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Procedia Manufacturing 30 (2019) 522–529

Procedia MANUFACTURING

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14th Global Congress on Manufacturing and Management (GCMM-2018)

# Prediction of atherosclerotic plaque life – Perceptions from fatigue analysis

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**Abstract**

Cardiovascular diseases are the leading causes of morbidity and mortality globally. Heart disease and stroke contribute to most fatalities in which atherosclerotic plaque disruption is the underlying pathology. The pulsatile blood flow in the arteries generates mechanical stresses that affect the rupture of the atherosclerotic plaque. Fatigue failure being the accumulation of the damage due to repeated loading that occurs when the stresses are much lower than those needed to rupture the plaque with normal loading. Therefore, fracture mechanics concepts were used to investigate the impact of morphology and blood pressure on the plaque life. Incremental fatigue crack propagation simulations were performed on idealized geometries based on the maximum circumferential stress criteria by using a finite element solver. XFEM, which extends the standard finite element formulation by introducing additional enrichment functions was used to model the fatigue crack growth simulations. Paris' Law was used to determine the fatigue crack growth rate. Cracks extended radially and fatigue crack growth rate increased with increase in pulse pressure. Further validation studies on the 3D printed arteries are necessary for better understanding the factors contributing to plaque rupture. The results could help in assessing the atherosclerotic plaque life under the fatigue environment of the cardiovascular system.


Selection and peer-review under responsibility of the scientific committee of the 14th Global Congress on Manufacturing and Management (GCMM-2018).

*Keywords: Atherosclerotic Plaque rupture, Extended Finite Element Method (XFEM), Fatigue, Crack Propagation.*

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10.1016/j.promfg.2019.02.073

## 1. Introduction

Atherosclerosis or hardening or narrowing of the arteries (blood vessels) is an inflammatory disease which is due to the accumulation of lipids inside the artery walls [1]. It is a chronic disease resulting in the build-up of plaque that develops from complex interactions between LDL cholesterol, constituents of blood such as monocytes and cells in the arterial wall. Atherosclerosis progresses within the artery walls long before they encroach into the lumen and can affect the arteries of the heart (coronary heart disease), brain (carotid artery disease), arms, legs, pelvis (peripheral artery disease) and kidney (chronic kidney disease). The possible causes of damage to the arterial wall are the elevated levels of cholesterol, high blood pressure, and smoking. The irritants like lipids and toxins present in the blood damage the endothelium, which acts as a barrier between blood flow and the blood vessels [2]. This damaged endothelium accommodates the irritants under its wall forming a fatty streak that further develops into a plaque that consists of cholesterol and dead macrophages bulging into the middle of the blood vessel causing inflammation. Initiation and progression of atherosclerosis is asymptomatic until a catastrophic event occurs as a result of plaque rupture or complete/partial blockage of the blood vessel leading to morbidity and mortality [3].

Plaque rupture occurs when stress, acting on the lesion, is greater than the strength. Rupture of the vulnerable plaque ultimately leads to a break of the endothelium and the fibrous cap, exposing the collagen to the blood stream that causes the aggregation of platelets and the formation of a thrombus. Plaque initiation, progression, and rupture are complex processes. Several factors like mechanical forces, plaque morphology, blood conditions, hypertension, living and eating habits influence the process. Plaque susceptible to attack or injury is called a vulnerable plaque. Plaque vulnerability is the combined effect of plaque burden, plaque composition, underlying biological processes and the mechanics. Plaque burden or stenosis is the cross-sectional narrowing of the lumen area and plaque composition comprises of fibrous cap, lipid pool, calcification, neovascularization and thrombus. Only a subset of plaques are vulnerable, and plaque composition is critical compared to plaque burden. Based on the percentage of lipid pool an assessment scale for plaque vulnerability was defined; stage III plaque as the most vulnerable plaque having a lipid pool more than 40% in lipid and stage II vulnerable plaque having a lipid pool of more than 20%, whilst a stage I plaque where the development is less advanced [4]. Although vulnerable plaques have large necrotic core which cause severe stenosis due to vascular remodeling, percentage of stenosis alone is not a predictor for plaque rupture. Unstable plaques vulnerable to rupture are characterized by a thin fibrous cap and inflammation, calcification, and intraplaque heamorrhage [5, 6].

Understanding the underlying pathophysiological mechanisms from initiation to stable or vulnerable plaque and rupture is imperative. Since the cardiovascular system resembles a fatigue environment under repeated systole and diastole phases, the biomechanical forces are critical to the development of the disease. Therefore, to study the biomechanics of atherosclerotic plaque rupture, various techniques and models including 2D & 3D idealized and patient specific models of carotid and coronary arteries were used by different research groups for performing different analysis such as structural only, fluid structure interaction and fatigue [7-11].

Bank et al. (2000) hypothesized that fatigue is a critical biomechanical mechanism underlying atherosclerotic plaque rupture and presented few resemblances between engineering fatigue and plaque rupture. Atherosclerotic plaque rupture is abrupt and occurs at points of stress concentration and also the stress levels are much lower than those needed to rupture the plaque with monotonic tension which is similar to the fatigue failure [12]. Later, Versluis et al. (2006) attempted to quantify the fatigue life in terms of pulsatile cycles, by using the most conservative biomechanical concept and investigated the impact of anatomy, tissue properties, and blood pressure on the fatigue mechanism [13]. Fatigue process in atherosclerotic plaques studied by developing a 2D fatigue crack propagation model for investigating the plaque initiation, crack path and crack growth rate for an idealized plaque model based on Paris Law resulted in minimum fatigue life for the cracks initiated in the midcap zone, shoulder region and backside zone [14] and for in vivo MRI-based patient specific imaging data of 27 patients with carotid artery disease explained the development of cracks in fibrous cap, which ultimately lead to rupture and matched with the locations of in vivo observed FC defects [15]. Despite the efforts on the fatigue crack propagation simulations of the atherosclerotic plaque, fracture paths have been rarely modelled using XFEM method and elastic

boundary conditions. Therefore the main goal of this work is the prediction of fatigue life of the atherosclerotic plaque using XFEM and elastic boundary conditions on an idealized 2D model.

## 2. Materials and Methods

This section describes the XFEM method, simulation setup, material properties and boundary conditions used for the prediction of fatigue life of a 2D idealized model. In view of the fact that the cardiovascular system resembles a fatigue environment under repeated systole and diastole phases, the biomechanical analysis of the plaque rupture seems to be a useful tool to investigate the relation between stresses and the disease. Thereby, understanding the fatigue failure of the plaque under pulsatile environment requires more insight and research for assessing the plaque vulnerability. The concepts of fracture mechanics were used to predict the fatigue life of the atherosclerotic plaque under the cardiovascular conditions. Ansys (version 17.2, ANSYS Inc., Canonsburg, PA, US) supplied by QUT was used for performing the crack propagation analysis.

### *2.1. Fracture Mechanics*

Fracture mechanics is the study of propagation of cracks in materials under a fatigue environment and fatigue is the weakening of the material caused by the accumulation of infinitesimal levels of damage in response to repeated loading. The fracture mechanics parameters describe the amplitude and deformation fields ahead of the crack tip. Stress intensity factor (SIF) is used to define the crack tip conditions and material properties were defined as linear elastic. For, isotropic linear elastic material properties the stress field ahead of the crack tip is proportional to $\frac{1}{\sqrt{r}}$ and is expressed as $\sigma_{ij} = \left(\frac{K}{\sqrt{2\Pi r}}\right) f_{ij}(\theta)$ [16].

Where r = distance of the element from the crack tip
$\theta$ = the angle with respect to the crack plane

Paris' Law [17] was used to determine the fatigue crack growth. According to Paris fatigue crack growth rate depends on the stress intensity factor and is expressed as

$$\frac{da}{dN} = C(\Delta K)^m \qquad (1)$$

Where a = crack length,
N = number of cycles,
$\Delta K$= stress intensity factor ($\Delta K = \Delta K_{max} - \Delta K_{min}$),
C and m are the material constants.
The maximum circumferential stress criteria [18] was adopted to calculate the crack propagation direction.

### *2.2. XFEM, Idealized Geometry and material properties*

eXtended Finite Element Method (XFEM) introduced by Belytschko and Black used to model the crack growth simulations. This method eliminates the need to remesh the crack-tip region and is based on the partition by unity method. Singularity based approach is used which accounts for crack-tip singularities and jumps in displacements across the crack surfaces. The level set method is used to define the crack in the model. Plane 182 elements with linear elastic isotropic material behavior was used for the analysis. The crack initiation location on the lumen was found based on maximum stress criteria. Later, XFEM fatigue crack propagation simulations were performed by defining the crack, crack front, co-ordinate system, singularity enrichment region, C and m constants for Paris law and stress ratio. The effect of the crack initiation location, pulse and mean pressure in relation to various components present in the atherosclerotic plaque were analyzed.

An idealized model as shown in Figure 1, with arterial wall, fibrous cap, lumen and lipid pool as constituents was used to study the effect of the boundary conditions and stress ratio on the fatigue life and crack initiation point. The material properties were assumed to be linear elastic as listed in Table 1 and Paris law constants were chosen as C=1, m=2.6 as suggested by previous studies [19].

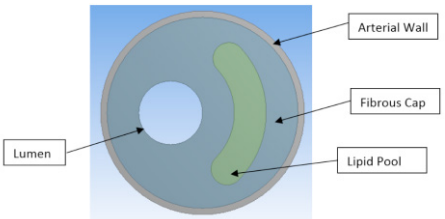



Figure 1: 2D Idealized atherosclerotic plaque model

Table 1: Material properties of different constituents of the blood vessel

| Component | Young's Modulus E (MPa) | Poisson's Ratio ν |
|---|---|---|
| Arterial wall | $E_{aw} = 0.3$ | 0.48 |
| Fibrous cap | $E_{fc} = 0.6$ | 0.48 |
| Lipid Pool | $E_{lp} = 0.02$ | 0.48 |
| Calcification | $E_{cal} = 10$ | 0.48 |

Three different boundary conditions as illustrated in Figure 2 were used. Maximum stress criteria was used to find the crack initiation location on the outer boundary elements. eXtended finite element method (XFEM) was used to model the cracks that eliminate the need for remeshing. Plane182, 2D structural solid elements were used to mesh the model and the adopted XFEM method internally remeshes the region around the crack tip with triangular elements. Stress intensity factor (K) was used to define the crack tip conditions. Maximum circumferential stress criteria was used to define the direction of crack propagation and is given by θ, Where KI and KII are stress intensity factors

$$\theta = \cos^{-1}\frac{3(K_I)_{\max} + (K_I)_{\max}\sqrt{(K_I)^2_{\max} + 8(K_{II})^2_{\max}}}{(K_1)^2_{\max} + 9(K_{II})^2_{\max}} \qquad (2)$$

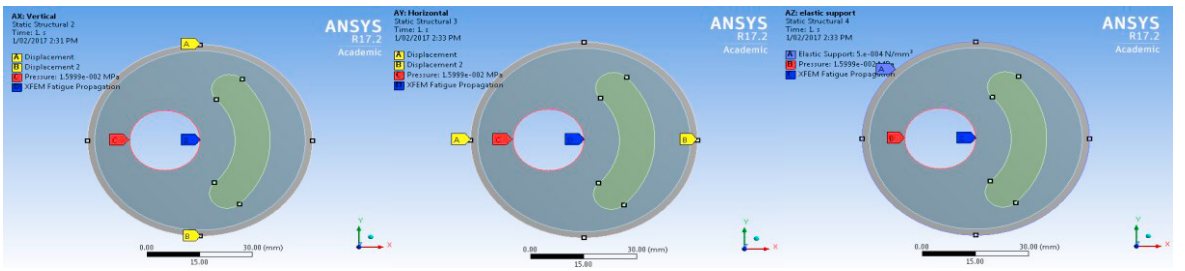



Figure 2: Different boundary conditions: Left: displacement support at vertex A and B (Vertical) with X component free and zero displacement for Y component for vertex A, and zero displacement for X and Y components of vertex B; Middle: displacement support at vertex A and B (Horizontal) with Y component free and zero displacement for X component for vertex A and zero displacement for X and Y components of vertex B; Right: Elastic support on the outer edge with a stiffness of 0.0005 N/mm$^3$.

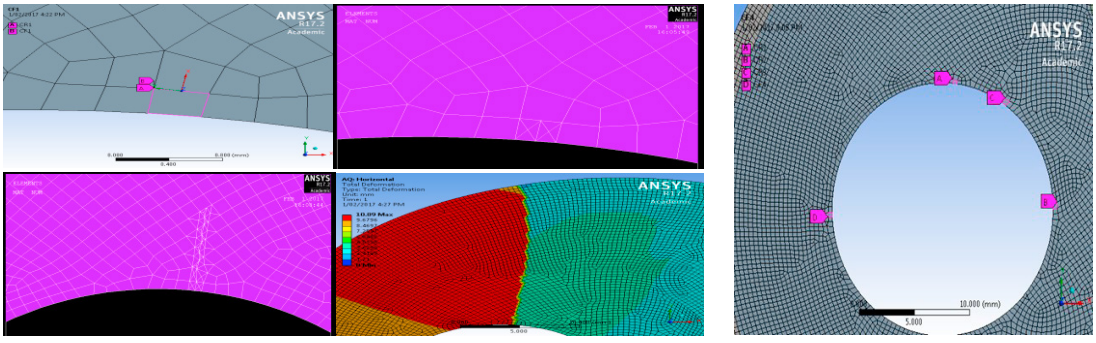
The life cycle method was used to define a constant amplitude pressure load where the crack propagates one element at a time. A cyclic pressure load was applied on the lumen to investigate the effect of pulse pressure, mean arterial pressure and stress ratio. Twelve different stress ratio as listed in Table 2 were used for the crack propagation simulations. A singularity based approach was used for fatigue crack propagation which accounts for crack tip singularities and jumps in displacements across the surface.

Table 2: Different cases of stress ratio analyzed

| Case | Systolic Pressure (SP) mm of Hg | Diastole Pressure (DP) mm of Hg | Pulse Pressure (PP) PP=SP-DP mmHg | Mean Arterial Pressure (MAP) MAP =DP + PP/3 mmHg | Stress Ratio SR = DP/SP |
|---|---|---|---|---|---|
| I | 180 | 80 | 100 | 113.33 | 0.44 |
| II | 200 | 100 | 100 | 133.33 | 0.5 |
| III | 180 | 100 | 80 | 126.67 | 0.55 |
| IV | 140 | 80 | 60 | 100 | 0.57 |
| V | 200 | 120 | 80 | 146.67 | 0.6 |
| VI | 160 | 100 | 60 | 120 | 0.625 |
| VII | 120 | 80 | 40 | 93.33 | 0.67 |
| VIII | 100 | 70 | 30 | 80 | 0.7 |
| IX | 140 | 100 | 40 | 113.33 | 0.714 |
| X | 120 | 90 | 30 | 100 | 0.75 |
| XI | 100 | 80 | 20 | 86.67 | 0.8 |
| XII | 120 | 100 | 20 | 106.67 | 0.83 |

## 3. Results and Discussion

The initial crack location (CR1) and crack front (CF1) are defined by selecting elements and a co-ordinate system was also defined at the crack tip with x-axis towards crack propagation direction as shown in Figure 3(a). Singularity enrichment region and enhancement radius were defined to include the singularity functions to account for the crack tip singularity around the crack tip. Different crack initiation locations were defined to study the effect of location on fatigue life as shown in Figure 3(b). The results show that, for all the three different boundary conditions i.e vertical boundary condition (VBC), horizontal boundary Condition (HBC) and elastic boundary condition (EBC), it is observed that with change in blood pressure there is no change in the initial crack location based on maximum stress criteria. Also, fatigue life increased with increase in stress ratio as shown in Figure 4. For the elastic boundary condition the fatigue life is observed to be more compared to the other two boundary conditions. Since, elastic support being more realistic than the other two conditions it is thus used for further simulations. Comparison of fatigue life for different boundary conditions with same stress ratio is shown in Figure 5(a).




(a) (b)

Figure 3(a): Top left- Initial crack, crack front and co-ordinate system; Top right- Remeshing at the crack tip by XFEM method; Bottom left- crack propagation with remeshing at crack tip; Bottom right- Total deformation along the crack propagation; 3(b): Different initial crack locations (A) Crack location based on stress criteria; (B) Middle region; (C) Shoulder region; (D) Back region

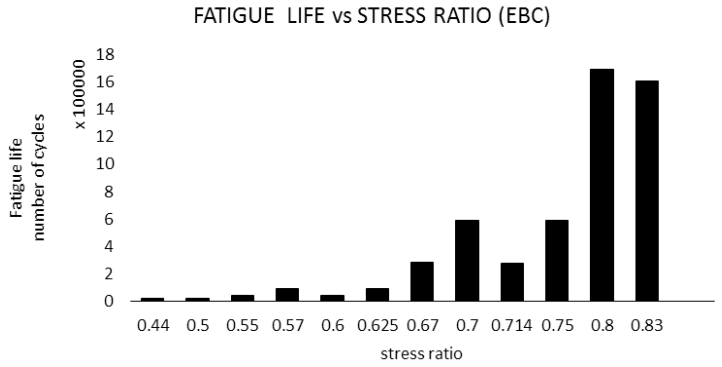



Figure 4: Variation of fatigue life with increase in stress ratio

Pulse pressure is observed to be the critical parameter rather than the mean arterial pressure. Figure 5(b) shows that the increase in pulse pressure, increased the crack growth rate thereby decreasing the fatigue life of the plaque. Also, for the same pulse pressure (20, 30 and 40 mmHg), an increase in the mean arterial pressure resulted in the slight decrease in fatigue life, while for pulse pressure above 40 mmHg an increase in the mean arterial pressure resulted in increase of the fatigue life. Figure 6 shows that an increase in the systole pressure decreased the fatigue life of the plaque. Fatigue life of the plaque at different locations on the lumen is shown in figure 7. The shoulder region and the middle region of the lipid pool are the critical regions of interest as they have less fatigue life compared to the back region.

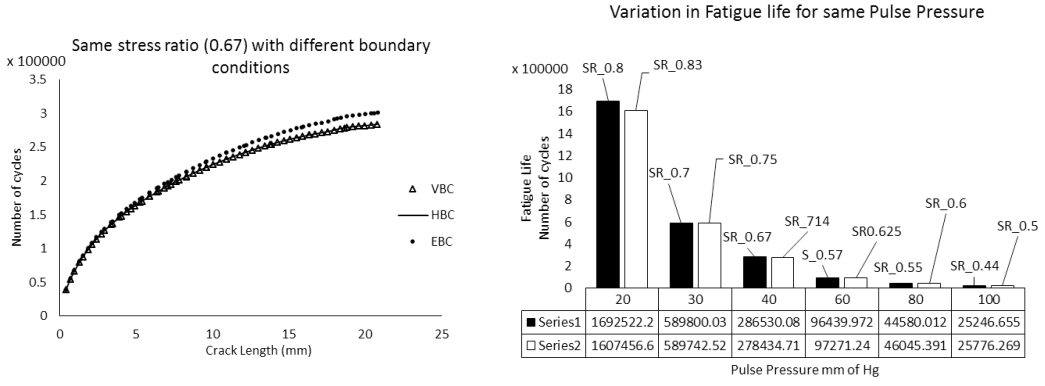



Figure 5(a): Comparison of fatigue life for different boundary conditions with same stress ratio; 5(b): Variation of Fatigue life for same Pulse pressure

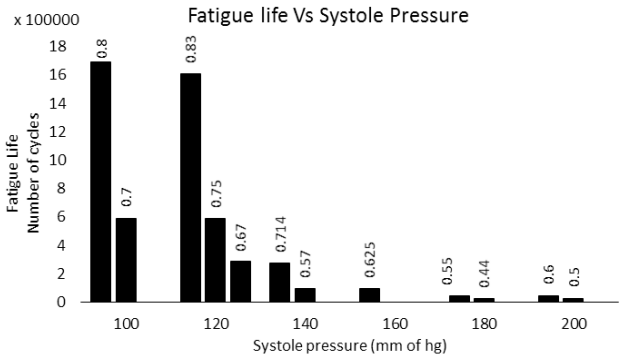



Figure 6: Variation of fatigue life with increase in Systole Pressure

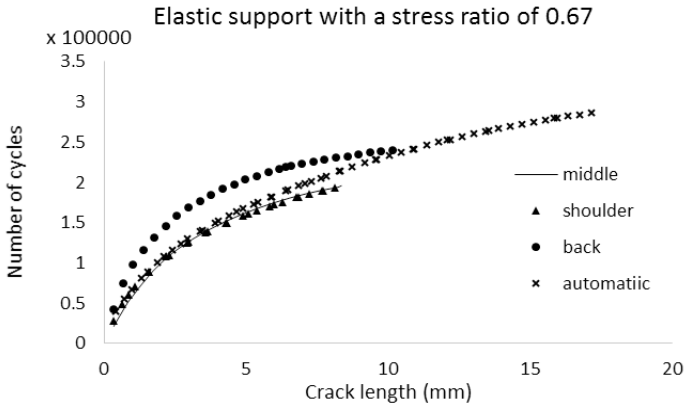



Figure 7: Comparison of fatigue life for different initial crack locations

## 4. Conclusion

Fatigue failure is the mechanism causing plaque rupture. Cracks are initiated at the lumen boundary, where there is maximum stress and this location did not change with change in pulse pressure or mean arterial pressure. Cracks extended radially and the crack growth rate increased with increase in pulse pressure. Crack growth rate also depends on the plaque morphology, constituents and their spatial location. The crack initiated at the maximum stress location is not always the critical crack location, because cracks initiated at the shoulder region and mid cap region, have less fatigue life. Therefore, from this basic idealized 2D study it is evident that understanding the fatigue behavior of the plaque under the cardiovascular environment is crucial for determining the plaque vulnerability. To have more confidence in the mechanism 3D simulations and experiments based on 3D printed blood vessels are required.

## Acknowledgements

The authors would like to acknowledge Sam Nardella from Leap Australia for providing his technical assistance and High performance computing team (QUT).

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