stented coronary arteries are constructed using ANSYS Gambit 2.4.6 and then exported to ANSYS Workbench 14.5. The edges of luminal side of the vessel wall are constrained. The surfaces perpendicular to the radial direction are free to displace, and the other remaining surfaces are assigned to zero displacement in the normal direction.

Table 3.4: Estimated transmural pressure for several geometries with varying NC and FC thicknesses

<table>
<thead>
<tr>
<th>Cases</th>
<th>Transmural pressure ((p_i - p_0)) (kPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3</td>
<td>60</td>
</tr>
<tr>
<td>4-6</td>
<td>45</td>
</tr>
<tr>
<td>7-9</td>
<td>49.2</td>
</tr>
<tr>
<td>10-12</td>
<td>37.8</td>
</tr>
</tbody>
</table>

The whole computational domain is discretized using mixed (hexahedral, prism) elements in the meshing module of ANSYS Workbench 14.5. To ensure grid-independent results, mesh sensitivity analysis is performed on five different meshes with the increasing number of elements (from 13 to 57) through the thickness of the vessel wall. Since the high stress values were concentrated in the immediate layers of the stent wire, the elements through plaque (FC, NC, F) layer were assigned twice than in AW layer. Volume weighted VMS average was calculated over each component of plaque and AW given by Equation 3.3.

\[
V_{avg} = \frac{\sum_{i=1}^{i=n} \sigma_i \delta v_i}{\sum_{i=1}^{i=n} \delta v_i}
\]  

(3.3)

where \(\sigma_i\) represents the VMS in the \(i_{th}\) element, \(\delta v_i\) is the volume of the \(i_{th}\) element and \(n\) is the total number of elements in the domain. \(V_{avg}\) values were compared and the differences between the meshes were found below 5% except for the coarsest mesh. No significant differences were recorded in the mesh densities finer than 24 elements through the thickness of the vessel. The maximum TP did not alter for any of the mesh size. A mesh size was chosen consisting of 24 elements through the thickness with the total number of approximately 22000 elements.

The calculations were performed using the static structural module of ANSYS Workbench 14.5. As the material properties of plaque component (FC, F) layers are described by the hyperelastic model, the large deflection is assigned. Simulations were carried out under static condition using solver target Mechanical APDL.
3.4 Verification of the model

The current model was compared to the finite element model proposed by Prendergast et al. (2003) for verification. Out of their four stent models, Tetra (Tetra stent, Guidant) design is used for the validation of the current model due to the similarity in the geometry. However, they may be different commercially. For closer comparison, only AW layer is created, and similar wall thickness and material properties (as used by Prendergast et al. (2003)) are adapted. The model is discretized using 7680 hexahedral mesh elements with 8 elements through the thickness of the vessel wall. The corresponding data of the test and reference models are displayed in Table 3.5.

<table>
<thead>
<tr>
<th>Stent cell model</th>
<th>Maximum prolapse (mm)</th>
<th>Expanded area of repeating unit (mm²)</th>
<th>Max. prolapse per unit area (mm/mm²)</th>
<th>Length of periphery of expanded repeating unit (mm)</th>
<th>Maximum prolapse per unit length (mm/mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>test</td>
<td>0.105</td>
<td>3.45</td>
<td>0.30×10⁻¹</td>
<td>11.20</td>
<td>0.0094</td>
</tr>
<tr>
<td>reference</td>
<td>0.117</td>
<td>4.35</td>
<td>0.26×10⁻¹</td>
<td>12.60</td>
<td>0.0093</td>
</tr>
</tbody>
</table>

The properties of human femoral arteries are used for the comparison in the data presented in Table 3.5. Differences in the peripheral length and expanded area of the repeating unit for both the models are 11% and 21%, respectively. However, the maximum prolapse and maximum per unit differed by 10% and 13%, respectively, whereas the maximum prolapse per unit length differed by only 1%. Figure 3.4 shows the maximum principal stresses in the mid-layer of the vessel models around the peripheral length. Except for few peak stresses and fluctuations in test model, the overall stress distribution is within the range of reference model shown in Fig. 3.4.

3.5 Results and discussion

This section presents and discusses the results of TP and VMS that are believed to provoke the progression of restenosis. The results are divided into two sub-sections. One section reports the maximum TP and the other section the VMS distribution in different layers of the vessel wall for various model geometries. Case 1 had an unconverged solution, and thus, its results are not presented for any discussion.

3.5.1 Tissue prolapse

Studies suggest that the deformation of the vascular tissue within the stent strut affects the local hemodynamics. Prendergast et al. (2003), Lally et al. (2005), and Capelli et al. (2009) have reported the dependence of TP on various design of the stent strut. Figure 3.5 shows the total deformation of the vessel wall in one repeated unit of stent cell model. The
3.5 Results and discussion

Figure 3.4: Maximum principal stresses in the mid-layer of test and reference models around the periphery of the repeating unit.

TP is evaluated as the maximum protrusion of the vessel wall in the lumen. Figure 3.5 depicts that the tissue displacement is zero along the peripheral length of luminal side. This path represents the contact of stent strut with the vessel wall, which is kept fixed. The vessel wall area which is at the farthest distance from strut location undergoes the maximum TP. A higher value of TP means more reduction in the free lumen and could be related to a lower scaffolding capability of the stent. This has been well demonstrated by Prendergast et al. (2003) and Capelli et al. (2009) for various designs of stents. However, they have ignored the presence of plaque and its components in their models.

Figure 3.5: Total deformation of the vascular tissue within the stent cell model

The current model incorporated two stenosis sizes and various thicknesses of FC and NC. The maximum TP for several models (Cases 1-12) are presented in the graphs in Fig.
3.6(a) and (b). The results reveal that the maximum TP decreases in the plaques when the thickness of FC is growing as shown in Fig. 3.6(a) and Fig. 3.6(b). Plaques (for the same thickness of FC) with thicker NC have relatively smaller TPs than with thinner NC. However, the difference is not very significant as the variation of NC ($\delta_2$) (Table 3.2) is small within the same thickness of plaque.

![Figure 3.6: Maximum TP in (a) Plaque1 and (b) Plaque2 with different thicknesses of NC and FC represented by Cases 2-6, and Cases 7-12 respectively.](image)

The statistical data in Fig. 3.6(a) and Fig. 3.6(b) shows that the range of TP is higher in Plaque1 (Cases 2-6) than in Plaque2 (Cases 7-12). This reveals the role of the stenosis severity in the deformation of the vessel wall tissue. The vascular wall is most vulnerable to prolapse for the severe stenosis with the thinnest FC. As discussed earlier, the overall rigidity of the plaque material becomes less stiff due to the growing NC (soft material) area with the increasing stenosis size. Possibly, the softer material will undergo larger strain. In fact, as the severity of plaque progresses, the NC is calcified and becomes stiffer material. However, in the current plaque models, the stiffness of NC was kept constant.

### 3.5.2 von Mises stress

The stresses that developed in different layers of vessel wall in several models of stented coronaries are discussed in this sub-section. Figure 3.7 demonstrates the average VMS induced in different layers (FC, NC, F) of Plaque1 and AW in the post-stenting stage. Volume weighted average in individual layers are calculated by the formula defined in Equation 3.3.

![Figure 3.7(a) shows the graph of the average VMS in Cases 2-3 that represents the plaque model with the same size of NC but a varying thickness of FC. Due to the very thin FC in Case 1, the solution did not converge, and the results are not presented. The average value of VMS in all the layers of the vessel wall is maximum when the FC is thinnest, while VMS reduces as the FC gets thicker. The range of VMS varies significantly in different layers of the vessel wall. Maximum VMS is observed in the FC layer that is the first](image)
layer in the atherosclerotic plaque and is in direct contact with the lumen. The stresses dramatically drop in the following layer, NC, which has a mechanically softer material property than its surrounding layers (FC, F) that are calcified and stiff. In comparison to the NC, the VMS significantly rises in the next layer, F, though not as high as in the FC. The last layer, AW, experiences the least amount of VMS. Figure 3.7(b) shows the graph of average VMS in Cases 4-6 that represents a relatively thicker NC than in the Cases 1-3. Similar to Cases 2-3, the stress distribution in all the layers of Cases 4-6 is highest in the thinnest FC. The level of stress range vary within layers with higher values in the FC and F layers than in the NC and AW layers. Differentiation between Fig. 3.7(a) and Fig. 3.7(b) shows that the range of VMS is higher when NC is thinner. However, the difference is not remarkable as the geometric difference among them is small.

![Graph A](image-a)

![Graph B](image-b)

Figure 3.7: Average VMS in different layers (fibrous cap (FC), necrotic core (NC), fibrosis (F), and arterial wall (AW)) of the vessel wall for (a) Cases 1-3 and, (b) Cases 4-6.

Figure 3.8 illustrates the distribution of the average VMS inside several layers of vessel wall of Plaque2. Notable difference in VMS values is observed among Fig. 3.8(a) and Fig. 3.8(b). Stresses are high in Cases 7-9 where NC is thinner. This behaviour is identical to Plaque1 and determines the role of the structural property of NC in elevating the level of stress within the vessel wall.

The distribution of stress in all the layers of plaque and AW of Plaque2 (Fig. 3.8) is much alike in Plaque1 (Fig. 3.7). However, the magnitude of VMS is observed significantly lower in Plaque2 especially in the FC layer. This explains the influence of the stenosis severity on the stresses within the distinct layers of vessel wall. It is already clear from the
previous study that the severe stenosis yields to higher resultant arterial stresses. Moreover, the current results also reveal the distribution of stresses in the distinct layers of the vessel wall in stented arteries. Although the arterial stresses are affected by the size of NC, the rate by which the stresses are altered is higher due to the severity of stenosis. Among all layers, the FC layer is the most sensitive to the structural changes in atherosclerotic plaque lesions.

![Graph](image)

Figure 3.8: Average VMS in different layers (fibrous cap (FC), necrotic core (NC), fibrosis (F), and arterial wall (AW)) of the vessel wall for (a) Cases 7-9 and, (b) Cases 10-12.

In addition to the mean distribution of VMS, it is equally important to observe the dispersion of stress through each layers of vessel wall. This type of analysis will show the concentration of stress of individual layers and would indicate their vulnerability to rupture in the post-stenting phase. Figure 3.9 demonstrates the probability density function (PDF) of VMS in each layers of atherosclerotic vessel wall of Plaque1. The VMS values plotted in the graphs are the mean value calculated over the nodal points of each computational mesh element. Individual sub-Figure 3.9(a), (b), (c), and (d) presents five graphs Case 2-6 for FC, NC, F, and AW layers of vessel wall respectively.

As discussed earlier (Fig. 3.7(a), FC), VMS is concentrated around 150 kPa in FC layer (Fig. 3.9(a)). From then, the graph sharply falls to high value of approximately 300 kPa. The maximum value of VMS stretches very long in the range with exceptionally high value over 1700 kPa. This values lie on the luminal edges of FC layer that are kept fixed in displacement. The stresses in FC elevates due to the add up of stresses from the other layers behind, since there is no movement of this edges and in it appears to be last in the sequence. No major differences are observed among VMS distributions of Cases 2-6 in
FC layer.

Figure 3.9: Probability density function (PDF) of VMSs in (a) Fibrous cap (FC), (b) Necrotic core (NC), (c) Fibrosis (F), and (d) Arterial wall (AW) layers of atherosclerotic vessel wall (Plaque1).

The distribution of VMS in NC layer (Fig. 3.9(b)) mimic a bell curve (Gaussian distribution) with one end more stretched than the other. Statistically, it shows that VMS falls sharply with values that are less than mean value, while it elongates with VMS that are higher than the mean value. Noticeable difference can be observed in the distribution of VMS in NC layer among several Cases 2-6. The bell curve shaped graph decreases its peak and enlarges the stretch to right side of the graph (VMS greater than mean value) when the thickness of FC decreases. This implies that as the FC becomes thicker, the distribution of VMS in NC layer gets closer to its mean value. VMS distribution in the following next layer, F, resembles a falling curve. Maximum region falls under lower values of VMS in F layer. In the AW layer, VMS is distributed with similar pattern to NC with the maximum concentration of stresses around mean value. The distribution of VMS in AW layer gets closer to its mean value when the thickness of FC increases, however the difference among several Cases 2-6 is not significant.
Figure 3.10 demonstrates the PDF of VMS distribution in various layers of vessel wall of Plaque2. Qualitatively, the graphs are similar to that presented in Fig. 3.9 (Plaque1), however there is significant difference among the layers quantitatively. Maximum VMS in FC layer of Plaque2 remarkably reduces to approximately 650 kPa. Similar to Plaque1, the graph of VMS distribution in NC layer is sensitive to the thickness of FC and NC. Figure 3.10(b) clearly show that the distribution of VMS in NC layer is concentrated around its mean value when FC becomes thicker. While VMS is more widely spread with local high stress values in the cases when the thickness of FC reduces. VMS distribution in F layer resembles a falling curve and can be easily distinguished among various cases. Plaques with thinner FC does not allow the formation of peak in stress distribution. Rather, it is more uniformly spread with higher VMS than in the cases with thicker FC. Also, the effect of NC thickness is visible in Fig. 3.10(c). VMS in F layer confines to mean value when the thickness of NC is thinner and is more widely distributed in the plaques having thicker NC. VMS in AW layer (Fig. 3.10(d)) is similar to that observed in Plaque1 (Fig. 3.9(d)). Notable difference is observed in the trend of VMS distribution with varying thickness of FC and NC. Like in other previous layers, the distribution of stress is restricted around
mean value in the plaques with thicker FC and NC, and the concentration of stress start to spread wide when FC and NC becomes thinner.

From the Fig. 3.9 and Fig. 3.10, one can observe the distinctive trend of stress distribution in various layers of atherosclerotic arteries in the post-stenting stage. The stenosis severity, thicknesses of FC and NC play a vital role in influencing the patterns of distribution. In most cases, the concentration of stress in each layers accumulated around their mean value which was below critical value of rupture (300 kPa). The dispersion results in wider distribution of stress, however, it elevates the maximal value of stress. This phenomenon is significantly influenced by the thicknesses of stenosis, FC and NC. Thus, it reveals that the morphological characteristics of various plaque type regulates the distribution of internal stress for a given stent design. A recent finding (Ohayon et al., 2014) suggested that a local wall stiffness plays a role in the initiation of atherosclerosis lesions. The presented analysis thus becomes important, as it determine the roles of individual vessel wall layer in post-stenting phase.

An additional analysis is made to study the variations of stresses on the edge of FC that was kept fixed. Nodal stresses are calculated over the boundary edge (luminal side) of the FC layer which resembles the contact of stent wire with the vessel wall tissue. Table 3.6 presents the maximum, mean, and standard deviation of VMS over the boundary edge of FC for several cases of Plaque1 and Plaque2.

Table 3.6: Maximum, mean, and standard deviation of VMS over the boundary edge (luminal side) of FC for several cases of Plaque1 (Cases 1-6) and Plaque2 (Cases 7-12).

<table>
<thead>
<tr>
<th>Stenosis</th>
<th>Stent cell model</th>
<th>Max. VMS (kPa)</th>
<th>Mean VMS (kPa)</th>
<th>Standard deviation of VMS (kPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaque1</td>
<td>Case 1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Case 2</td>
<td>2360</td>
<td>343</td>
<td>190</td>
</tr>
<tr>
<td></td>
<td>Case 3</td>
<td>1116</td>
<td>400</td>
<td>253</td>
</tr>
<tr>
<td></td>
<td>Case 4</td>
<td>2348</td>
<td>447</td>
<td>369</td>
</tr>
<tr>
<td></td>
<td>Case 5</td>
<td>1875</td>
<td>264</td>
<td>142</td>
</tr>
<tr>
<td></td>
<td>Case 6</td>
<td>804</td>
<td>246</td>
<td>152</td>
</tr>
<tr>
<td>Plaque2</td>
<td>Case 7</td>
<td>2460</td>
<td>917</td>
<td>513</td>
</tr>
<tr>
<td></td>
<td>Case 8</td>
<td>2491</td>
<td>932</td>
<td>550</td>
</tr>
<tr>
<td></td>
<td>Case 9</td>
<td>2219</td>
<td>840</td>
<td>487</td>
</tr>
<tr>
<td></td>
<td>Case 10</td>
<td>2278</td>
<td>827</td>
<td>463</td>
</tr>
<tr>
<td></td>
<td>Case 11</td>
<td>1872</td>
<td>700</td>
<td>406</td>
</tr>
<tr>
<td></td>
<td>Case 12</td>
<td>1951</td>
<td>719</td>
<td>422</td>
</tr>
</tbody>
</table>
The results in Table 3.6 show that the maximum value of VMS on the FC edge is more sensitive in Plaque1 for different thicknesses of FC. The higher values of standard deviation indicate that the nodal stresses are more spread out on the FC edge of Plaque2 than in Plaque1. This result reveals that the stresses induced in the FC layer due to the stent insertion are more influenced by the stenosis severity and thickness of FC than the NC layer.

3.6 Summary

The current computational model is proposed to investigate the TP and the distribution of the internal stresses within the vessel wall during the post-stenting stage. The model incorporates a fully expanded 3D stent with distinct homogeneous layers of the atherosclerotic plaque and AW. Considering the repeated units in the stent strut, only one unit is taken into account where this unit is repeated three times in the circumferential direction and seven times in the longitudinal direction. FEA is performed in several 3D stent-plaque-artery models mimicking the plaques at various stages of atherosclerosis.

One unit of the repeated units in stent strut is extracted over which two sizes of plaque representing two different stenosis are constructed. Plaque is modeled as a multi-layered domain consisting of FC, NC, and F layers. A single layer of AW is created over the plaque layer. FC, F, and AW layers are modeled by stiff hyperelastic material where NC is modeled as soft isotropic material. Twelve stent-plaque-artery models mimicking the plaques are defined. The boundary edge (luminal side) of FC layer is kept fixed representing the contact of stent wire with arterial tissue. Transmural pressure within the vessel wall is calculated to impose the normal pressure (representing the force by which an expanded artery acts on stent) on the exterior side of stented artery, while a mean luminal pressure is applied on the internal side of the artery. Finite element simulations are performed in the static condition to obtain the deformed state of vessel tissue within the stent strut. The current stent-plaque-artery model is first verified with the Tetra stent of previous studies by Prendergast et al. (2003). The comparison is possible because of the similarity between the geometries of the repeated unit of the stents. For appropriate comparison, only AW (without stenosis) is taken into account. The TP and stress between the models vary by small margins.

The results show the post-stenting tissue deformation and stresses generated within the vessel wall of atherosclerotic plaques. TP within the stent strut depends on the severity of stenosis. Severe stenosis leads to a higher prolapse for a given stent configuration. However, in general, a higher value of prolapse can also be related to the lower scaffolding capability of the stent. The proportion of mass occupied by NC in plaques has an impact on the deformation of the vessel wall. The differences in prolapse from different NCs presented in the results are not large, as the applied geometric differences among them are small. Nonetheless, it simply illustrates how the TP is affected with the variation of NC. The most sensitive layer to TP among all the layers of the vessel wall is FC. A significant change in the rate of prolapse is observed when the thickness of FC varies. Plaques
having the thinnest FC are most likely to have a maximum TP.

The distribution of stresses within the vessel layers vary from layer to layer. This result agrees with the results of the 2D axisymmetric stent-plaque-artery model discussed in Chapter 2. In all cases, the maximum stresses (VMS) are concentrated in the FC irrespective of the degree of stenosis, proportion of NC, and thickness of FC. It is obvious that the insertion of stent boosts the internal stresses particularly in the FC layer that is in direct contact with the stent. This confirms the fact about the critical role of FC that experiences the maximum amount of stress in it (Hajiali et al., 2013). The level of stresses in FC is also influenced by the size of NC. Stress in NC is much lower than in FC. Moreover, the stresses within NC are elevated in the plaques with thinner FC. A similar effect of FC thickness is seen in the F and AW layers. The stresses are higher in the F layer than in NC, which is located next to NC from the lumen. Since the FC and F layers are surrounding NC and stiffer materials, they inhibit the transmission of high stresses to NC. AW experiences the least amount of stresses among all the layers.

The 3D stent-plaque-artery model demonstrates how stresses are transmitted through several layers of the atherosclerotic plaque of stented coronary artery in post-stenting stage. It also illustrates the influence of geometrical property of plaque on the elevation/declination of stresses that provoke the progression of restenosis. Moreover, it also determines the vulnerability of the vessel wall rupture depending on the stress values getting closer to critical rupture values. However, this model is limited to the idealized and homogeneous assumptions of plaque geometries.
3 Idealized 3D model of stent-plaque-artery
4 Idealized 3D model of stent-plaque-artery-lumen

This chapter presents fluid-solid simulations of 3D stent-plaque-artery models in the post-stenting stage. The importance of vessel wall morphology in inducing the stresses both inside and over the surface is well demonstrated in Chapter 2 and Chapter 3. Their results showed that the stresses on the surface of vascular wall are affected by the stenosis sizes and expansion pressures. However, applied transmural pressures are identical for all plaques at the various stages of atherosclerosis and the model is limited to only one stent strut in 2D (Chapter 2). The inter-strut prolapse of vessel wall tissue in the 3D stent is reported to be influenced by the plaque structure (Chapter 3). Now, it could be interesting to investigate the impact of vascular wall morphology on the luminal blood flow distribution in the 3D models of stented coronary artery. LaDisa Jr et al. (2005) carried out 3D flow simulations where the emphasis was on the stent design considering the vessel wall as smooth surface and ignoring the TP within the struts. Murphy and Boyle (2010) included the vessel wall deformation to their blood flow analyses. However, the atherosclerotic vessel wall was ignored with the TP between the stents struts predicted numerically.

In this model, an effort is made to simulate the blood flow over a more realistically deformed vessel wall around the stent strut. Twelve different vessel wall models (multi-layered plaque and a single layer of AW) are taken into account (as discussed in Chapter 2). In the first step, the solid deformation (vessel tissue prolapse around the stent) is performed statically. In the second step, the deformed luminal surface of vessel wall is extracted and a fluid domain (lumen) is created to simulate blood flow both in static condition. VMSs and WSSs are presented inside the arterial tissue and over the deformed arterial surface, respectively.

The chapter begins with the description of the stent geometry and consideration of atherosclerotic plaque model. Then, the following section describes the implementation of solid and fluid domains in the simulations. Boundary conditions and grid analysis are discussed for both solid and fluid domains. Results and discussion section includes the discussion of VMS and WSS distributions in various models. Finally, the chapter concludes with a summary of the whole model.

4.1 Geometric model

4.1.1 Stent geometry

For simplicity, a slotted tube and basic design, Palmaz-Schatz (PS) stent is chosen. This stent is of the balloon-expandable type adapted from the work of Gu et al. (2010). In the crimped state, the stent has an outer diameter of 1.2 mm, axial length of 15 mm and a thickness of 0.1 mm. Figure 4.1 shows a schematic diagram of one repeated unit of the PS stent in its initial (unexpanded) state. There are five units in the longitudinal and twelve units in the circumferential direction.
After the expansion, the PS stent was assumed to have an internal diameter of a healthy coronary lumen, 2.8 mm, and a fixed longitudinal length (15 mm). The geometry of the expanded stent was reconstructed by calculating the angles between stent struts that would exist in principle when the internal diameter of the stent is raised from 1.2 mm to 3 mm. However, in practice, the stent struts may not be straight and can have bendings/curvatures. Taking the advantage of repeating units in the PS stent, only one unit (1/12th) is reproduced in the circumferential direction and five units (full) in the longitudinal direction. Such approach has been implemented by a computational study on the interaction with the vascular wall by Migliavacca et al. (2004). The entire geometry of the expanded stent employed in the model is shown in Fig. 4.2.

Figure 4.2: Schematic diagram of expanded stent taken into consideration. Dimensions are in millimeters.

## 4.1.2 Atherosclerotic vessel model

Plaque with a presence of soft NC and a single layer of AW is modeled as discussed in Section 3.1.2 of Chapter 3. Two different stenosis sizes and various thicknesses of NC and FC are taken into account. In all, twelve model cases representing the plaque of different types are modeled as described in Chapter 3. Geometric layers of plaque-artery are constructed below the expanded stent configuration (Fig. 4.2) representing a 1/12th portion of the expanded vessel wall in the circumferential direction. The stent is assumed as fixed structure while the elastic vessel wall is made to deform towards the stent. The shorter length of plaque would create contact problems in the simulations. Thus, the plaque layer is modeled as cuboid with the longitudinal length and width equal to that of the stent structure. Plaque at both of its end is made blunt to avoid sharp edges and to reduce the area of recirculation in the later flow domain. The cross-section of the stent-plaque-artery in the longitudinal direction is shown in Fig. 4.3. The thickness and
the total length of AW is 0.5 mm and 30 mm, respectively. The thickness of FC is the distance between the NC layer and luminal surface of the plaque layer. The thicknesses for FC, NC, and the total thicknesses of plaque are implemented as presented in Table 3.1 and Table 3.2 of Chapter 3.

![Figure 4.3: Schematic diagram of stent-plaque-artery model.](image)

### 4.2 Material property and boundary conditions

#### 4.2.1 Solid (vessel wall) part

Two separate computational domains for the solid deformation and blood flow are created. In the first step, the geometry of the solid body domain is created in ANSYS Gambit 2.4.6. Then, the geometry file is exported to the program Comsol Multiphysics 4.4 where the whole process of solid simulation is performed. The material property of plaque (F) and the NC and AW layers are the same as described in Section 3.2 of Chapter 3. The model shown in Fig. 4.3 illustrates the condition when the geometry (stent, plaque, and AW) are expanded to a desired lumen diameter. The opening of the stent triggers the stresses inside the vessel wall in such a way that the elastic arteries try to retain their original position with a force acting from artery to the stent. The derivation of this force is explained in Section 3.3 of Chapter 3. The calculated transmural pressures for different model cases are presented in Table 3.4.

As shown in Fig. 4.3, the AW layer is geometrically divided into three zones. The transmural pressure is applied from the outer surface to one of the AW zones (middle), which lies exactly below the stent. The remaining two zones are free with their far ends constrained by fixed displacement in the radial direction (0.54 mm and 0.4 mm for Plaque1 and Plaque2, respectively). This condition would restrict the large deformation of AW and describe the support of connecting tissue as a whole artery so that it does not just act as a stand-alone segment. AW, plaque and NC are defined with a bonded contact that does not allow slides between the surfaces. Stent geometry is kept fixed and is not allowed to move in any direction. Solid simulations are performed in the static condition.

#### 4.2.2 Fluid (lumen) part

Out of the deformed configuration of the whole vessel model, the luminal surface is extracted over which a lumen is created for blood flow simulations. In real, a 1/12th portion
of the cylindrical artery would be like a triangle with a circular base. However, for simplicity, the flow domain is made rectangular with a height (radius) of 1.5 mm. Figure 4.4 shows the computational domain created for blood flow simulations with the deformed luminal surface around the stent struts. Reynolds number for all the flow domains was around 200. A laminar inflow with an average velocity of 0.22 m/s is applied as the inlet boundary condition (Jung et al., 2006) while the zero pressure condition is applied at the outlet. The side walls along the flow are defined as symmetry boundary. The stent and the luminal surface are considered as wall with no slip condition.

Figure 4.4: Blood flow domain (lumen) with the deformed surface of atherosclerotic artery tissue.

Blood is modeled as a Newtonian incompressible flow with a density of $\rho = 1060 \text{ kg} \cdot \text{m}^{-3}$ and a dynamic viscosity of 0.0035 Pa·s (Jiménez and Davies, 2009; Mejia et al., 2009). Convergence criteria for continuity and momentum equations were set to $10^{-7}$. Blood flow simulations are performed in the static condition using Navier-Stokes equations defined in Comsol Multiphysics 4.4.

4.3 Mesh sensitivity analysis

Before presenting the results, two separate tests, each for solid and fluid models, are performed to study the sensitivity of the mesh. For the solid model, five different meshes starting from 3962 to 74735 tetrahedral elements with finer elements near the sharp edges are created. Volume weighted average VMS is calculated over the 3D domains of plaque, NC, and AW. The differences of the average VMS among the meshes over these domains were 5% (F), 6% (NC), and 4% (AW). All these three differences reduced to 1% in the meshes finer than 40569 elements. Thus, a mesh with a total number of 40569 tetrahedral
elements was selected for the solid domain.

Six different meshes with the increasing number of elements starting from 22469 to 214324 were generated for the fluid domain. The average value of WSS magnitude over the luminal surface of vessel wall was measured. WSS magnitude differed by maximum 8% among all the meshes. The variation was less than 1% in the meshes finer than 186701 elements. Furthermore, a 2D plane was created cutting the domain from the middle along the flow direction. An average of velocity magnitude differing by 3% was measured among the meshes through the longitudinal plane. The difference in the average velocity remained same in the meshes finer than 186701 elements. A final mesh with a boundary layer up to 10 elements and a total number of approximately 186701 tetrahedral elements was chosen for the flow simulations.

4.4 Results and discussion

This section presents the results from solid and fluid simulations. The TP and distribution of VMS are discussed in the first sub-section and the distribution of WSS are discussed in detail in the second sub-section. The third sub-section discusses flow simulation with the non-Newtonian properties of blood viscosity.

4.4.1 Solid (vessel wall) simulations

The deformation of arterial tissue is measured in the free areas of the stent strut design. It makes more sense to study the prolapse in the region of arterial tissue surrounded by the repeated unit of stent strut (as presented in Sub-section 3.5.1 of Chapter 3). Such analysis describes the scaffolding capability of a particular stent design. But, on the other hand, it is also influenced by the morphology of vascular wall (demonstrated in Chapter 3). However, the stent-plaque-artery model implemented in Chapter 3 is a domain with homogeneous layers of plaque and AW. The axial lengths of plaque, NC and AW are different in the model of the current chapter. This would explain how the maximum prolapse and the distribution of stresses inside the wall layers are affected by NC and FC thicknesses when they have various lengths in the axial direction.

Figure 4.5(a) and (b) display the undeformed and deformed configuration of the stent-plaque-artery model. Figure 4.5 illustrates the state when the stent is fully expanded, and the displaced elastic artery recoils back around the vacant spaces of the stent. The ends of the AW are constrained to fixed displacement in the radial direction to provide support of the neighbouring tissue. These values of the displacement are adjusted to make the lumen diameter of 3 mm (corresponding to the healthy section of the artery). For analysis, the maximum TP is only measured on the tissue that is covered by stent. Maximum TP for Cases 1-12 are presented in Table 4.1.
Table 4.1: Maximum TP for different Cases 1-12 of Plaque1 and Plaque2.

<table>
<thead>
<tr>
<th></th>
<th>Maximum TP (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>0.110</td>
</tr>
<tr>
<td>Case 2</td>
<td>0.111</td>
</tr>
<tr>
<td>Case 3</td>
<td>0.119</td>
</tr>
<tr>
<td>Case 4</td>
<td>0.122</td>
</tr>
<tr>
<td>Case 5</td>
<td>0.118</td>
</tr>
<tr>
<td>Case 6</td>
<td>0.116</td>
</tr>
<tr>
<td>Case 7</td>
<td>0.102</td>
</tr>
<tr>
<td>Case 8</td>
<td>0.101</td>
</tr>
<tr>
<td>Case 9</td>
<td>0.098</td>
</tr>
<tr>
<td>Case 10</td>
<td>0.097</td>
</tr>
<tr>
<td>Case 11</td>
<td>0.084</td>
</tr>
<tr>
<td>Case 12</td>
<td>0.089</td>
</tr>
</tbody>
</table>

Figure 4.5: (a) Undeformed configuration of stent-plaque-artery model (Case 7) and (b) deformed configuration of stent-plaque-artery model (Case 7).
In all cases, the maximum value of TP occurred at the regions of luminal surface below which the NC was located. A general trend was observed in values of max TP for Cases 4-12 with the thinnest FC produces larger TP, whereas the opposite trend was observed for Cases 1-3 with larger TP occurring when the FC is thinnest. This behaviour is similar to TP reported in Sub-section 3.5.1 of Chapter 3. The larger values of TP are observed for Cases 4-6 with the largest value in Case 4. Among all cases, the thickness of NC is largest in Cases 4-6 with Case 4 having the thinnest thickness of FC. This reveals that the plaques with larger NC and thinner FC are more vulnerable to prolapse. Earlier studies (Prendergast et al., 2003; Lally et al., 2005) have reported that the stent geometry is responsible for the extent of TP. In addition, this result reveals that for a given stent design, the morphology of plaque especially, the NC and FC layers also contribute to the prolapse that occurs in the post-stenting stage.

The distribution of average VMS in the plaque (F), NC, and AW layers for several model cases is demonstrated in Fig. 4.6. Each sub-figure 4.6(a), (b), (c), and (d) illustrates the cases with the similar thickness of NC while each individual graph represents the average VMS for three thicknesses of FC. Volume weighted average VMS is calculated over separate domains using Equation 3.3 as reported in Section 3.3 of Chapter 3. In the plaque (F) layer, the VMS distribution has two different ranges. Cases 1-3 and Cases 7-9 have identical range of values and Cases 4-6 and Cases 10-12 have the similar values of VMS. There is a significant difference of approximately 20% between these two ranges of VMS distribution. VMS range with lower values represents the cases with relatively thicker NCs. This demonstrates that the higher stresses are concentrated in the F layer of plaques with thinner NC than in thicker NC. However, there is no significant change in VMS values in the F layer when the thicknesses of FC vary.

The effect of FCs is observed in the distribution of stresses in the NC layer. In all cases, the thinner FC yields higher values of VMS in NC. Geometrically, thinner FC would mean that the NC layer is closer to the stent and thus vulnerable to higher stresses. The behaviour and the range of VMS in the NC layer is similar to that presented in Sub-section 3.5.2 of Chapter 3. The AW experiences the lowest concentration of stresses among the other layers. No significant differences are observed in the values of VMS in the AW layer when NC and FC vary.
Figure 4.6: Average VMS distribution in plaque (F), NC, and AW layers for (a) Cases 1-3, (b) Cases 4-6, (c) Cases 7-9, and (d) Cases 10-12.

4.4.2 Fluid (blood) simulations

Blood flow is simulated in the lumen having a deformed wall of the stented atherosclerotic coronary arteries. The flow analyses are presented in twelve different domains constructed over the walls of deformed vessel discussed in Section 4.4.1. The WSS is measured over the luminal surface of vessel wall as shown in Fig. 4.4. The direction of blood flow is
from left to right in Fig. 4.7 and Fig. 4.8. WSS is shown only on the segment of vessel wall that covers the full length of stent in the longitudinal direction, while it is not shown on the stent and the other remaining areas of flow domain. Several cases (Cases 1-6, 7-12) from Plaque1 and Plaque2 are presented in Fig. 4.7 and Fig. 4.8, respectively.

Figure 4.7: Distribution of WSS along the luminal surface for different model cases (Cases 1-6) of Plaque1.

Figure 4.8: Distribution of WSS along the luminal surface for different model cases (Cases 7-12) of Plaque2.
From Fig. 4.7 and Fig. 4.8 it can be observed that the WSS magnitude is close to zero near the vicinity of stent struts. It is high in the regions that are at the farthest distance from the struts of stent. Maximum deflection of tissue in these open areas of stent helps the blood to flow away with high velocities resulting in high WSS (approximately 2.5-3 Pa). The values of WSS magnitude in all cases of Fig. 4.7 and Fig. 4.8 are elevated near the central struts of the stent. This behaviour is caused by the presence of the NC layer that lies exactly underneath the middle strut of the stent. The soft material assigned to NC makes the surrounding region of plaque tissue relatively less stiff than in other areas of plaque and allows the tissue to undergo large deformation. The value of maximum WSS magnitude is observed at the left-upper corners of every plot and is ignored in the current analyses. This region is the end of stent where the tissue has the least support from the stent.

The overall range of WSS is lower in Fig. 4.8 than in Fig. 4.7. The highest WSS values concentrated below the NC layer for Plaque1 are approximately 2.5-3 Pa while the value for Plaque2 is below 2.5 Pa. Though the difference is not large, it simply demonstrates the impact of stenosis size in elevating the magnitude of WSS. It is difficult to examine any effect of FC and NC thicknesses on WSS distribution qualitatively. However, in the quantitative technique, the area-averaged mean and percentage of luminal surface with WSS area less than 0.5 Pa are analysed. The WSS values are calculated at every nodal point by most of the CFD programs. Since the distance between every two successive nodes vary, the calculation of normal algebraic mean is not a good representation. Thus, area weighted WSS mean value WSSavg is calculated as

$$ WSS_{avg} = \frac{\sum_{i=1}^{n} \tau_i A_i}{\sum_{i=1}^{n} A_i} $$

where $\tau_i$ is the face-averaged WSS value at the face $i$, $A_i$ is the surface area of the face $i$, and $n$ is the total number of faces (elements). Similar technique is implemented to calculate percentage of WSS values that are below 0.5 Pa. These values for several cases are given in Table 4.2.

The mean value $WSS_{avg}$ has a common trend to decrease, as the FC becomes thicker in Cases 1-3, 4-6, 7-9, and 10-12. This can be related to the thicknesses of FC and the prolapse of vessel tissue. Thinner FC would mean smaller distance between NC and luminal surface, which allows larger deformation. In such conditions, WSS value elevates resulting in higher mean value. Furthermore, cases with larger NC induce relatively large values of WSS magnitude. Their difference is not significant since the variation in the percentage of NC for a given plaque thickness considered in the current model was very small. However, it reveals the role of NC thickness in the distribution of WSS. It is a
well-established fact that the low values of WSS are associated with the localization of the plaque. Regions with WSS value below a threshold value of 0.5 Pa are considered as the regions prone to restenosis. Results of WSS (<0.5 Pa) presented in Table 4.2 show that the plaques with severe stenosis are more likely to have WSS values below 0.5 Pa.

Table 4.2: Area weighted average WSS and percentage of WSS (<0.5 Pa) over luminal surface of several model cases.

<table>
<thead>
<tr>
<th>Case</th>
<th>WSS$_{avg}$ (Pa)</th>
<th>WSS(&lt;0.5 Pa) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>1.285</td>
<td>35.21</td>
</tr>
<tr>
<td>Case 2</td>
<td>1.267</td>
<td>35.08</td>
</tr>
<tr>
<td>Case 3</td>
<td>1.243</td>
<td>32.70</td>
</tr>
<tr>
<td>Case 4</td>
<td>1.296</td>
<td>34.23</td>
</tr>
<tr>
<td>Case 5</td>
<td>1.271</td>
<td>35.54</td>
</tr>
<tr>
<td>Case 6</td>
<td>1.250</td>
<td>31.54</td>
</tr>
<tr>
<td>Case 7</td>
<td>1.247</td>
<td>31.16</td>
</tr>
<tr>
<td>Case 8</td>
<td>1.231</td>
<td>29.50</td>
</tr>
<tr>
<td>Case 9</td>
<td>1.234</td>
<td>28.47</td>
</tr>
<tr>
<td>Case 10</td>
<td>1.234</td>
<td>29.09</td>
</tr>
<tr>
<td>Case 11</td>
<td>1.230</td>
<td>28.93</td>
</tr>
<tr>
<td>Case 12</td>
<td>1.231</td>
<td>28.69</td>
</tr>
</tbody>
</table>

Besides the representation of mean value, the distribution of WSS provides more details about how the values are spread with relation to the fraction of luminal surface area. Figure 4.9 and Fig. 4.10 illustrate the distribution of WSS for all the cases of Plaque1 and Plaque2, respectively. The bars represent the normalized area with the range of WSS values along the horizontal axis (note that the WSS is calculated only over the luminal wall area covered by the stent). The bin widths of the bar are 0.06 Pa.

As already observed from Table 4.2, the graphs in Fig. 4.9 and Fig. 4.10 show decline in mean values with the decrease in stenosis severity and thicknesses of FC and NC. The graphs also show that the distribution of major WSS values lies between 1 Pa and 2 Pa. Only a small fraction of the luminal surface area experiences high WSS of 3.5 Pa. These values are higher than the WSS values reported for the P-S stent by Murphy and Boyle (2010). Such variation in results can be caused by the implementation of different conditions (inflow velocity, fluid rheology, flow field boundaries, etc.). Two peaks can be observed in Cases 1-3 with one concentrated around the mean value and the other around 0.5 Pa. In Cases 4-6, a smaller peak (around 0.5 Pa) starts to fade slowly and vanishes eventually in the remaining Cases 7-12. The larger size of the stenosis (Plaque1) makes WSS distribution to disperse more than in smaller stenosis (Plaque2).
Figure 4.9: Distribution of WSS with the bars representing normalized area for Plaque1 (Cases 1-6).

Figure 4.10: Distribution of WSS with the bars representing normalized area for Plaque2 (Cases 7-12).
4.4 Results and discussion

4.4.3 Non-Newtonian blood rheology

In a Newtonian fluid, the relation of viscous stress and shear rate (velocity gradient) induced by the fluid is linear. Thus, the viscosity remains constant at every point in the flow and may not even change over time. A non-Newtonian fluid is defined as a fluid in which the relation of shear stress and shear rate is different (not linear) and can be time-dependent.

A fundamental study of flow in the tubes and arteries is well demonstrated in the work by Liepsch (1985). This study showed the flow in rigid and elastic models with Newtonian and non-Newtonian fluids. The rheological characteristics of blood are determined by the properties of its component and their interactions with each other as well as with the surrounding structures. Since the impact of non-Newtonian effects is also dependent on the shape and size of the flow conduits, it is a good approximation to model Newtonian blood flow in arteries like aorta. Such a large sized artery is generally exposed to high shear rates, and hence, non-Newtonian effects, which are basically induced at low shear rates, are not significant (Perktold et al., 1999; Bodnár et al., 2011). However, large arteries may have certain zones like bends and bifurcation junctions with low shear rates where non-Newtonian effects may play an important role in the blood flow (Gijsen et al., 1999; Fisher and Rossmann, 2009), while medium sized coronary arteries usually experience low shear rates and are often at the risk of associating with atherosclerosis. The presence of stenosis and stent induces low values of WSS in their vicinity in coronary arteries. Johnston et al. (2006) performed blood flow simulations in the coronary artery and suggested applying non-Newtonian model for achieving greater details. The influence of non-Newtonian properties of blood on WSS in stenosed coronaries was shown by Liu and Tang (2011). They reported variations in estimating the WSS values by different blood models mainly at the regions of low (<1 Pa) and high (>2 Pa) WSS.

In the Newtonian blood flow, the viscosity is assumed constant, and hence, the value of WSS relies on the shear rates. Blood inflow velocities can directly affect the shear rates. In the post-stenting stage of stenosed coronaries, the deformation of arterial tissue within the stent gaps also alters the local shear rates. Results presented in the previous sub-section showed the dependence of WSS on the deformed vessel wall within stented arteries. Also the regions with critical low values of WSS (<0.5 Pa) for in-stent restenosis were affected by the morphology of various stenosed arteries. It would be interesting to investigate the influence of non-Newtonian properties of blood on WSS and compare it with the Newtonian blood in the post-stenting stage of various stenosed arteries.

Though many non-Newtonian models of blood rheology have been used to simulate blood flow, the Carreau and Power-Law models have been commonly used in recent years (Cho and Kensey, 1990; Johnston et al., 2004; Seo et al., 2005; Murphy and Boyle, 2010; Morlacchi et al., 2011; Liu and Tang, 2011). In this study, two non-Newtonian models (Carreau and Power-Law) of blood are compared with the Newtonian blood flow presented in Sub-section 4.4.2. The Carreau model with viscosity-shear rate relation is given by
Equation 4.2.

\[ \eta = \eta_0 + (\eta_0 - \eta_\infty) \left[ 1 + (\lambda \dot{\gamma})^2 \right]^{\frac{1}{2}} \]  

(4.2)

where \( \eta_0 = 0.056 \text{ Pa} \cdot \text{s} \) is the zero shear rate viscosity, \( \eta_\infty = 0.00345 \text{ Pa} \cdot \text{s} \) is the infinite shear rate viscosity, \( \lambda = 3.313 \text{s} \) is a parameter, and \( x = 0.3568 \) is a dimensionless parameter (Cho and Kensey, 1990; Johnston et al., 2004; Liu and Tang, 2011). Power-Law model with viscosity-shear rate relation is given by Equation 4.3.

\[ \eta = \eta_0 (\dot{\gamma})^y \]  

(4.3)

where \( \eta_0 = 0.035 \text{ Pa} \cdot \text{s} \) and Power-Law index \( x \) equals to 0.6 (Cho and Kensey, 1990; Johnston et al., 2004; Liu and Tang, 2011). All other blood flow parameters are kept same as those in the Newtonian blood flow. Simulations are performed at the steady flow condition.

Figure 4.11 and Fig. 4.12 demonstrate the distribution of WSS along the luminal surface of Case 4 (Plaque1) and Case 10 (Plaque2) for three different models (Newtonian, Carreau, and Power-Law) of blood viscosity respectively. Among these three models, the Carreau and Newtonian models show close values of WSS distribution, whereas the Power-Law model gives much lower WSS values. This observation is consistent with the previous studies of Cho and Kensey (1990), Johnston et al. (2004), and Liu and Tang (2011) who reported that at high inlet velocities, the Newtonian and Carreau models are very similar, while Power-Law model produces much lower values of WSS.
Figure 4.12: Distribution of WSS along the luminal surface of Case 10 (Plaque2) for (a) Newtonian, (b) Carreau, and (c) Power-Law viscosity models of blood flow.

Notable difference was observed in the average magnitude of WSS in three blood models. The Carreau model predicted the highest WSS magnitude in comparison to the Newtonian and Power-Law models for all stenosis sizes. It is reported that the blood viscosity properties have a considerable effect on the magnitude of WSS, especially where the disturbed flow is observed. Liu and Tang (2011) showed that at regions of low (<1 Pa) WSS magnitude, the Newtonian model gives an underestimated WSS in stenotic coronary arteries. To examine this, a comparison of the percentage of luminal surface with WSS area (<0.5 Pa) is made among three models of blood viscosity. Table 4.3 presents the WSS (<0.5 Pa) values in Case 4 (Plaque1) and Case 10 (Plaque2) for one Newtonian blood model and two non-Newtonian (Carreau and Power-Law) blood models.

Table 4.3: Comparison of WSS (<0.5 Pa) values in Case 4 and Case 10 for Newtonian, Carreau, and Power-Law models of blood viscosity.

<table>
<thead>
<tr>
<th>WSS(&lt;0.5 Pa)(%)</th>
<th>Newtonian</th>
<th>Carreau</th>
<th>Power-Law</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 4</td>
<td>34.23</td>
<td>32.85</td>
<td>33.18</td>
</tr>
<tr>
<td>Case 10</td>
<td>29.09</td>
<td>27.54</td>
<td>27.95</td>
</tr>
</tbody>
</table>

At critically low values of WSS (<0.5 Pa), the Newtonian blood model overestimated by approximately 3% more than the other two non-Newtonian models, which give similar WSS values among each other. The differences between all three models are not significantly large; however, it is in contrast with the observation of Liu and Tang (2011) who reported that the Newtonian model underestimates WSS at the regions of low mag-
nitude of WSS (<1 Pa) in stenotic coronary arteries. This alteration may be related to the presence of stent and creation of TP between the stent struts.

4.5 Summary

The main idea of this part of the study was to investigate how the blood flow dynamics is influenced by the TP that happens in the post-stenting stage of coronary arteries. A complete computational analysis including the solid (artery) and fluid (blood) simulations is performed. This is accomplished by incorporating a symmetrical segment of expanded PS stent with various models of atherosclerotic arteries making in total of different 12 cases.

A 1/12th segment of expanded PS stent in circumferential direction is taken into account. The diseased coronary artery is modeled with equal width in circumference and thicknesses defined by two plaques each having six different cases. The coronary AW is extended further in the axial direction to represent the continuous artery and to avoid the geometry as a stand-alone segment. Twelve atherosclerotic vessel models represent different morphologies of plaque, NC and FC layers as defined in Chapter 3. Solid (deformation) simulation is performed where transmural pressures (generated during stent expansion) are calculated theoretically to produce realistic prolapse of the artery tissue around the stent struts. The lumen (flow domains) is created over the deformed luminal surface of all the twelve models. The blood is assumed to be Newtonian incompressible fluid and simulated by applying laminar inflow in the static condition. Stresses inside the vessel wall layers and over the luminal surface are measured and discussed.

The results from the solid simulations show that the TP is sensitive to the location of NC. Maximum prolapse was observed at regions where NC was located than in other regions of the vessel wall. The thinner FC would induce larger TP. Plaques having larger thickness of NC with thin FC layer would have maximum prolapse of the tissue. The distribution of stresses vary from layer to layer with the maximum in plaque (F) layer and minimum in AW layer. The thinner NC generates high stresses inside plaque layer. The stresses inside the NC layer elevates as the geometric distance reduces between the stent and NC. Similar to all other results presented in this thesis work, AW experiences the least amount of stresses with no sensitivity to the thicknesses of FC and NC.

Blood flow simulations demonstrated that the region with maximum TP is under high values of WSS. This is the region where NC is located. The range of WSS is affected by the stenosis size with severe stenosis generating higher values. The thickness of FC influenced the average WSS magnitude. Plaques with the thinner FC that are more likely to undergo large deflection caused higher values of average WSS. Maximum difference between the average WSS among twelve cases was approximately 5%. Also plaques with thicker NC resulted in high values of the WSS magnitude. The percentage of luminal surface area with WSS values less than 0.5 Pa is altered by stenosis size. Low values of WSS (<0.5 Pa) are more observed in relatively less severe stenoses reducing the risk of
restenosis. However, these values are not significantly influenced by the thicknesses of FC and NC. An additional analysis with non-Newtonian properties of blood confirmed that at high inlet velocities, Newtonian and Carreau models are similar, while Power-Law gives much lower values of WSS. At regions of low WSS, the Newtonian model overestimates WSS values than in non-Newtonian blood properties in post-stented flow.

The current 3D solid-fluid model revealed the effect of realistic TP on the stresses inside and on the surface of the vessel wall in the post-stenting stage. Variations in the results are clearly observed when the morphology of the vessel wall is changed. This approach of implementing the actual deformation obtained from various atherosclerotic vessel walls for measuring blood flow dynamics improves the physiological accuracy to a significant extent, which has been ignored in past studies. This should contribute to enhance the stenting technique and hence reduce the occurrence of restenosis.
4 Idealized 3D model of stent-plaque-artery-lumen
5 Conclusions

More and more people die every year from CVDs than any other diseases worldwide. CAD is the most common type of CVD caused by atherosclerosis. Coronary stenting is a widely accepted treatment procedure to re-open stenosed or blocked arteries. A stent is a mechanical device usually made of metals that is driven and expanded in the blocked areas and acts as a scaffold to keep the arteries open. The presence of a non-biological device inside an artery causes inflammation or re-growth of atherosclerotic lesions. Although the stenting has been a successful technique, it is often associated with the risk of restenosis.

Computational methods have widely emerged as essential and widely adopted tools for the assessment and optimization in the field of biomedical engineering. It has not only helped to compensate the limitations of clinical and experimental research, but also to acquire high accuracy in the outcomes. Numerous studies have demonstrated the factors affecting the rate of restenosis. Several researches have been performed to design the optimal shape of stent that would cause least arterial injury and help to sustain the removal of maximum blockage. On the other hand, many studies illustrated that the morphology of particular atherosclerotic tissue elevates the internal stresses that play a critical role in determining its vulnerability to provoke the process of restenosis. The extent of protrusion of arterial wall tissue created between the void spaces of stent alters the local fluid dynamics. Only few work have concentrated to build a direct link between the response of arterial tissue and the alteration of blood flow dynamics in the post-stenting stage. Moreover, not much attention is paid to the morphology of atherosclerotic arteries in these works.

In the presented work, an attempt is made to investigate stent-plaque-artery interactions in post-stenting stage where atherosclerotic coronary arteries are modeled as multi-layered (FC, NC, F, and AW) wall. The reported study is divided in three different parts. Each part discusses a separate model to assess and evaluate the post-stented stresses in stenosed coronary arteries.

1. In the first analysis, an idealized 2D axisymmetric model of stent-plaque-artery was formed. This computational model of stenosed coronary arteries consisted of a single layer of AW and multi-layer (FC, NC, and F) plaque presented at different stages of atherosclerosis by the percentage of stenosis. Stent was assumed to be a periodically repeated ring-like structure and atherosclerotic artery as a cylindrical tube. Simulations were performed only around a single stent strut. VMSs were presented inside the layers of the vessel wall and WSSs were discussed over the luminal surface of the vessel wall.

2. In the second analysis, FEA simulations were performed in 3D stent-plaque-artery model within a repeated unit of the stent. This model consisted of a homogeneous multi-layer (FC, NC, and F) plaque and a single layer of AW incorporated with the
stent cell geometry of the expanded 3D stent. 3D static simulations were performed for twelve separate models mimicking the atherosclerotic vessel with different morphologies. The maximum TP within the stent and the distribution of VMSs inside each individual layer were presented and discussed.

3. In the third analysis, a 3D fluid-solid model of stent-plaque-artery-lumen was proposed. Initially, the solid domain consisted of plaque with the presence of NC and a layer of AW incorporated with a 3D expanded PS stent. Solid simulations were performed in twelve models representing different morphology of atherosclerotic arteries. Then, the lumen was created over the deformed luminal surfaces where steady blood flow simulations were performed. The maximum TP around the stent strut, VMSs inside the vessel wall and WSSs over the luminal surface were reported.

The results from the idealized 2D axisymmetric model of stent-plaque-artery revealed that the FC thickness has a significant influence on the stresses within the layers of atherosclerotic vessel. The thick FC layer appeared to play a protective role by reducing the level of stresses within the next plaque NC, F, and AW layers regardless of the stenosis size. These results are in agreement with those presented by Finet et al. (2004). However, the VMS inside the FC layer was highly dependent on the stenosis size. The stresses elevated in the thinnest FC (∼27 µm) applied in this study, when the lumen of the 80% stenosed arteries was expanded to the diameter of a healthy diameter. This suggests that the higher pressures applied to the 80% plaque with very thin FC would induce a higher risk of vascular injury. The results of WSS agreed with the earlier finding that the insertion of stent reduces the WSS on the artery wall (Murphy and Boyle, 2010). They also confirm the influence of the strut thickness on the rate of restenosis. The WSS magnitude in the post-stenting stage was significantly affected by the pressures applied to open stenosed arteries. Various stenosis sizes when expanded to a fixed lumen diameter resulted in a similar magnitude and distribution of WSS regardless of the stenosis size, whereas the WSS magnitude rose remarkably with the severity of stenosis when a fixed pressure was applied to open several stenoses sizes. It is obvious that identical WSSs are obtained when the diameter and inflow conditions of the domain are similar, but in the post-stenting stage, the blood flow is driven by the deflection of the luminal surface within the stent. This deformation depends upon the force (acting from the artery to the stent) that is generated by the expansion pressure and the combination of morphology and material properties of the wall. In this 2D axisymmetric model, a single value of transmural pressure was applied to create the TP in all the stenosis sizes; however, the total wall thicknesses were different. This model is limited to the use of transmural pressure that is generated within the vessel wall during the expansion. The pressure applied for opening stenosed arteries do not represent the real values of clinical arteries. The balloon expansion of the stent was also not considered, and the initial stresses induced due to the stent expansion were ignored.

FEA simulations in a repeated unit of 3D stent showed the post-stented tissue deformation within the stent and the distribution of stresses in the distinct layers of atherosclerotic coronaries. It has been reported in previous studies that the TP within the stent cell is
directly affected by the design of the stent struts (Prendergast et al., 2003; Capelli et al., 2009). On the other hand, this study illustrated that the morphology of artery walls also influences the extent of TP. For a particular stent design, the severe stenosis size would lead to a higher prolapse. In general, a higher prolapse would mean lower scaffolding capability of the stent. Moreover, the size of NC had influences on the rate of TP though the difference among them was small. The TP was most sensitive to the thickness of FC. Plaques with the thinnest FC were most likely to have the maximum TP. The analyses of stress in the atherosclerotic arteries were consistent with the earlier findings (Gu et al., 2010) stating that the severe stenosis yields higher resultant arterial stresses. The distribution of stresses inside the diseased artery varied from layer to layer as reported in the 2D axisymmetric model. The maximum stresses concentrated in the FC layer irrespective of the stenosis, NC, and FC sizes in all twelve cases. This behaviour can be expected as the stent insertion elevates internal stresses with, the FC layer, direct in contact with the stent. The stresses declined dramatically in the following next layer, NC. The fibrous layer (FC and F) composed of stiff material surrounding the soft NC absorbed high stresses and inhibited its transmission to the NC layer. The stresses inside NC were elevated in the plaques with the thinner FC. Morphologically, the thinner FC means smaller distance between the NC and luminal surface that is in contact with the stent. This 3D stent-plaque-artery model describes how the morphology influences the TP and stress distribution in distinct layers of atherosclerotic arteries. Moreover, it determines the role of each individual wall layer that helps to determine its vulnerability to restenosis. However, this model was limited to the idealized and homogenous assumptions of the atherosclerotic plaque geometry.

Previous two experiments made it clear about the impact of tissue deformation and their dependency on the arterial wall morphology when evaluating stresses in the post-stenting stage. Thus, a sequential 3D fluid and solid model was introduced with more realistic conditions. Unlike in previous experiments where the NC was a homogenous layer, solid (artery) body deformation revealed that the TP was sensitive to the locations of NC. The maximum prolapse of the plaque tissue along the stent occurred rather at the location of NC than any other regions. Plaques with larger thickness of NC and a very thin FC layer were more likely to undergo maximum prolapse. These results were consistent with the TP measured in the repeated unit of 3D stent (Chapter 3). The stresses in the fibrous layer (F) of plaque were significantly raised when the NC was thicker. As discussed earlier (results in Chapter 3), the fibrous layers of plaque absorb the maximal amount of stresses allowing least stresses to penetrate through the NC. Under identical conditions, plaques with larger mass of NC would mean relatively less mass of fibrous layer causing stresses to elevate in it. This is in agreement with the findings of Akyildiz et al. (2011) who reported the effects of plaque morphology on stresses. However, in this work, the stent was not included, and simulations were performed in the cross-sections of the artery. Deflection of the tissue in post-stenting significantly affected the distribution of WSS. The regions with the maximum prolapse experienced high magnitudes of WSS. Plaques with thinner FC that underwent larger deflection raised the WSS magnitude. In addition, WSS was also influenced by the stenosis size where severe stenosis resulted higher values. On
the contrast, regions with low values of WSS ($<0.5$ Pa), which are important in determining the risk of restenosis, were affected by the stenosis size with severe stenosis under higher risk of developing restenosis. In the post stented flow, the estimation of WSS varied among the Newtonian and non-Newtonian viscosity model of the blood properties.

By summarizing the thesis, it can be concluded that the morphology of atherosclerotic artery has a critical role in regulating the process of restenosis in the post-stenting stage. The finding revealed that each layer of the diseased coronary artery has a distinct response to the stent insertion and their contribution in altering the post-stented hemodynamics. In addition, the impact of the stenosis size, strut profiles, expansion pressures, and time-dependent flow were extensively discussed. This thesis presented a unique computational approach to assess the post-stented stresses. The findings will enhance the existing knowledge and thus contribute to the better understanding of the restenosis. However, the work in this thesis is limited to the idealized and simplified assumptions of the arterial anatomy.
6 Future suggestions

The reported work was performed in several diseased coronary arteries to assess post-stented stresses. The results revealed the significance of various geometrical compositions of stenosed artery and their role in inducing the stresses that contribute to restenosis. However, as a limitation to the current work, some future suggestions are listed below.

- **Evaluation of oscillatory shear index**: As the blood inflow in coronary arteries is pulsatile in nature, more time-dependent simulations need to be performed. In addition to WSS, quantities like wall shear stress gradient (WSSG) and oscillatory shear index (OSI) must be evaluated to determine the risk of neo-intimal hyperplasia (excessive growth of new tissue), which is an essential cause to restenosis in stented arteries.

- **Two-way coupling between the artery and blood flow**: It is a fact that the pulsatile flow conditions exert pressure on the arterial walls and as a result distended artery drives the blood flow making an inter-dependent relation. In this reported work, the blood flow is simulated around the distorted walls of arteries, which represents the one-way effect. Moreover, there is a need for simulations considering the effect of blood pressure on the rate of arterial wall distension to have a complete two-coupling in real time.

- **Variable mechanical properties of arterial wall**: Studies have demonstrated that the mechanical properties of arterial wall change during the progression of atherosclerotic plaque. However, in this work, only geometrical parameters were varied while keeping the materials of artery wall constant with the development of plaque. A model linking the growth of plaque (stenosis size) and the corresponding changes in the mechanical properties of the wall shall be considered.

- **Multi-layer plaque model with different stent configurations**: It is been well demonstrated that the stent design is one of the key factors influencing the TP and local hemodynamics. Current multi-layered atherosclerotic plaque model must be tested with different stent configuration to make wider and concrete conclusions.

- **Simulations in full 3D (stent-plaque-artery) models**: The models implemented in this work were localized within a certain region of the artery, and hence, the geometries of plaque layers were considered homogeneous in the circumferential direction. However, real plaques are quite often eccentric in shape. Thus, simulations need to be performed with a complete 3D shape of plaque along with the full length of coronary arteries including the tapering effect at the distal end.

- **Simulations in the realistic anatomy of arteries**: The simulations reported in this work were performed in an idealized geometry of atherosclerotic arteries. The assumptions of symmetry for simplification may produce a comprised accuracy in the results. Mansuri et al. (2012) showed the variations in estimating WSS between
idealized and the geometries reconstructed from CT images. Although it is a challenging task, simulations with realistic geometries shall be performed for improved precision in the results where the local details are of utmost importance.
References


555. HEINONEN, JARI. Chromatographic recovery of chemicals from acidic biomass hydrolysates. 2013. Diss.

556. HELLSTÉN, SANNA. Recovery of biomass-derived valuable compounds using chromatographic and membrane separations. 2013. Diss.


559. GRÖNMAN, KAISA. Importance of considering food waste in the development of sustainable food packaging systems. 2013. Diss.


561. NISULA, ANNA-MAIJA. Building organizational creativity – a multitheory and multilevel approach for understanding and stimulating organizational creativity. 2013. Diss.

562. HAMAGUCHI, MARCELO. Additional revenue opportunities in pulp mills and their impacts on the kraft process. 2013. Diss.


565. RAHIALA, SIRPA. Particle model for simulating limestone reactions in novel fluidised bed energy applications. 2013. Diss.

566. VIHOLAINEN, JUHA. Energy-efficient control strategies for variable speed controlled parallel pumping systems based on pump operation point monitoring with frequency converters. 2014. Diss.


568. SEMYONOVOV, DENIS. Computational studies for the design of process equipment with complex geometries. 2014. Diss.

569. KARPPINEN, HENRI. Reframing the relationship between service design and operations: a service engineering approach. 2014. Diss.
572. RIUNGU-KALLIOSAARI, LEAH. Empirical study on the adoption, use and effects of cloud-based testing. 2014. Diss.
573. KINNARINEN, TEEMU. Pressure filtration characteristics of enzymatically hydrolyzed biomass suspensions. 2014. Diss.
574. LAMMASSAARI, TIMO. Muutos kuntaorganisaatiossa – tapaustutkimus erään kunnan teknisestä toimialasta. 2014. Diss.
576. LANKINEN, JUKKA. Local features in image and video processing – object class matching and video shot detection. 2014. Diss.
577. AL-SAEDI, MAZIN. Flexible multibody dynamics and intelligent control of a hydraulically driven hybrid redundant robot machine. 2014. Diss.
578. TYSTER, JUHO. Power semiconductor nonlinearities in active du/dt output filtering. 2014. Diss.
580. ALEXANDROVA, YULIA. Wind turbine direct-drive permanent-magnet generator with direct liquid cooling for mass reduction. 2014. Diss.
581. HUHTALA, MERJA. PDM system functions and utilizations analysis to improve the efficiency of sheet metal product design and manufacturing. 2014. Diss.
582. SAUNILA, MINNA. Performance management through innovation capability in SMEs. 2014. Diss.
583. LANA, ANDREY. LVDC power distribution system: computational modelling. 2014. Diss.
584. PEKKARINEN, JOONAS. Laser cladding with scanning optics. 2014. Diss.
585. PELTOMAA, JYRKI. The early activities of front end of innovation in OEM companies using a new FEI platform as a framework for renewal. 2014. Diss.
587. PHAM, THUY DUONG. Ultrasonic and electrokinetic remediation of low permeability soil contaminated with persistent organic pollutants. 2014. Diss.
588. HOKKANEN, SANNA. Modified nano- and microcellulose based adsorption materials in water treatment. 2014. Diss.
591. IKÄHEIMONEN, TUULI. The board of directors as a part of family business governance – multilevel participation and board development. 2014. Diss.