Development of a Novel Numerical Platform for the Assessment of Atherosclerotic Plaque Vulnerability

by

Mehrdad Zareh Bannad Kouki

B.Sc., Sharif University of Technology, 2014

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF APPLIED SCIENCE

in

THE COLLEGE OF GRADUATE STUDIES

(Mechanical Engineering)

THE UNIVERSITY OF BRITISH COLUMBIA

(Okanagan)

February 2016

© Mehrdad Zareh Bannad Kouki, 2016
Abstract

It is well known that mechanics of atherosclerotic plaques significantly depend on plaque geometry, location, composition, and loading conditions. Computational studies have shown great potential to characterize this mechanical behavior. Different types of plaque morphologies and mechanical properties have been used in two-dimensional (2D) and three-dimensional (3D) computational platforms mostly based on the finite element method to estimate the stability of rupture-prone plaques and detect their locations.

It is well-known that 2D models are not reliable as they do not provide a consistent assessment on the vulnerability of plaques and are highly erroneous. 3D models offer a more effective evaluation but creating 3D models to be further assessed by computational means such as the finite element method is time-consuming. However, 2D models are easier to develop and are less time-consuming to assess. In this thesis, a novel computational platform was developed by which the plaque vulnerability is assessed using only 2D plaque models.

We develop idealistic 2D models and their corresponding idealistic 3D models. The idealistic 3D models resemble the worst- and best-case scenarios for each 2D model. Using these 3D idealistic models, a standard error (SE) is estimated and then added to the peak stress values calculated earlier using 2D models. These SEs are also used to assess the probability of plaque stability. In this platform, the effect of viscoelasticity and anisotropy of the plaque composition is taken into consideration and the transmural pressure considered is similar to that of physiological conditions. Also, for the first time heart rate (HR) was introduced as a major predictor of vulnerable plaque ruptures that should be taken into account while mechanics of plaques is studied. A tunable viscoelastic constitutive material model was developed for the fibrous cap tissue in order to calculate the peak cap stress (PCS) in normal
physiological conditions while HR changes from 60 bpm to 150 bpm. A critical discussion on stress distribution in the fibrous cap area is made with respect to HR. Results strongly suggest the viscoelastic properties of the fibrous cap tissue and HR together play a major role in the estimation of the PCS values. The results obtained in this thesis may provide a better understanding of the mechanics of atherosclerosis.
All of the presented research henceforth was conducted in the University of British Columbia (UBC), HVPL Lab, in the School of Engineering under supervision of Dr. Mohammadi and Dr. Naser.

All aspects of this thesis, including literature review, method, data collection and analysis was performed by the author of this thesis.

A version of Chapter 3, 4 and 5 has been published in the journal of Cardiovascular System [Zareh M, Fradet G, Naser G, Mohammadi H. Are two-dimensional images sufficient to assess the atherosclerotic plaque vulnerability: a viscoelastic and anisotropic finite element model. Cardio Vasc Syst. doi: http://dx.doi.org/10.7243/2052-4358-3-3]. I was responsible for data collection, analysis and interpretation, as well as the majority of manuscript composition.

A version of Chapter 3, 4 and 5 has been submitted to the Journal of Biomechanics [Zareh M, Naser G, Fradet G, Mohammadi M. A Novel Finite Element Model on the Assessment of the Vulnerability of Atherosclerotic Plaques. J of Biomechnic. Submitted BM-D-15-01246]. I was responsible for data collection, analysis and interpretation, as well as the majority of manuscript composition.
# Table of Contents

Abstract........................................................................................................................................... ii  
Preface................................................................................................................................................ iv  
Table of Contents.............................................................................................................................. v  
List of Tables...................................................................................................................................... vii  
List of Figures..................................................................................................................................... ix  
List of Abbreviations......................................................................................................................... xiii  
Acknowledgment............................................................................................................................... xiv  
Dedication............................................................................................................................................ xv  

## Chapter 1: Introduction.................................................................................................................. 1  
1.1 Atherosclerosis and Atherosclerotic Plaques......................................................................... 1  
1.2 Research Motivation................................................................................................................. 2  
1.3 Research Objective.................................................................................................................. 5  
1.4 Contribution of Thesis............................................................................................................. 5  
1.5 Thesis Outline.......................................................................................................................... 6  

## Chapter 2: Background.................................................................................................................. 7  
2.1 General...................................................................................................................................... 7  
2.2 Formation and Rupture of Atherosclerotic Plaque................................................................. 8  
2.2.1 Plaque Formation.............................................................................................................. 8  
2.2.2 Plaque Rupture................................................................................................................. 9  
2.2.3 Thrombosis...................................................................................................................... 9  
2.3 Detection of Vulnerable Plaque.............................................................................................. 9  
2.3.1 Visualization of Plaque Composition.............................................................................. 11  
2.3.2 Computational Techniques............................................................................................. 12  

## Chapter 3: Method (The Finite Element Analysis)....................................................................... 17  
3.1 General...................................................................................................................................... 17  
3.2 Modeling Strategy..................................................................................................................... 19  
3.2.1 Geometrical Models of Atherosclerotic Plaques............................................................. 20  
3.3.2 Constitutive Model for Plaque Components.................................................................. 23  
3.3.3 Boundary Conditions....................................................................................................... 28
Chapter 4: Results

4.1 General

4.2 Validation Study

4.3 Mesh Independency Study

4.4 Effect of Viscoelasticity of Fibrous Cap

4.5 Assessment of the PCS in the idealistic 2D Models

4.6 The Assessment of the PCS in the Idealistic 3D Models

4.7 Effect of Viscoelastic Fibrosis on the PCS

4.8 Data Obtained from Patients

4.8.1 Application on Data Obtained from Patients

4.9 Effect Heart Rate Elevation on Peak Cap Stress

4.9.1 Heart Rate effect on Peak Cap stress Inside Idealistic Models

4.9.2 Heart Rate Effect in Realistic Models

4.9.3 Comparison of PCS Increase for Different Hear Rate Elevation

Chapter 5: Conclusion

5.1 Summary

5.1.1 Vulnerability Assessment Based on 2D Images

5.12 Heart Rate Effect

5.2 Future Work

References
List of Tables

Table 2.1  A short list of finite element structural studies on vulnerability of atherosclerotic plaques .............................................................. 15
Table 3.1  Mechanical properties of fibrous cap. θ represents the circumferential direction, r, the radial direction and z, the axial direction ................. 24
Table 3.2  Elements of time Prony series as considered for the high viscoelastic model .................................................................................. 27
Table 3.3  Elements of time Prony series for plaque with low viscosity .................. 28
Table 3.4  Tabular data for dynamic pressure ........................................................ 29
Table 3.5  Number of elements and mesh model specifications in each model .......... 31
Table 4.1  Material properties used in the validation study - Arterial wall and fibrous cap are defined by anisotropic elastic material model and necrotic core is assumed to be an isotropic and quasi-incompressible material ..................................................................................34
Table 4.2  Mesh independency study, the PCS for each model along with the number of elements used are shown in row A and B. In row B, models were meshed with more elements in comparison with models in row A. Results show an acceptable range for discrepancy of PCS in each plaque model; thus, the mesh models employed in row A are sufficiently precise to be used for our computational approach. Also, results are time dependent due to time-dependency of the material properties and pressure. In this pre-study, results of PCS at t=0.2s have been considered for this comparison. *S denotes the sphere-like models and *C the cylinder-like models ......................................................... 35
Table 4.3  Comparison of 2D models results with 3D models ................................. 40
Table 4.4  Comparison of estimated PCS in models with pure elastic and viscoelastic material. As it can be seen in the table, PCS in models with pure elastic material is higher than PCS in models with Viscoelastic material. PCS at t=4.2s has been considered for this comparison. * S for sphere-like models and C for cylinder-like models.

Table 5.1  The platform by which the PCS2D is used for plaque stability risk assessment. The lower and upper limits are calculated using idealistic 3D models explained earlier.
List of Figures

Figure 1.1 Atherosclerotic plaque in the coronary artery, blue line shows the bloodstream.................................................................2

Figure 2.1 Illustration of different sections of arterial wall and plaque components: (a) healthy Artery, (b) artery with atherosclerotic plaque; as it can been seen, plaque builds up within intima layer.................. 10

Figure 2.2 Plaque rupture and formation of thrombosis.................................................. 10

Figure 3.1 This figure shows a typical geometrical model (right) developed on a histology image of an atherosclerotic plaque................................. 20

Figure 3.2 A, B, C, D: Selected IVUS images which are the representative of all types of plaque morphologies. This classification is based on the geometry of the fibrous cap which is considered to be: nodal (A), linear (B,C), and curve-linear (D), and the corresponding idealistic models are defined as: E (nodal), F (linear) and G (curve linear) (9). Cap thickness=70 μm and/or 100 μm); F, fibrous cap; NC, necrotic core................................................................. 21

Figure 3.3 The 3D idealistic models corresponding to each 2D idealistic model. In each group, cross sections of 3D models are identical to their corresponding 2D models. NC, necrotic core; FC, fibrous cap................. 22

Figure 3.4 Illustration of the linear physical models used to describing behaviour of viscoelastic materials. A, Maxwell Model; B, Kelvin-Voight Model; C, Standard Linear Solid; D, Wiechert Model. E and η refers to elastic and viscous part of the model, respectively. E∞ and Em refers to the elasticity at infinite time and elasticity of Maxwell arm, respectively. σ represents the stress (load) imposed on the system................................. 25

Figure 3.5 Illustration of the boundary conditions.......................................................... 29

Figure 3.6 Dynamic blood pressure in heart rates of 60, 90, 120, 150 bpm.................. 30
Figure 3.7 This figure shows the mesh models in 2D and 3D models. In 3D models, Necrotic core and some parts of fibrous cap were hidden to reveal the mesh density in critical zone.

Figure 3.8 Right: normal and shear stresses imposed on a three-dimensional element. Left: normal and shear stresses imposed on a two-dimensional element. Note that shear stresses for three- and two dimensional models follow these rules:

\[ \sigma_{xy} = \sigma_{yx}, \quad \sigma_{xz} = \sigma_{zx}, \quad \sigma_{yz} = \sigma_{zy} \] and \( \tau_{xy} = \tau_{yx} \)

Figure 4.1 This figure illustrate the geometrical model and boundary conditions (A, outer wall fixed in radial direction; B, blood pressure of 18 kPa) used in a study by Ohayon (1). FC, fibrous cap; NC, necrotic core; L, lumen.

Figure 4.2 The validation study: (A) The mesh model by Ohayon et al, (B) The mesh model in the current study, (C) The stress distribution and the peak cap stress (PCS) obtained by Ohayon et al. (2), and (D) The stress distribution and the peak cap stress obtained in the current study. For the current model, the PCS is 378 kPa which is 2 kPa larger than the computed PCS in that study. This small discrepancy may be because of the differences in the mesh models.

Figure 4.3 a) The variation of PCS for viscoelastic fibrous cap for a typical plaque. When \( t=0.2 \) s the PCS is maximum (cycle 1) which is considered numerical artifact. The actual PCS is considered when the peak stresses are settled (after cycle 4).

Figure 4.4 The PCS and stress distribution in idealistic 2D models, Cap thickness=70 µm. F, fibrous cap; NC, necrotic core.

Figure 4.5 Stress distribution in the idealistic 3D models. Figs. A, B and C provide the lower limit regarding models in Figs. 1E, 1F, and 1G, respectively, and Figs. D, E, and F provide the upper limit regarding models in Figs. 1E, 1F, and 1G, respectively. Some parts of models are intentionally hidden for better exhibition of critical regions. FC, fibrous cap; NC, necrotic core; L, lumen.
Figure 4.6  The range of safe value for PCS (green bar) and the total range of PCS (yellow bar). Comparison between the length of yellow bar outside and inside of green bar presents practical information about probability of rupture in a plaque. In all of these models, plaque is more likely to be stable due to the greater stability probability than that of instability.

Figure 4.7  Images A, B, C, and D, show the 2D geometry of the data obtained from patients. The yellow region indicates the necrotic core area and the purple region exhibits the fibrous tissue. The thickness of fibrous cap for each case is denoted as “Thk.” Using the proposed computational platform the PCS related to each case is calculated. FC, fibrous cap; NC, necrotic core; L, lumen.

Figure 4.8  Illustration of the results obtained through idealistic models. LV and HV refer to high and low viscoelastic properties of the fibrous cap tissue, respectively. (a) shows the values of PCS for the idealistic models when cap thickness is set to 70 μm, and (b) shows the values of PCS in the idealistic models when the cap thickness is set to 100 μm. F, fibrous cap; NC, necrotic core.

Figure 4.9  This figure illustrates the patient-oriented geometrical models used in this study and their estimated PCS values through both HV and LV materials (LV and HV refer to high and low viscoelastic properties of the fibrous cap tissue, respectively); The imaging modalities used in this study are IVUS & OCT combined (models A, B, and C) and histology (models H1, H2, H3, and H4) (4-7). In cad models (second row); blue: fibrous tissue, yellow: necrotic core and red: calcified regions.
Figure 4.10  The comparison of values of PCS to that obtained when HR=60 bpm for both idealistic and realistic models. Two thicknesses and two viscoelastic models are considered for the idealistic models (Figure 4.8a, b), and all realistic models (Figure 4.9c). LV and HV refer to low and high viscoelastic material properties for the fibrous cap tissue, respectively.

Figure 5.1  Increase in PCS values due to degree of viscoelasticity of the fibrous cap tissue and HR. Blue bar shows the increase in PCS moving from elastic model to low viscoelastic model for the fibrous cap tissue when HR=60 bpm, red bar shows the increase in PCS moving from elastic model to high viscoelastic model for the fibrous cap tissue when HR=150 bpm.
List of Abbreviations

AMI	Acute Myocardial Infarction
CFD	Computational Fluid Dynamics
CT	Computed Tomography
FE	Finite Element
FSI	Fluid-Structure Interaction
HR	Heart Rate
IVUS	Intravascular Ultrasound
LDL	Low-Density Lipoprotein
MD	Molecular Dynamics
MRI	Magnetic Resonance Imaging
NC	Necrotic Core
OCT	Optical Coherence Tomography
PCS	Peak Cap Stress
SE	Standard Error
SMCs	Smooth Muscle Cells
WSS	Wall Shear Stress
Acknowledgment

I would like to express my sincere thanks to Dr. Mohammadi and Dr. Naser for their encouragement and support over the last year. It would be impossible for me to work through this research without their invaluable guidance.

My especial thanks to my committee members for their priceless comments on my thesis and for serving in my defense meeting despite their busy schedule.

I would like to express my deepest grateful to my family and my friends for their support and their kind friendship during my graduate studies.
Dedication

To My Parents
Chapter 1: Introduction

1.1 Atherosclerosis and Atherosclerotic Plaques

Atherosclerosis is a chronic, progressive syndrome where plaques are developed in the walls of arteries. A plaque consists of deposits of cholesterol and other lipids, calcium, and large inflammatory cells known as macrophages. Several problems can be caused by these plaques, including:

- Plaques can accumulate inside the artery and completely and partially obstruct blood flow,
- Plaques can suddenly rupture, forming a thrombus or blood clot leading to sudden blockage of the artery, and
- Plaques can deteriorate the wall of the artery and cause the arterial wall to lose stiffness. This may cause radial expansion of the artery and develop an aneurysm. The bursting of an aneurysm frequently leads to severe internal bleeding.

A typical atherosclerotic plaque in the left coronary artery is shown in Figure 1.1.

Three zones are identifiable in each plaque:

- The atheroma, which is a burden of soft and yellowish jelly-like material at the center of a large plaque. In other words, the atheroma is the degeneration of arterial walls due to accumulation of fatty deposits and scar tissue,
- Primary areas of cholesterol crystals
- Calcified nodules in more advances plaques.
For simplicity, atherosclerotic plaques are sectioned into two major parts: fibrosis, also known as fibrous cap, and lipid core (necrotic core). The fibrous cap is a separating layer between the necrotic core and blood stream. Rupture of this layer in vulnerable plaques cause necrotic core substances into the blood stream, leading to clot formation inside the coronary or carotid arteries. This may cause an acute blockage of arteries in the heart or brain.

1.2 Research Motivation

The primary reason of major morbidity and mortality in majority of countries around the world is atherosclerotic cardiovascular disease (3). This disease is most commonly caused by thrombotic blockage of a high-risk coronary plaque leading to myocardial infarction or cardiac death, or embolization from a high-risk carotid plaque leading to stroke. The lesions prone to result in such clinical issues are known as vulnerable or high-risk plaques, and their
identification may result in the development of mechanical or pharmacological intervention strategies to prevent such issues.

Autopsy investigations from patients who died of acute myocardial infarction (AMI) or sudden death have suggested that such issues usually arise from particular classes of atherosclerotic plaques, most often the thin-cap fibroatheroma (4, 5). Recently, it has been suggested that coronary plaques that are possible to cause future cardiac issues, regardless of angiographic severity, are characterized by a relatively small lumen area, a large plaque burden, and/or thin-cap fibroatheromas (6, 7). It should be noted that plaque morphology is usually determined using imaging techniques by which the morphology of lumen area, plaque burden and fibrous cap in plaque sections are characterized. Given the importance of imaging techniques, identifying supplementary invasive and non-invasive imaging modalities may improve detection of high-risk atherosclerotic plaques.

This thesis focuses on mechanical strategies to detect vulnerable plaques. Mechanical failure of a thin fibrous cap of an atherosclerotic plaque can easily lead to AMI and angina. Even though multiple clinically effective therapies are available for restricting infarction size, such as thrombolytic therapy, acute-adrenergic blockade, and acute mechanical intervention, the ability to detect unstable and culprit atherosclerotic plaques prior to rupture is of particular significance. Available computational models developed on the biomechanics of atherosclerosis are implemented to compute stress and strain distributions in an intended plaque. These models are either two-dimensional (2D) or three-dimensional (3D) in which the regions of necrotic core, fibrous cap, and calcific nodules are clearly identifiable. The likelihood of mechanical properties of the plaque regions, i.e., fibrous cap, necrotic core, and calcific nodules, are available. However, accurate mechanical properties during the
atherosclerosis progression are still unknown. The conventional material models used in 2D and 3D finite element (FE) models are mostly homogeneous, isotropic, and the pressure wave (internal blood pressure or transmural pressure) passing through the plaques is considered steady-state. The current “gold standard” for determining plaque stability in FE models is a maximum allowable circumferential stress in the fibrous cap area which is considered 300 kPa (8). This criterion has been characterized by a fibrous cap thickness of 70 microns in 2D plaque models (9). It is known that 2D models are less consistent as they are not accurate, do not provide a reliable assessment on the vulnerability of plaques and are highly erroneous. 3D finite element models offer a more effective evaluation, but generating 3D models to be further studied by computational means is time-consuming. In contrast, 2D models are much easier to develop and are less time-consuming to assess. Despite numerous computational studies which have employed various material properties to detect characteristics of vulnerable plaques, an effective model which takes into account realistic material in accurate physiological conditions is yet to be developed.

Material models and loading conditions as applied in FE models of plaques need to be improved. It is well understood that the atheroma is viscoelastic in nature (10). Also, the physiological pressure wave, known as the systemic blood pressure or the transmural pressure is time-varying. It is hypothesized that dynamic stresses obtained in new conditions in the fibrous cap tissue are significantly different than static stresses obtained in steady-state conditions, which are considered conventionally. In other words, heart rate (HR) might be influential in the assessment of the mechanics of plaques, given that the plaque composition is considered to be viscoelastic. By considering realistic viscoelasticity for the atheroma in realistic physiological conditions, a novel computational platform is proposed based on the
nonlinear finite element method in order to provide more insight into the biomechanics of atherosclerotic plaque rupture.

1.3 Research Objective

In this thesis, a novel computational platform is proposed where the plaque vulnerability is assessed using only 2D plaque models. The advantage of the proposed platform is to take advantage of the availability of 2D plaque models and the precision of 3D models at the same time. In the first step, idealistic 2D models and their corresponding idealistic 3D models are developed. The idealistic 3D models are designed to resemble the worst- and best-case scenarios for each 2D model. Using these 3D idealistic models, a standard error (SE) is estimated and then added to the peak stress values calculated earlier using the 2D models. These SEs are also used to assess the probability of plaque stability for the first time.

In this platform, the effect of viscoelasticity and anisotropy of the plaque composition is taken into consideration. As well, the transmural pressure considered is similar to that of physiological conditions (dynamic pressure). For the first time, heart rate is introduced as a major predictor of rupture-prone plaques, emphasizing the plaque composition must be considered viscoelastic. The current study may suggest a more realistic insight to the prediction of atherosclerotic plaques rupture using 2D images.

1.4 Contribution of Thesis

The major contributions of this thesis include the following:
(1) A novel computational FE based platform for the detection of vulnerable plaques using 2D images;

(2) An explanation of how viscoelastic properties of the fibrous cap tissue and HR together can influence the mechanics of the atherosclerotic plaques

(3) An explanation of how dynamic stresses obtained in this thesis are significantly more important than static stresses obtained in steady-state conditions that are considered conventionally;

(4) Applying the proposed platform on data obtained from patients demonstrating the effectiveness of the proposed platform.

1.5 Thesis Outline

This thesis is organized in 5 chapters.

In chapter 2, the formation and rupture of atherosclerotic plaque is described and a summary of previous studies on plaque vulnerability assessment, including methods and results, is provided.

In chapter 3, methods and techniques used in this study will be described.

In chapter 4, results are illustrated in tables and figures containing numerical data obtained through our proposed FE models.

In Chapter 5, conclusions and limitations are presented, and as well, subjects for future work will be discussed.
Chapter 2: Background

2.1 General

Acute myocardial infarction (AMI) is caused by coronary thrombosis, which is mainly due to the rupture of vulnerable plaques (11-13). Plaques with vulnerable morphology are located at multiple sites on the coronary tree. Thus, accurately identifying plaques with the highest risk of rupture is of crucial importance. The detection of vulnerable plaques prior to rupture would considerably reduce the occurrences of AMI. Despite substantial efforts towards the early detection and therapy of unstable coronary plaques, AMI still remains the leading cause of death worldwide (14, 15). A comprehensive set of imaging-based studies indicate that vulnerable plaques at the site of thrombosis are frequently characterized by a thin fibrous cap (16) and a large necrotic core (17). However, studies have shown that intracoronary diagnostic approaches based solely on the evaluation of plaque morphology and composition may be insufficient (16). The main issue with imaging methods is that prediction of plaque rupture requires not only an accurate assessment of the plaque morphology, but also a precise knowledge of the mechanical properties of the plaque constituents at any given stage of the atherosclerotic progression. Plaque rupture is a mechanical incident that occurs when the amount of stress in the plaque exceeds a critical value. Therefore, techniques that measure or calculate the stress distribution in the plaque provide important surrogate metrics of plaque instability. The overall goal of this dissertation is to develop and implement a more realistic computational platform using the FE method to enable the measurement or estimation of
peak stress inside the atherosclerotic plaque. This will potentially facilitate detection of vulnerable plaques with the highest propensity to rupture in patients.

2.2 Formation and Rupture of Atherosclerotic Plaque

2.2.1 Plaque Formation

The term, “plaque formation” is widely used to describe the accumulation of low-density lipoprotein (LDL) cholesterol\(^1\), monocytes\(^2\), macrophages\(^3\) and foam cells\(^4\) at a place of inflammation inside arterial walls, causing atherosclerotic diseases (22). Lipid core and fibrous cap are the two terms commonly used for the identification of major constituting parts of atherosclerotic plaques (Figure 2.1). The lipid core comprises of debris from dead cells, esterified cholesterol and cholesterol crystals. The fibrous cap contains smooth muscle cells (SMCs) and collagen\(^5\) fibers (21, 23).

---

1 Low-density lipoprotein is one type of lipoproteins, which transfer fats like cholesterol through the blood. LDL can transfer fat substances into the artery wall and then, by attracting macrophages, initiate atherosclerosis (18, 19).
2 Monocytes are a type of white blood cells and they have various roles in immune system. This cell can contribute to atherosclerosis progression by producing inflammatory molecules and metalloproteinase (20).
3 This cell is a type of white blood cells and its function is to digest foreign substance, microbes, etc. Breakdown of collagen networks by this cell leads to weak tissue in plaque, which increases the risk of rupture.
4 Monocytes are converted to macrophages after transporting into the subendothelial layer, then transform into foam cells (21).
5 Type I is the most abundant collagen in a human body. It is present in cornea, tendons, skin, artery walls, etc. In plaque, it helps stability by hardening the fibrous tissue.
2.2.2 Plaque Rupture

The fibrous cap and lipid core are two major parts of atherosclerotic plaque. The fibrous cap keeps thrombogenic core substances out of the bloodstream. A plaque rupture leads to leaking the lipid core substance into the blood via the structural gap in the cap (18).

These substances form a clot that may block the artery and cause a heart attack or brain stroke (19).

2.2.3 Thrombosis

Thrombosis is the obstruction of the bloodstream due to clot formation inside of blood vessels (Figure 2.2). Plaque rupture is known to be the most prevalent cause of thrombosis (24, 25). Plaque material found in thrombi supports this idea and proves the coincidence of rupture and thrombosis (18). Assessment of the time relationship between plaque rupture and onset of the syndrome is difficult, as rupture itself has no symptoms and the process of thrombosis is unpredictable (18). Observed plaque materials interspersed within the thrombus indicate that thrombosis may occur immediately after rupture (26, 27). Another possibility is dynamic response of thrombosis, as a layered thrombus can be developed over days. Blood may wash away and carry the thrombus, causing distal embolization of myocardial (18).

2.3 Detection of Vulnerable Plaque

The term “vulnerable plaque” has been extensively used in scientific resources as a definition for a plaque at high risk of rupture. Other terminologies, such as “instable plaque” and
Figure 2.1- Illustration of different sections of the arterial wall and plaque components: (a) healthy Artery, (b) artery with atherosclerotic plaque; as it can been seen, plaque builds up within intima layer (28, 29).

Figure 2.2- Plaque rupture and formation of thrombosis (29).

“rupture-prone plaque” have been also used interchangeably. This section explores the techniques applied for detection of vulnerable plaques.
2.3.1 Visualization of Plaque Composition

There are two main types of imaging modalities used for this purpose: (1) non-invasive techniques, and (2) catheter-based techniques. Non-invasive techniques such as magnetic resonance imaging (MRI) or computerized tomography (CT), are extensively used for the characterization and to some extent, the detection of rupture-prone plaques (30, 31). Catheter-based diagnostic techniques such as Intravascular Ultrasound (IVUS) and Optical Coherence Tomography (OCT), are known to provide a higher resolution for both the characterization and the detection of rupture-prone plaques compared to non-invasive techniques (31-34).

MRI is a non-invasive technique that uses magnetic fields and radio waves to produce images of the blood vessel structure. Cardiac MRI is consistent with other imaging techniques such as echocardiography, cardiac Computed Tomography (CT) and nuclear medicine. MRI has extensive applications in the assessment of myocardial ischemia and viability, myocarditis, cardiomyopathies, vascular diseases, congenital heart disease, and several others (35). However, MRI cannot be applied for the geometrical characterization in atherosclerotic plaques due to its constant motion (30, 31). Computed Tomography (CT) is also a non-invasive technique that applies computer-processed X-rays to generate tomographic images (known as virtual slices) of an intended area. While CT allows the user to visualize the inside of the vessel without cutting, it does not provide any estimate of the fibrous cap thickness due to its insufficient spatial resolution (31).

IVUS is a sound-based invasive technique. A customized catheter with an extremely small ultrasound probe attached to the distal end is sent to the intended destination. The proximal end of the catheter is connected to ultrasound equipment with a piezoelectric transducer. This
technology can capture inside of the vessel wall through to the surrounding blood column (32). IVUS is extensively implemented in the epicardial coronary arteries to measure the severity of an atherosclerotic plaque progression. Low resolution of images by IVUS (resolution of 100 μm), makes it impractical to precisely detect critical cap thicknesses (31). As a light-basis invasive technique, OCT uses low-coherence interferometry or near-infrared light. The implementation of relatively long wavelength light allows the light to influence into the scattering medium (33). In comparison with IVUS, the penetration depth of OCT is low. However, OCT provides images with much higher resolution in the range of 5 μm to 10 μm (14, 27). Furthermore, typical plaque constituents have different optical properties, OCT provides satisfactory contrast to distinguish between different parts of plaque such as lipid, calcium and fibrous tissue. The ability for microscopic analysis of different plaque components such as fibrous cap thickness, macrophage infiltration, and lipid content makes this technique a useful tool for assessing plaque structures (34).

### 2.3.2 Computational Techniques

Computational methods are complementary to the information obtained using imaging modalities. The role of mechanical properties of plaques’ constituents in the assessment of instability of rupture-prone plaques is only possible using computational methods. There are a few major computational models which have been extensively applied to assess the mechanics of atherosclerotic plaques: Computational Fluid Dynamics (CFD) models, Finite Element (FE) Structural Analysis, Fluid-Structure Interaction (FSI) models, and multiscale models. CFD models are applied to incorporate hemodynamic features such as blood-flow-induced wall shear stresses (WSS), on the endothelium into the mechanics of atherosclerotic
plaques (36-38). FE Structural Analysis provides a strong and flexible computational platform for the assessment of stress distribution within atherosclerotic plaques (39-47). Coupled CFD-FE Structural Analysis, also known as FSI models, might be used to assess the mechanics of atherosclerosis from both structural and hemodynamic standpoints (48-51). Multiscale models are fairly new in which the mechanical properties of the fibrous cap tissue are simulated using molecular dynamics (MD). The MD region is then integrated to the remaining regions, which are modeled using FE modeling (52). The main advantage of a multiscale platform is that the mechanical properties of the fibrous cap tissue can be developed more accurately. The collagen fibers, SMCs and macrophages concentration with respect to location can be incorporated into a more realistic constitutive material model.

Table 2.1 outlines the available computational models proposed in literature. The major issues with the available conventional models are:

1. The constitutive material models considered for the plaque composition are either elastic or hyperelastic in a way that viscous properties of plaques have been either overlooked or somehow oversimplified.

2. The proposed models were developed for steady-state conditions only.

Computational models are available in two- (2D) and three- dimensional (3D) platforms mostly based on FE Structural Analysis. It is known that 2D models are not reliable as they do not provide a consistent assessment on the vulnerability of plaques and are highly erroneous (42, 53, 54). While the 3D models are expected to offer a more realistic understanding, they are difficult to develop due to limitations of biomedical imaging techniques. In comparison, 2D models are easier to develop and more computationally efficient. This study proposes a novel computational platform by which the plaque
vulnerability is assessed using only 2D plaque models. First, three idealistic 2D models, representing different plaque morphologies, are created. Then, for each of these 2D models, two 3D models are developed such that they have similar cross section to their corresponding 2D model. The idealistic 3D models resemble the worst- and best-case scenarios for each 2D model. Using these 3D models, range of probable peak stress for each 2D model is estimated and a standard error (SE) is calculated, which can be used to estimate peak stress range for any 2D realistic plaque model obtained directly through biomedical imaging techniques.

SE is also used to assess the probability of plaque stability. In this platform, the effect of viscoelasticity and anisotropy of the plaque composition are considered. Moreover, the transmural pressure is studied similar to that of physiological conditions (dynamic pressure). The current study may suggest a more realistic insight to the prediction of atherosclerotic plaque rupture using 2D images.
Table 2.1 - A short list of finite element structural studies on vulnerability of atherosclerotic plaques.

<table>
<thead>
<tr>
<th>Researcher/year</th>
<th>Geometrical model</th>
<th>Material models</th>
<th>Blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veress et al. 1993 (40)</td>
<td>2D model</td>
<td>Isotropic Elastic Material</td>
<td>Static 16 kPa</td>
</tr>
<tr>
<td>Finet et al. 2004 (43)</td>
<td>2D model</td>
<td>Transverse Isotropic Elastic Material</td>
<td>Static 16-20 kPa</td>
</tr>
<tr>
<td>Ohayon et al. 2008 (41)</td>
<td>2D model</td>
<td>Anisotropic Elastic Material</td>
<td>Static 18.7 kPa</td>
</tr>
<tr>
<td>Akyilidiz et al. 2011 (39)</td>
<td>2D model</td>
<td>isotropic hyperelastic material model (neo-Hookean)</td>
<td>Static 15 kPa</td>
</tr>
<tr>
<td>Buffinton et al. 2014 (45)</td>
<td>2D model</td>
<td>isotropic hyperelastic (Mooney-Rivlin) and orthotropic elastic material</td>
<td>Static 18.7 kPa</td>
</tr>
<tr>
<td>Akyilidiz et al. 2015 (47)</td>
<td>2D model</td>
<td>isotropic hyperelastic material model (neo-Hookean)</td>
<td>Static 18.7 kPa</td>
</tr>
<tr>
<td>Ohayon et al. 2005 (42)</td>
<td>2D/3D model</td>
<td>orthotropic elastic material</td>
<td>Static 13.33 kPa</td>
</tr>
<tr>
<td>Kiousis et al. 2009 (35)</td>
<td>3D</td>
<td>anisotropic nonlinear material</td>
<td>Static 18.7 kPa</td>
</tr>
<tr>
<td>Cilla et al. 2012 (44)</td>
<td>3D model</td>
<td>isotropic and anisotropic hyperelastic material</td>
<td>Static 18.7 kPa</td>
</tr>
<tr>
<td>Cardoso et al. 2014 (55)</td>
<td>3D model</td>
<td>hyperelastic material (neo-Hookean, Mooney–Rivlin and Holzapfel models)</td>
<td>Not provided</td>
</tr>
</tbody>
</table>

It is well known that thin fibrous caps are severely inflamed and the percentage of macrophage density is as high as ~14% (56), which is even higher (>26%) for ruptured plaques. Since the fibrous cap tissue is thin, its ability to accommodate macrophages is very
low. Also, apoptosis in the fibrous cap tissue is limited to macrophages alone. This is due to
the amount of vascular SMCs decreasing to nothing throughout plaque progression until
rupture occurs (56). In other words, change in macrophages and SMCs density might lead to
change in viscous properties of the fibrous cap tissue (57-59). Given the viscous nature of the
thin fibrous cap area, heart rate is hypothesized to play a major role in assessing peak cap
stress (PCS). In this study, a tunable viscoelastic constitutive material model is proposed to
computationally assess PCS in the fibrous cap tissue with respect to HR in a 2D
computational platform. This model uses normal physiological (dynamic) conditions while
HR changes from 60 bpm to 150 bpm. A critical discussion on stress distribution in the
fibrous cap area is made with respect to HR for the first time. The results of current study
may provide a better understanding of the mechanics of atherosclerosis.
Chapter 3: Method (The Finite Element Analysis)

3.1 General

Despite a long history of research on detection and therapy of instable plaques, thrombus mediated ischemic cardiovascular disease still remains the leading cause of death in the world (14, 15). The rupture of instable atherosclerotic plaque in the coronary artery regularly results in a significant number of ischemic cardiovascular events. Conventional procedures for prediction of rupture based on imaging plaque morphology and composition (60, 61) still provides rather inaccurate and insufficient predictors of risk (62). The challenge for imaging methods is that prediction of the coronary plaque rupture requires not only an accurate quantification of fibrous cap thickness (41, 63) and necrotic core morphology (64, 65), but also a precise knowledge of the mechanical properties of the arterial wall and plaque components at any given stage of the atherosclerotic progression (66-69).

Finite element method have been extensively used to assess the effect of mechanical effects on instability of plaque rupture (10, 11, 35, 40, 44-47, 54, 65). Assuming a constant transmural pressure, in 1993, Verses et al. (40) developed a 2D FE model with linear isotropic material properties for plaque components. Despite their relatively successful model, unrealistic material properties defined for the plaque components were the major drawback in their study. In 2004, Finet et al. (43) proposed a 2D FE model with orthotropic material properties for plaque components and arterial wall. They studied the effect of fibrous cap thickness, lipid pool composition and blood pressure on instability of plaque rupture. This model provided more realistic mechanical properties to the plaque constituents.
but there is still room for improvement because the hyperelastic nature of the tissue was not taken into account. Akyildiz et al. (2011) developed a 2D FE model to study the effect of material properties and plaque morphology on stress distribution on the fibrous cap tissue (39). They considered isotropic and hyperelastic material model (neo-Hookean) for plaque components and anisotropic hyperelastic material model for arterial wall. This model was definitely a significant move forward, but it was still 2D and as well the material properties used were not realistic because viscous properties were lacking. Cilla et al. (2012) developed an idealistic 3D FE model with a nonlinear (hyperelastic) isotropic and anisotropic material for plaque components (44). They evaluated the effect of morphological factors and residual stresses on instability of plaque rupture. Recently, Cardoso et al. (2014) developed an idealistic a 3D FE model to assess the effect of calcified nodules on vulnerability of plaques. They applied three constitutive models of neo-Hookean, Mooney–Rivlin and Holzapfel for plaque components (55). In all proposed computational models: 1) viscous properties of atherosclerotic plaque constituents are either overlooked or somewhat oversimplified, and 2) the modeling is implemented for steady-state conditions.

The main aim of this study is to develop a novel computational platform, that improves the estimation of mechanical stresses applied on the fibrous cap under actual physiological loading conditions. In this dissertation, the fibrosis is assumed to be viscoelastic and the transmural pressure is considered to be dynamic.

It is well known that 2D models are not reliable as they do not provide a consistent assessment on the vulnerability of plaques and are highly erroneous. While 3D models offer a more realistic evaluation (42), creating such models is often computationally expensive. In contrast, 2D models are mathematically less complex and are more computationally efficient.
This dissertation offers a novel computational platform by which the plaque vulnerability is assessed using 2D models. In the first step, idealistic 2D models and their corresponding idealistic 3D models are developed. The idealistic 3D model resembles the worst- and best-case scenarios for the 2D model. The worst- and best-case scenarios are respectively referring to the most and least critical cases for plaque. Using these 3D idealistic models, a standard error (SE) is estimated and then added to the peak stress values obtained from the 2D models. The estimated standard errors are transformed to the probability of plaque stability and provide a risk of rupture for a rupture-prone plaque. Given the fibrous cap tissue has a viscous nature, the effect of heart rate is hypothesized to be significant and HR can be used as a new predictor along with others, such as necrotic core size and fibrous cap thickness, for plaque rupture. For the first time, it is proposed that viscoelastic properties of the fibrous cap and HR together play a major role in the estimation of the peak cap stress (PCS) values and, subsequently, in plaque vulnerability.

3.2 Modeling Strategy

This research uses stress distribution within plaque to assess plaque vulnerability as it is conventional in literature (7, 10, 11, 35, 39, 42, 44-47, 53, 54, 69). In order to solve the governing equations of plaque mechanics, FE method is employed. FE method requires the following steps:

- **Geometrical models:** to describe the domain on which the governing equations are solved. A typical geometrical model for plaque is illustrated in Figure 3.1.
- **Material properties (constitutive equations):** to define the physics of plaque constituents.
• **Boundary conditions**: which refer to the blood pressure on lumen wall and displacement of outer wall of plaque (see Figure 3.1).

![Figure 3.1](image)

Figure 3.1- This figure shows a typical geometrical model (right) developed on a histology image of an atherosclerotic plaque (47). NC, necrotic core; FC, fibrous cap

The following sections extensively present the finite element models used in this research.

### 3.2.1 Geometrical Models of Atherosclerotic Plaques

Geometry of atherosclerotic plaques is random due to the random shape of necrotic core, fibrous cap and other constituents of each plaque. In computational studies, idealistic models are sometimes used instead of realistic models (44, 55, 65). This is because using idealistic models showing a particular technical point can be achieved more efficiently. In this study, we developed 2D idealistic models with various plaque morphologies. Then, two 3D idealistic models are developed to represent the worst- and best- case scenarios for each idealistic 2D model.

2D Models- 4 representative IVUS images are carefully selected to represent the geometry of the thin fibrous cap tissue. This geometry is then categorized into three types (65): nodal
(Figure 3.2A), linear (Figure 3.2C), and curve-linear (Figure 3.2D). In all of these models, cap thickness is set to 70 \( \mu \text{m} \) and 100 \( \mu \text{m} \) and the diameter of plaque is set to 3.3 mm (Figure 3.3). Using these IVUS images, 3 idealistic 2D models are generated corresponding to each category: nodal (Figure 3.3E), linear (Figure 3.3F) and curve-linear (Figure 3.3G). A random geometry of a 2D realistic plaque can be created by one or a combination of two or three of these idealistic models.

![Figure 3.2](image)

**Figure 3.2**- A, B, C, D: Selected IVUS images which are the representative of all types of plaque morphologies (65) (@ 2014 World Scientific Publishing Co., Inc. adapted with permission). This classification is based on the geometry of the fibrous cap which is considered to be: nodal (A), linear (B, C), and curve-linear (D), and the corresponding idealistic models are defined as: E (nodal), F (linear) and G (curve linear) (65). Cap thickness=70 \( \mu \text{m} \) and/or 100 \( \mu \text{m} \); F, fibrous cap; NC, necrotic core

3D models- For each 2D idealistic model in previous section, two idealistic 3D models are developed. These two 3D models must have the same geometry as the related 2D idealistic
models at the section of plaque. These 3D idealistic models represent the worst- and best-case scenarios related to each corresponding 2D model. In the FE study, which will be discussed further later, performed on these idealistic 2D and 3D models, PCS obtained from the 2D models is always between that of the corresponding 3D models. The upper limit corresponds to the worst case scenario and the lower limit corresponds to the best case scenario.

Figure 3.3- The 3D idealistic models corresponding to each 2D idealistic model. In each group, cross sections of 3D models are identical to their corresponding 2D models (NC, necrotic core; FC, fibrous cap).
Chapter 3: Method (The Finite Element Analysis)

3.3.2 Constitutive Model for Plaque Components

In this section material models used in this study are comprehensively described. The challenge is to assign the right mechanical properties to the major components of plaque such as necrotic core and fibrous cap.

Necrotic Core- Necrotic core is conventionally considered to be isotropic and elastic. In the present study, it is assumed that necrotic core or lipid pool is incompressible with the Poisson’s ratio of 0.49 (8), and isotropic elastic, with a Young’s modulus of 1kPa (42).

Fibrous Cap- In this study, the fibrous cap tissue is assumed to be anisotropic and viscoelastic. In previous studies, several distinctive material models; isotropic elastic (40), orthotropic elastic (43), isotropic hyperelastic (39, 44) and anisotropic hyperelastic (44, 65), have been employed to model fibrous cap. Fibrous cap is a fiber-reinforced tissue due to the presence of collagen fibers which make the tissue stiffer and more resistant to fracture in the direction of fibers (58). In this study, these fibers are assumed to be aligned in the circumferential direction (65). In order to define mechanical properties to the fibrous cap tissue, a local cylindrical coordinate system is defined for the fibrous cap tissue and two principal directions of the radial and circumferential are defined. The assigned mechanical properties using this system are outlined in Table 3.1.

To add viscoelastic behaviour to fibrosis, two types of material behaviour can be used; linear and non-linear viscoelastic model. This study uses the linear model (25, 36) in which creep and relaxation functions are only time dependent, i.e., stress is proportional to the strain at a given time.
Table 3.1- Mechanical properties of fibrous cap (42). $\theta$ represents the circumferential direction, r, the radial direction and z, the axial direction

<table>
<thead>
<tr>
<th>$E_r$ (kPa) = $E_z$ (kPa)</th>
<th>$E_\theta$</th>
<th>$v_{r\theta}$</th>
<th>$v_{rz}$=$v_{oz}$</th>
<th>$G_{rz}$=$G_{ro}$=$G_{oz}$ (kPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>1000</td>
<td>0.01</td>
<td>0.27</td>
<td>500</td>
</tr>
</tbody>
</table>

Using different arrangement of springs (elastic elements) and dashpots (viscous elements) linear viscoelastic behaviour can be mathematically described which are known as the Maxwell Model, Kelvin-Voight Model, Standard Linear Solid and Wiechert Model (Figure 3.4) (70). This study employs the Wiechert Model to define viscoelastic behaviour of fibrous cap, as it can more accurately match creep and relaxation behaviour of material in comparison with Standard Linear Solid. The Wiechert Model consists of a spring and a number (n) of Maxwell elements (i.e. series of spring and dashpot).
Figure 3.4- Illustration of the linear physical models used to describing behaviour of viscoelastic materials. A, Maxwell Model; B, Kelvin-Voight Model; C, Standard Linear Solid; D, Wiechert Model. $E$ and $\eta$ refers to elastic and viscous part of the model, respectively. $E_\infty$ and $E_m$ refers to the elasticity at infinite time and elasticity of Maxwell arm, respectively. $\sigma$ represents the stress (load) imposed on the system.

The constitutive equation of this model is developed as follows ($\sigma$, stress; $\varepsilon$, strain, $E$, elasticity modulus; $\eta$, viscosity or damping coefficient);

<table>
<thead>
<tr>
<th></th>
<th>Time domain</th>
<th>Laplace domain</th>
</tr>
</thead>
<tbody>
<tr>
<td>spring arm (elastic arm):</td>
<td>$\sigma = E_e \varepsilon$</td>
<td>$\bar{\sigma}_e(s) = E_e \bar{\varepsilon}(s)$</td>
</tr>
<tr>
<td>For each Maxwell arm:</td>
<td>$\dot{\varepsilon} = \frac{\dot{\sigma}_m}{E_m} + \frac{\sigma_m}{\eta}$</td>
<td>$\bar{\sigma}_m(s) = E_m \left( \frac{s}{s + \frac{1}{\tau}} \right) \bar{\varepsilon}(s)$</td>
</tr>
<tr>
<td></td>
<td>$\dot{\varepsilon} = \frac{d\varepsilon}{dt}$, $\dot{\sigma} = \frac{d\sigma}{dt}$</td>
<td>$\tau = \frac{\tau}{E_m}$</td>
</tr>
<tr>
<td>Total</td>
<td>$\sigma = \bar{\sigma}_e + \bar{\sigma}_m$</td>
<td></td>
</tr>
</tbody>
</table>
For a Wiechert model with one Maxwell arm:

\[
\sigma(s) = \left[ E_e + E_m \left( \frac{s}{s + \frac{1}{\tau_m}} \right) \right] \frac{\varepsilon_0}{s}
\]  

(3.1)

By taking the inverse Laplace transform, the constitutive equation is developed as:

\[
\sigma(t) = \left[ E_e + E_m e^{-\frac{t}{\tau_m}} \right] \varepsilon_0
\]  

(3.2)

And the relaxation modulus is defined as:

\[
E(t) = \frac{\sigma(t)}{\varepsilon_0} = E_e + E_m e^{-\frac{t}{\tau_m}}
\]  

(3.3)

Using the Prony series, the relaxation modulus (equation 3.3) is modified for a Wiechert model with \( n \) Maxwell arms. Generally, the relaxation modulus is obtained through shear relaxation data and the shear relaxation modulus are used in FE commercial codes. Thus, notation \( E(t) \) is substituted with \( G(t) \), where \( G_\infty \) is the fully relaxed shear modulus at time equal to infinity,

\[
G(t) = G_\infty + \sum_{i=1}^{n} G_i e^{-\frac{t}{\tau_i}}
\]  

(3.4)

At \( t=0 \):

\[
G_0 = G_\infty + \sum_{i=1}^{n} G_i
\]  

(3.5)

Comparing (3.4) with (3.5):

\[
G(t) = G_0 - \sum_{i=1}^{n} G_i (1 - e^{-\frac{t}{\tau_i}})
\]  

(3.6)

Dividing (3.6) by \( G_0 \) turns out \( g(t) \), relative moduli at \( t; \overline{g}_i^P \), relative relaxation moduli; \( \tau_i \), relaxation time);
\[ g_R(t) = 1 - \sum_{i=1}^{n} \bar{g}_i^p (1 - e^{-t/\tau_i}) \]  

(3.7)

Elements of equation (3.7), also known as the Prony series model, are conventionally obtained by curve-fitting of stress-versus-time data obtained in mechanical experiments on the material sample. Using stiffness matrix, \( D \), the matrix form of equation (3.2) is defined as follows (\( D_0 \), instantaneous elasticity tensor or elasticity tensor at \( t=0 \); \( \varepsilon \), strain tensor (71));

\[ \sigma = D(t)\varepsilon; \quad D(t) = g_R(t)D_0 = (1 - \sum_{i=1}^{n} \bar{g}_i^p (1 - e^{-t/\tau_i}))D_0 \]  

(3.8)

Values of the Elements of matrix \( D_0 \) are outlined in Table 3.1.

The material parameters used in the viscoelastic material model as applied to properties of plaque constituents are reported in (72). In this study, an experimental-numerical technique to find parameters of a time Prony series with five spring-damper elements was performed. Table 3.2 outlines the values obtained in that study.

**Table 3.2- Elements of time Prony series (72) as considered for the low viscoelastic model**

<table>
<thead>
<tr>
<th>Index i</th>
<th>Relative Module</th>
<th>Relaxation time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1595</td>
<td>0.001</td>
</tr>
<tr>
<td>2</td>
<td>0.1177</td>
<td>0.01</td>
</tr>
<tr>
<td>3</td>
<td>0.0623</td>
<td>0.1</td>
</tr>
<tr>
<td>4</td>
<td>0.1612</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>0.2101</td>
<td>10</td>
</tr>
</tbody>
</table>
In this study, two viscoelastic models are considered; (1) a low viscoelastic model (Table 3.2), and (2) a high viscoelastic model. The elements of Table 3.2 are modified so that the new model can represent the mechanical behavior of the fibrous cap tissue with high viscosity, which is caused by the high density of SMCs and monocytes inside the plaque. To reach this end, relative modules are increased by 40% (see Table 3.3).

<table>
<thead>
<tr>
<th>Index i</th>
<th>Relative Module</th>
<th>Relaxation time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.2233</td>
<td>0.001</td>
</tr>
<tr>
<td>2</td>
<td>0.1648</td>
<td>0.01</td>
</tr>
<tr>
<td>3</td>
<td>0.087</td>
<td>0.1</td>
</tr>
<tr>
<td>4</td>
<td>0.2257</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>0.2944</td>
<td>10</td>
</tr>
</tbody>
</table>

It should be noted that the nature of lower viscoelastic behavior is closer to a pure elastic or hyperelastic material model.

### 3.3.3 Boundary Conditions

Two types of boundary conditions (known variables) are used in this study: (1) Displacement, and (2) Load. Atherosclerotic plaque is circumscribed by the artery wall; thus, the outer wall of plaque is assumed to be fixed in all directions as the outer surface of plaque
experiences negligible displacement in physiological condition (73, 74). Figure 3.5 illustrates this displacement boundary condition. Load in this study is referred to blood pressure. Given that the constitutive material models defined for the fibrous cap tissue is viscoelastic, the transmural pressure is considered the actual physiological blood pressure in the coronary arteries which is cyclic and time-dependent in nature. The numerical values related to the transmural pressure are outlined in Table 3.4.

![Figure 3.5- Illustration of the boundary conditions.](image)

### Table 3.4- Tabular data for dynamic pressure.

<table>
<thead>
<tr>
<th>Time (s)</th>
<th>0</th>
<th>0.2</th>
<th>0.8</th>
<th>1.2</th>
<th>1.8</th>
<th>2.2</th>
<th>2.8</th>
<th>3.2</th>
<th>3.8</th>
<th>4.2</th>
<th>4.8</th>
<th>5.2</th>
<th>5.8</th>
<th>6.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure (kPa)</td>
<td>12</td>
<td>18.7</td>
<td>10.7</td>
<td>18.7</td>
<td>10.7</td>
<td>18.7</td>
<td>10.7</td>
<td>18.7</td>
<td>10.7</td>
<td>18.7</td>
<td>10.7</td>
<td>18.7</td>
<td>10.7</td>
<td>18.7</td>
</tr>
</tbody>
</table>

Also, four heart rates of HR=60, HR=90, HR=120, and HR=150 bpm are considered in this study (see Figure 3.6).
Figure 3.6- Dynamic blood pressure in heart rates of 60, 90, 120, and 150 bpm. These graphs are used for the evaluation of HR effect on plaque vulnerability.

### 3.3 The Finite Element Analysis

In this step, the required CAD models of plaque are created by SOLIDWORKS 14. These models are then transferred to ANSYS 15 for mesh generation and assigning the physics of the problem, such as the constitutive material models and boundary conditions. A comprehensive mesh independency study is performed to ensure that the results are independent of mesh numbers (Figure 3.7). In this mesh study, in order to more effectively approximate the geometry of the fibrous cap tissue, unstructured mesh was applied. 10-node tetrahedral and 6-node triangular elements are used for 3D and 2D models, respectively. The number of elements used to mesh each geometrical model is provided in Table 3.5.

By creating mesh models, ANSYS discretizes the governing equation of plaque mechanics and produces a set of algebraic equations. To find unknown nodal displacements and forces,
these equations are solved by Mechanical APDL 2015 running on an Intel® Core™ 2 Due T6670 @ 2.2GHz and 2.00 GB of RAM.

![Figure 3.7](image)

**Figure 3.7-** This figure shows the mesh models in 2D and 3D models. In 3D models, Necrotic core and some parts of fibrous cap were hidden to reveal the mesh density in critical zone.

<table>
<thead>
<tr>
<th>Models</th>
<th>E</th>
<th>F</th>
<th>G</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2D</td>
<td>3D S</td>
<td>3D C</td>
</tr>
<tr>
<td>Elements</td>
<td>3,411</td>
<td>112,150</td>
<td>114,605</td>
</tr>
</tbody>
</table>

**Table 3.5-** Number of elements and mesh model specifications in each model

Stress distribution (with assumption of plane strain for 2D models) is considered for comparison between 2D and 3D models. There are six (three) distinctive stresses for a three-(two) dimensional element (see Figure 3.8).
As plaque rupture is strongly believed to be a mechanical failure, this research employs von Mises criterion, a Mechanical failure criterion stating that the material starts yielding as the calculated von Mises stress (see 3.9) exceeds its strength.

![Diagram](image)

**Figure 3.8-** Right: normal and shear stresses imposed on a three-dimensional element. Left: normal and shear stresses imposed on a two-dimensional element. Note that shear stresses for three- and two dimensional models follow these rules: \( \sigma_{xy} = \sigma_{yx}, \sigma_{xz} = \sigma_{zx}, \sigma_{yz} = \sigma_{zy} \) and \( \tau_{xy} = \tau_{yx} \)

\[
\sigma_v = \sqrt{\sigma_{xx}^2 + \sigma_{yy}^2 + \sigma_{zz}^2 - \sigma_{xx}\sigma_{yy} - \sigma_{yy}\sigma_{zz} - \sigma_{zz}\sigma_{xx} + 3(\tau_{xy}^2 + \tau_{yz}^2 + \tau_{zx}^2)}
\] (3.9)

Using post-processing options available in ANSYS 2015, for each model the von Mises stress is calculated as a measure for evaluation of plaque instability.

Preliminary results indicate that the maximum stress occurs at the first cycle and then a small stress relaxation occurs. Given that heart beats almost one hundred thousand times a day, the maximum value at this cycle seems to be a computational artifact and that stress reduces due to the viscoelastic behaviour of fibrous cap; therefore, the settled values of the PCS (maximum von-Mises stress) is considered at cycle 4 (75).
Chapter 4: Results

4.1 General

Following the method section, the finite element results are presented and discussed in this chapter. For a variety of case studies, the stress distribution is assessed within the plaque and then compared to the gold standard of 300 kPa. The representative stress within the plaque is considered as the von Mises stresses which was discussed in the previous chapter. Two objectives are followed here: 1) developing a novel computational platform, by which a better and more effective application of 2D images for the detection of rupture-probe plaques is proposed, and 2) Heart rate as a new predictor of rupture in atherosclerotic plaques is introduced and discussed.

4.2 Validation Study

In order to validate our proposed computational platform, the results in the study by Ohayon et al. (41) were carefully selected, reproduced and resolved (Figure 4.1. and Table 4.1). In this model, the peak cap stress (PCS) of the model with the same morphology, mechanical properties, blood pressure, etc., was calculated and compared. Results indicate that the PCS obtained by our solver (378 kPa) and that of Ohayon et al (376 kPa) shows 2 kPa discrepancy (less than 1% error) (Figure 4.2). This small discrepancy could be because of minor differences between the two mesh models.
Figure 4.1- This figure illustrate the geometrical model and boundary conditions (A, outer wall fixed in radial direction; B, blood pressure of 18 kPa) used in a study by Ohayon (8). FC, fibrous cap; NC, necrotic core; L, lumen.

Table 4.1- Material properties used in the validation study - Arterial wall and fibrous cap are defined by anisotropic elastic material model and necrotic core is assumed to be an isotropic and quasi-incompressible material.

<table>
<thead>
<tr>
<th></th>
<th>Young’s Modus kPa</th>
<th>Shear Modulus</th>
<th>Poisson Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$E_r$</td>
<td>$E_{\theta z}$</td>
<td>$G_{\theta}$</td>
</tr>
<tr>
<td>Artery wall</td>
<td>10</td>
<td>100</td>
<td>52</td>
</tr>
<tr>
<td>Fibrous cap</td>
<td>115.6</td>
<td>2312</td>
<td>1175</td>
</tr>
<tr>
<td>Necrotic core</td>
<td>$E=1000$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 4.2- The validation study: (A) The mesh model by Ohayon et al, (B) The mesh model in the current study, (C) The stress distribution and the peak cap stress (PCS) obtained by Ohayon et al. (41), and (D) The stress distribution and the peak cap stress obtained in the current study. For the current model, the PCS is 378 kPa which is 2 kPa larger than the computed PCS in that study. This small discrepancy may be because of the differences in the mesh models.
4.3 Mesh Independency Study

Mesh independency of our results is of particular significance in this study which is done by performing further computation for each plaque model with higher mesh density. The mesh size is decreased until the point where by increasing the mesh density the results are not improved. The result of the mesh independency study is outlined in Table 4.2.

Table 4.2- Mesh independency study, the PCS for each model along with the number of elements used are shown in row A and B. In row B, models were meshed with more elements in comparison with models in row A. Results show an acceptable range for discrepancy of PCS in each plaque model; thus, the mesh models employed in row A are sufficiently precise to be used for our computational approach. Also, results are time dependent due to time-dependency of the material properties and pressure. In this pre-study, results of PCS at t=0.2s have been considered for this comparison. *S denotes the sphere-like models and *C the cylinder-like models.

<table>
<thead>
<tr>
<th>Models</th>
<th>1E</th>
<th>1F</th>
<th>1G</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2D</td>
<td>3D S</td>
<td>3D C</td>
</tr>
<tr>
<td>A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCS kPa</td>
<td>393</td>
<td>116</td>
<td>485</td>
</tr>
<tr>
<td>Elements</td>
<td>3411</td>
<td>112150</td>
<td>114605</td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCS kPa</td>
<td>391</td>
<td>117</td>
<td>491</td>
</tr>
<tr>
<td>Elements</td>
<td>6135</td>
<td>189184</td>
<td>187733</td>
</tr>
<tr>
<td>Comparison %</td>
<td>0.5</td>
<td>0.8</td>
<td>1.2</td>
</tr>
</tbody>
</table>
4.4 Effect of Viscoelasticity of Fibrous Cap

The idealistic model shown in Figure 3.2E is considered. The fibrous cap thickness was set to 95 µm, the diameter of artery is assumed to be 3.3 mm, and the lumen area was considered elliptic with diameters of 2.50 mm x 2.00 mm, representing a typical plaque.

In Figure 4.3, the PCS values for 2D models (Figure 3.2E) are shown at different times. As observed, the maximum PCS occurs at t=0.2s and then decreases by time due to the viscoelastic behavior of fibrosis. The PCS values in the other cycles which occur at t=1.2, 2.2 and 3.2s, are approximately 357, 346 and 340 kPa, respectively. After cycle 4, the PCS almost remains unchanged. If the simulation is run for only one cycle the PCS obtained is 393 kPa but the plaque experiences 100,000 cycles a day, As such, the maximum PCS should be considered as its value after cycle 4 which drops by 15% to the value of 336 at t=4.2s.

Figure 4.3- a) The variation of PCS for viscoelastic fibrous cap for a typical plaque. When t=0.2s the PCS is maximum (cycle 1) which is considered numerical artifact. The actual PCS is considered when the peak stresses are settled (after cycle 4). In this simulation, Table 3.4. is used to define blood pressure.
4.5 **Assessment of the PCS in the idealistic 2D Models**

The idealistic 2D models represented in Figure 3.2E, 3.2F, and 3.2G are solved for the value of PCS in the fibrous cap area (Figure 4.4). Results indicate that the maximum PCS (336 kPa) occurs in model 3.2E in which the fibrous cap geometry is focal. It follows with the model with a linear fibrous cap area (Figure 3.2F) in which the PCS is estimated to be 299 kPa (11% decrease) and then the curve-linear fibrous cap geometry (Figure 3.2G) with the PCS being 216 kPa (36% decrease).

![Figure 4.4- The PCS and stress distribution in idealistic 2D models, Cap thickness=70 µm. F, fibrous cap; NC, necrotic core](image)

The area with the maximum PCS in all models are located in the vicinity of the NC and not the lumen, which is consistent with previous studies (41, 65). Also, numerical values for the
PCS are consistent with those obtained by Mohammadi et al. (65) with a discrepancy of 10% which is because the thinner fibrous cap considered in these models (70 µm).

### 4.6 The Assessment of the PCS in the Idealistic 3D Models

In this study, two idealistic 3D models (Figure 3.3) are developed for each idealistic 2D model (Figure 3.2E, 3.2F, and 3.2G). Both these 3D models have the same geometry in the cross sectional area to that of the 2D model. The objective for emerging these models is that although they share the same cross sectional area of the 2D models, they are designed to yield the minimum and maximum PCS in the fibrous cap area. The stress distribution in the plaque model for these 6 idealistic 3D models is shown in Figure 4.5.

The range of the PCS for the 3D models in the group E is 99 kPa to 412 kPa, while the PCS in the 2D model is 336 kPa. Since the range of 300 kPa - 99 kPa = 201 kPa (lower limit) is greater than the range of 412 kPa - 300 kPa = 112 kPa (upper limit), the 2D plaque is more likely to be stable.

For the other models, the range of PCS for the 3D models corresponding to Figure 3.2F is 176 kPa to 385 kPa, whereas the PCS in the 2D model is 299 kPa. Since the range of 300 kPa - 176 kPa = 124 kPa (lower limit) is greater than the range of 385 kPa - 300 kPa = 85 kPa (upper limit), the 2D plaque is more likely stable.

The range of PCS for the 3D models corresponding to Fig 3.2G is 144 kPa to 351 kPa, whereas the PCS in the 2D model is 216 kPa.
Figure 4.5 - Stress distribution in the idealistic 3D models. Figs. A, B and C provide the lower limit regarding models in Figure 1E, 1F, and 1G, respectively, and Figs. D, E, and F provide the upper limit regarding models in Figure 1E, 1F, and 1G, respectively. Some parts of models are intentionally hidden for better exhibition of critical regions. FC, fibrous cap; NC, necrotic core; L, lumen.

Since the range of 300 kPa - 144 kPa = 156 kPa (lower limit) is significantly greater than the range of 351 kPa – 300 kPa = 51 kPa (upper limit), the 2D plaque is again likely stable. Results are outlined in Table 4.3, in which the discrepancy of the lower and higher limits of PCSs is compared with that of obtained from 2D models. The traditional way of evaluation of the vulnerability of plaques which is based on 2D models, easily recommend of stability of plaques shown in Figure 3.2F and 3.2G and instability of plaque shown in Figure 3.2E.
Table 4.3- Comparison of 2D models results with 3D models, $\frac{\text{PCS in 3D} - \text{PCS in 2D}}{\text{PCS in 2D}} \times 100$

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Sphere-like</th>
<th>Cylinder-like</th>
<th>Peak Cap Stress (kPa)</th>
<th>Comparison with 2D model (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model E</td>
<td>336 kPa</td>
<td>99 kPa</td>
<td>412 kPa</td>
<td></td>
<td>-70%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-70%</td>
<td>23%</td>
<td></td>
<td>99 kPa</td>
</tr>
<tr>
<td>Model F</td>
<td>299 kPa</td>
<td>176 kPa</td>
<td>385 kPa</td>
<td></td>
<td>-41%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-41%</td>
<td>28%</td>
<td></td>
<td>176 kPa</td>
</tr>
<tr>
<td>Model G</td>
<td>216 kPa</td>
<td>144 kPa</td>
<td>351 kPa</td>
<td></td>
<td>-33%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-33%</td>
<td>63%</td>
<td></td>
<td>144 kPa</td>
</tr>
</tbody>
</table>

Figure 4.6 shows the safe range for PCS value (PCS<300 kPa, green bar) and range of PCS (yellow bar) obtained using finite element models presented in this study. In order to assess the risk of plaque rupture, the length of the yellow bar is divided by its length inside the green zone to estimate the probability of plaque stability, as it is implemented in the following formula (4.1):

$$Probability\ of\ stability\ of\ plaque = \frac{300 - lower\ limit}{upper\ limit - lower\ limit} \times 100$$ (4.1)

### 4.7 Effect of Viscoelastic Fibrosis on the PCS

In this step, all nine 3D and 2D models are solved for PCS using elastic and viscoelastic material models discussed in chapter 3. Results outlined in Table 4.6 show that in all models the PCS obtained using elastic material model is higher than that of obtained using viscoelastic material model. For all 2D models this discrepancy is between 30-32%, whereas for 3D models this discrepancy falls within the range of 23-52%.
Figure 4.6- The range of safe value for PCS (green bar) and the total range of PCS (yellow bar). Comparison between the length of yellow bar outside and inside of green bar presents practical information about probability of rupture in a plaque. In all of these models, plaque is more likely to be stable due to the greater stability probability than that of instability.

Table 4.4- Comparison of estimated PCS in models with pure elastic and viscoelastic material. As it can be seen in the table, PCS in models with pure elastic material is higher than PCS in models with Viscoelastic material. PCS at t=4.2s has been considered for this comparison. * S for sphere-like models and C for cylinder-like models
4.8 Data Obtained from Patients

In this section, 2D geometries of the atherosclerotic plaque obtained from 4 patients were developed using the combination of OCT and IVUS techniques (co-registered image) as shown in Figure 4.7A to 4.7D. In these 2D models, a clear geometry of the fibrous cap and the necrotic core is available. These 2D models are solved using the proposed computational platform for the PCS (same material properties and boundary conditions discussed in chapter 3).

4.8.1 Application on Data Obtained from Patients

Figure 4.7-A1 shows the stress distribution in the entire tissue of the model shown in Figure 4.7A. In this model, the cap thickness is measured to be 118 μm and the PCS is estimated to be 355 kPa. By comparing this 2D model and the idealistic 2D models developed earlier, it is seen that this plaque has morphology similar to model 1G (Figure 3.2G) in general, and in particular has a similar morphology to model 1E (Figure 3.2E) where the cap thickness is minimal (118 μm). In order to choose similar idealistic models to an intended actual data obtained from patients, the area in which the cap thickness is minimal is considered. Following the idealistic models and their corresponding 3D models, the probable range for the PCS for such geometry is 106 kPa to 437 kPa and the probability of the plaque stability is calculated to be \( \frac{300-106}{437-106} = 59\% \).

The conventional assessment applied for this plaque suggests that the plaque will definitely fail, but our proposed computational platform suggests that since the 3D structure of the plaque is not known, there is a 59% chance that the plaque may stay stable.
Figure 4.7B1 shows the stress distribution in the entire tissue regarding the model shown in Fig. 4.7B. In this model, the cap thickness is measured to be 67 µm mm and the PCS is estimated to be 493 kPa. Comparing this 2D model and the idealistic 2D models developed earlier, this plaque has morphology similar to model 1F (Figure 3.2F). Following the idealistic models and their corresponding 3D models, the probable range for the PCS for such geometry is 0.6 PCS-1.28 PCS which is 296kPa-631 kPa, and the probability of the plaque stability is calculated to be $\frac{300-296}{631-296} = 1\%$. The conventional assessment applied for this plaque suggests that the plaque will definitely fail, and our proposed computational platform reinforces this regardless what the 3D structure of the plaque might be.

Figure 4.7C1 shows the stress distribution in the entire tissue for the model shown in Figure 4.7C. In this model, the cap thickness is measured to be 141 µm and the PCS is estimated to be 270 kPa. After comparing this 2D model and the idealistic 2D models developed earlier, this plaque has morphology similar to model 1E (Figure 3.2E). Following the idealistic models and their corresponding 3D models, the probable range for the PCS for such geometry is 81.1 kPa to 332kPa and the probability of the plaque stability is calculated to be $\frac{300-81}{332-81} = 87\%$. The conventional assessment suggests that the plaque is most likely unstable, but our proposed computational platform suggests that since the 3D structure of the plaque is not known to us, there is a chance of 13% that the plaque may fail.

Figure 4.7D1 shows the stress distribution in the entire tissue regarding the model shown in Figure 10D. In this model, the cap thickness is measured to be 106 µm and the PCS is estimated to be 178 kPa. When comparing this 2D model and the idealistic 2D models developed earlier, it is seen that this plaque has morphology similar to model 1G (Figure 3.2G).
Figure 4.7 - Images A, B, C, and D, show the 2D geometry of the data obtained from patients. The yellow region indicates the necrotic core area and the purple region exhibits the fibrous tissue. The thickness of fibrous cap for each case is denoted as “Thk.” Using the proposed computational platform the PCS related to each case is calculated. FC, fibrous cap; NC, necrotic core; L, lumen.

Following the idealistic models and their corresponding 3D models, the probable range for the PCS for such geometry is 119 kPa to 290 kPa and the probability of the plaque stability is calculated to be $\frac{300 - 119}{290 - 119} > 100\%$. The conventional assessment applied for this plaque suggests that the plaque is definitely stable and our proposed computational platform proves the stability of this plaque.
4.9 Effect Heart Rate Elevation on Peak Cap Stress

This section presents the results obtained in idealistic and realistic models when heart rate (HR) elevates from 60 to 150 bpm.

4.9.1 Heart Rate effect on Peak Cap stress Inside Idealistic Models

Fig. 4.8 illustrates the values of PCS in 3 idealistic models (presented in Chapter 3) with respect to HRs of 60, 90, 120, and 150 bpm. Two thicknesses (70 μm and 100 μm) and two viscoelastic models (low and high viscosities) are considered for the fibrous cap tissue. As it was discussed before, PCS decreases by time due to the viscosity of material model; however, after a few cycles the values of PCS are settled and remain approximately unchanged in the following cycles; the settled values are considered in this study. Results clearly indicate that HR noticeably affects the values of PCS. When the cap thickness is set to 70 μm and a low viscosity is applied to define material properties of fibrous cap tissue, the variations of PCS values regarding HR fall within the range of 15-25 kPa. This range increases to 35-45 kPa for when a high viscoelastic is assigned to the fibrous cap tissue (Figure 4.8a). For when cap thickness is set to 100 μm, these ranges drops to ~15 kPa and to 20-35 kPa for the low viscoelastic and high viscoelastic fibrous cap model, respectively (Figure 4.8b). For the high viscoelastic fibrous cap model, variations in values of PCS are higher in comparison to that of the low viscoelastic fibrous cap model as HR elevates, assuming all other conditions, i.e., cap thickness, lumen maximum pressure, etc., remain unchanged. Comparing the results outlined in Figure 4.8a and 4.8b, it is evident that if a
higher viscoelastic model is used for the fibrous cap tissue, lower values (15%) for PCS are obtained.

Figure 4.8 - Illustration of the results obtained through idealistic models. LV and HV refer to high and low viscoelastic properties of the fibrous cap tissue, respectively. (a) shows the values of PCS for the idealistic models when cap thickness is set to 70 μm, and (b) shows the values of PCS in the idealistic models when the cap thickness is set to 100 μm. F, fibrous cap; NC, necrotic core.
For the idealistic models of I1 and I3 (to prevent confusion with previous section, models captions changes from E, F and G to I1, I2 and I3, respectively), the values of PCS decreases as the cap thickness is set from 70 μm to 100 μm for both high and low viscoelastic fibrous cap models. However, for the idealistic model of I2 the values of PCS are approximately in the same range with an error less than ~2%, regardless of the fibrous cap thickness being 70 μm or 100 μm. This inconsistency might suggest that the geometry of the plaque section and HR combined together could be more influential on PCS than solely the thickness of the fibrous cap tissue.

### 4.9.2 Heart Rate Effect in Realistic Models

The estimated PCS values inside realistic models under the same boundary conditions, i.e., dynamic lumen pressure and displacement boundary conditions, are illustrated in Figure 4.9. The present results further reinforce the hypothesis developed regarding the effect of viscosity on PCS inside the idealistic models that if a higher viscoelastic model is assigned to the fibrous cap tissue, the effect of HR on PCS is intensified and the values of PCS decreases by ~15%.

### 4.9.3 Comparison of PCS Increase for Different Hear Rate Elevation

Figure 4.10 illustrates the increase in PCS with respect to that of when HR=60 bpm shown in Figure 4.8 and 4.9 to better demonstrate the effect of viscoelasticity and HR on the PCS values. For both low and high viscoelastic models, results evidently indicate that jump in PCS from HR=90 bpm to HR=120 bpm is higher than that of from 120 bpm to 150 bpm.
Depending on the level of applied viscoelastic models and HR, the values of PCS increase from 2% (in which HR=90 bpm) to 18% (in which HR=150 bpm).

Figure 4.9- This figure illustrates the patient-oriented geometrical models used in this study and their estimated PCS values through both HV and LV materials (LV and HV refer to high and low viscoelastic properties of the fibrous cap tissue, respectively); The imaging modalities used in this study are IVUS & OCT combined (models A, B, and C) and histology (models H1, H2, H3, and H4) (47, 56, 76, 77). In cad models (second row); blue: fibrous tissue, yellow: necrotic core and red: calcified regions.
Figure 4.10- The comparison of values of PCS to that of obtained when HR=60 bpm for both idealistic and realistic models. Two thicknesses and two viscoelastic models are considered for the idealistic models (Figure 4.8a, b), and all realistic models (Figure 4.9c). LV and HV refer to low and high viscoelastic material properties for the fibrous cap tissue, respectively.
Chapter 5: Conclusion

5.1 Summary

The present thesis investigated mechanical vulnerability assessment of atherosclerotic plaques from two major standpoints;

1- Improvement of reliability in detection of vulnerable plaques using two-dimensional (2D) images;

2- Effect of heart rate (HR) on the mechanics of the atherosclerotic plaques with respect to viscoelastic properties of the plaque tissue

5.1.1 Vulnerability Assessment Based on 2D Images

In this study, a novel computational platform was developed to evaluate vulnerability risk of an atherosclerotic plaque by using only 2D models. FE models of this computational platform were defined such that a suitable anisotropic material model with viscoelastic behaviour was considered for plaque composition and the transmural pressure was assigned to be similar to the physiological blood pressure (dynamic condition). Results strongly indicate that the viscoelastic properties of the plaque composition are of particular significance for the estimation of the PCS as implementation of elastic material model instead of viscoelastic model for 2D models may contribute to up to 32% and 52% error for 2D and three-dimensional (3D) models, respectively. Besides, when viscoelastic material
model is implemented, the discrepancy between the PCSs estimated in the first and the fourth cycles (settled PCS) is almost 15%.

For geometrical models, idealistic 2D models and their corresponding 3D models (two 3D models for each) were developed, which provide the worst (most critical) and best (the least critical) case scenarios for each 2D model. As the 3D morphology of the plaque is unknown to us, defining the worse and best case scenarios could be helpful. First, the peak cap stress (PCS) is estimated in the 2D model (denoted as PCS$_{2D}$) and then estimation of PCS inside the idealistic 3D models provides its corresponding lower and upper limits which are considered here as the standard errors (SE). Using the lower and upper limits, the probability of the plaque stability is estimated. For a given realistic 2D model obtained from patients, the following procedure is applied;

I. Morphology of the objective plaque obtained from patient is compared to the idealistic 2D models and the similar idealistic 2D model is found,

II. The lower and upper limits (SE) corresponding to the idealistic 2D model are assigned,

III. PCS$_{2D}$ is estimated for the 2D model of patient-oriented plaque,

IV. The assigned SE is applied on the estimated PCS$_{2D}$ to calculate the lower and upper limits of PCS for the objective plaque,

V. The risk of plaque rupture is evaluated.

The lower and upper limits for the idealistic models presented in this study, are outlined in Table 5.1. The proposed computational platform seems to be useful as it provides more
realistic insight and more reliability into to the assessment of plaque rupture propensity using only 2D images.

Table 5.1- The platform by which the PCS$_{2D}$ is used for plaque stability risk assessment. The lower and upper limits are calculated using idealistic 3D models explained earlier.

<table>
<thead>
<tr>
<th>Idealistic 2D model</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Probability of the plaque stability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fig. 1E</td>
<td>$0.3 \times$ PCS$_{2D}$</td>
<td>$1.23 \times$ PCS$_{2D}$</td>
<td>$\frac{300 - \text{Lower limit}}{\text{Upper Limit} - \text{Lower Limit}} \times 100$</td>
</tr>
<tr>
<td>Fig. 1F</td>
<td>$0.59 \times$ PCS$_{2D}$</td>
<td>$1.28 \times$ PCS$_{2D}$</td>
<td></td>
</tr>
<tr>
<td>Fig. 1G</td>
<td>$0.67 \times$ PCS$_{2D}$</td>
<td>$1.63 \times$ PCS$_{2D}$</td>
<td></td>
</tr>
</tbody>
</table>

5.12 Heart Rate Effect

Conditions of blood pressure in the majority of the hemodynamics computational and experimental studies are set according to a fixed HR of 72 beat per minute (bpm), which does not comprehensively represent the entire possible physiological hemodynamic conditions; such as, in resting status, sleeping status, etc., where HR could be as low as 60 bpm. In contrast, jogging, running and emotional shocks could elevate HR to be as high as 150 bpm. Besides, daily emotional conditions, such as stress and anxiety, may affect the HR. Therefore, a range of 60-150 bpm for HR seems to be reasonable normal HR conditions for cardiovascular related studies. In the current study, estimated PCS values within the plaque models with respect to HR variation and different viscoelastic models demonstrate the significance of HR and viscoelastic material model of the fibrous cap tissue for the assessment of atherosclerotic plaque vulnerability. As presence of smooth muscle cells (SMCs) and macrophages add viscoelastic behaviour to the fibrous cap tissue, the degree of
viscoelasticity depends highly on plaque composition. The present results suggest that HR must be considered as a predictor for the mechanical instability of rupture-prone plaques, along with other factors such as cap thickness, necrotic core size and plaque morphology. Moreover, results evidently indicate impact of HR on vulnerability of plaque is strongly associated with the degree of tissue viscosity since higher viscosity in the fibrous cap tissue can intensify the effect of HR on PCS values (see Figure 5.1).

Figure 5.1- Increase in PCS values due to degree of viscoelasticity of the fibrous cap tissue and HR. Blue bar shows the increase in PCS moving from elastic model to low viscoelastic model for the fibrous cap tissue when HR=60 bpm, red bar shows the increase in PCS moving from elastic model to high viscoelastic model for the fibrous cap tissue when HR=150 bpm.
5.2 Future Work

In order to improve the current work, more data from patients is required for estimation of PCS in more 2D and 3D models of realistic plaque models. Applying the procedure introduced in previous section on these new 2D models and then comparing the results with the estimated PCS obtained from 3D imaging data acquired from patients could help further strengthen the computational platform developed in this study.

As observed in the results of this thesis, the vulnerability assessment of atherosclerotic plaque is highly dependent on 3D geometrical properties of plaque. Hence, it is strongly recommended to develop more comprehensive idealistic 3D models which would be helpful to investigate more geometrical features of rupture-prone plaques.

The present results showed significant influence of viscoelastic properties of plaque tissue and HR on vulnerability of plaques. To further study these introduced factors, mechanical experiments are required to obtain more accurate viscoelastic properties of plaque tissue with respect to its constituent cells and molecules. Also, a computational method, such as Fluid-Structure Interaction (FSI), would be applied to more comprehensively analyze the effect of HR and plaque tissue viscosity on rupture-propensity of plaques.

In the literature, it is widely accepted to compare the estimated stress inside plaque with the gold standard of 300 kPa, the strength of tissue material, regardless of the material models assigned to the plaque tissue. It was observed in the results of this thesis, changing material model from pure elastic to viscoelastic model could noticeably affect estimated PCS and, subsequently, influence vulnerability assessment of plaque if the results compared to the constant gold standard of 300 kPa. Therefore, future studies should investigate the effect of
various material models on vulnerability assessment of plaque which would lead to define specific material strength for each model.
References


