The Relation between Atherosclerosis Plaque Composition and Plaque Rupture

Abstract

Background: Intima, media, and adventitia are three layers of arteries. They have different structures and different mechanical properties. Damage to intima layer of arteries leads to an inflammatory response, which is usually the reason for atherosclerosis plaque formation. Atherosclerosis plaques mainly consist of smooth muscle cells and calcium. However, plaque geometry and mechanical properties change during time. Blood flow is the source of biomechanical stress to the plaques. Maximum stress that atherosclerosis plaque can bear before its rupture depends on fibrous cap thickness, lipid core, calcification, and artery stenosis. When atherosclerotic plaque ruptures, the blood would be in contact with coagulation factors. That is why plaque rupture is one of the main causes of fatality. Method: In this article, the coronary artery was modeled by ANSYS. First, fibrous cap thickness was increased from 40 μm to 250 μm by keeping other parameters constant. Then, the lipid pool percentage was incremented from 10% to 90% by keeping other parameters unchanged. Furthermore, for investigating the influence of calcium in plaque vulnerability, calcium was modeled in both agglomerated and microcalcium form. Results: It is proved that atherosclerosis plaque stress decreases exponentially as cap thickness increases. Larger lipid pool leads to more vulnerable plaques. In addition, the analysis showed maximum plaque stress usually increases in calcified plaque as compared with noncalcified plaque. Conclusion: The plaque stress is dependent on whether calcium is agglomerated near the lumen or far from it. However, in both cases, the deposition of more calcium in calcified plaque reduces maximum plaque stress.

Keywords: Atherosclerosis plaque, biomechanical stress, calcification, fibrous cap thickness, lipid core

Introduction

The arteries are composed of three distinct layers with different structures and functions. The sequence of layers from outside to inside is adventitia, media, and intima. Adventitia is an outermost layer that provides support and strength for the artery. Media plays a pivotal role in changes of vascular diameter and the maintenance of vascular tone.[1] Intima includes endothelium, sub-endothelium, and internal elastic lamina. Cells in the innermost layer of intima are in contact with the blood stream. Damage to the intima can initiate the process of atherosclerosis.[2] Atherosclerosis is one of the main causes of death worldwide, which accounts for around two-thirds of all death.[3,4] The exact cause of atherosclerosis is unknown. Recently, it is understood as an inflammatory/proliferative disease. Usually, the atherosclerotic process starts from childhood and progresses slowly.[5] Atherosclerosis is identified by the accumulation of pathologically activated cells. The cellular players in atherosclerotic plaque formation include endothelial cells, immune cells, lipid-laden cells, smooth muscle cells.[4] In atherosclerosis, artery’s wall thickens because of the accumulation of fat, fibrous tissue, and calcium deposit. As intima thickens, arterial lumen narrows. The plaque hardens gradually and ultimately ruptures. Rupture of plaques initiates the thrombotic cascade.[4] Rupture of plaques makes blood be in contact with subendothelial coagulation factors. Clot formation leads to heart diseases such as acute myocardial infarction and Angina...
The question is “What leads to plaque rupture?” According to researches plaque rupture is a biomechanical phenomenon that depends on the complex interplay between plaque composition and applied stresses. Atherosclerosis plaques mainly include lipid pool, fibrous tissue, and calcium. The fibrous cap is stiffer than lipid core so it can sustain more stress. The cap thickness of 60–250 μm contributes to plaque stability. At the shoulders, the plaque becomes thinner, so the abrupt transition between mildly and highly stressed areas makes the shoulders more vulnerable areas. Furthermore, pulsatile blood flow gradually weakens the fibrous cap and causes fatigue.

**Finite element analysis of atherosclerosis**

The coronary artery wall is constantly exposed to flow-induced wall shear stress. Researches have demonstrated that high mechanical stress condition over the plaque surface results in plaque vulnerability. Furthermore, circumferential stress may play an important role in plaque rupture. Furthermore, plaque rupture locations may be related to maximal stress conditions on the plaque. Similarly, it has been suggested that pulsatile blood pressure results in plaque fatigue failure. There are some relationships between plaque vulnerability and its composition. According to previous studies, the overall average plaque rupture threshold is around 300 kPa. Both Finite Element Method and experimental analysis demonstrated that thinning of fibrous cap is associated with increased plaque rupture vulnerability. Moreover, fluid-structure interaction simulations reconstructed from intravascular ultrasound imaging indicated that mechanical stress (Von Mises Stresses) increases exponentially with thinning of the fibrous cap. In another study, different mechanical properties of plaque components were examined to find maximum plaque stress. In that simulation, eliminating the lipid pool and replacing it by fibrous cap resulted in a dramatic decrease in maximum stress in the plaque. Therefore, lipid core was shown to have a remarkable effect in the vulnerability of the plagues. Furthermore, it was revealed that maximum stress is not correlated with the percentage of calcification. In stable plaques with a high amount of calcium, the calcium gets the intensity of pressure. Hence, eliminating a great amount of calcium from atherosclerosis plaques leads to the vulnerability of plaques. Li et al. used ABAQUS finite element analysis to understand whether calcium increases stress in lesions or not. In their study, blood pressure was time-dependent, and the calcium was placed in different locations of atherosclerosis plaques such as artery’s wall, lipid pool, and fibrous cap to find Von Mises stress. They concluded calcium in fibrous cap may lead to stress concentration in it. In addition, the difference between mechanical properties of fibrous cap and calcium contributes to crack propagation. Therefore, atherosclerosis plaques with a calcified fibrous cap are classified as vulnerable plaque. On the other hand, calcium in lipid core far from the fibrous cap does not enhance biomechanical stress and may result in the stability of plaques. Similarly, it was shown that microcalcification in cap considerably increases the risk of plaque rupture.

In summary, previous studies suggest that altering plaque composition changes plaque vulnerability. In this paper, the maximum peripheral stress, maximum peripheral strain, maximum radial stress, and maximum radial strain caused by a blood pressure of 120 mmHg were found by considering different compositions of fibrous cap thickness, lipid pool percentage, and calcification.

**Methods**

The goal of this project is to find the maximum stress in atherosclerosis plaque with various compositions. The plaque composition, including fibrous cap, lipid pool, and calcium, are considered as key players for finding the maximum peripheral stress. Plaque stability depends on its morphology, components, and hemodynamic stress. Plaque stress is influenced by these factors altogether. To analyze the influence of plaque geometry, ANSYS 2014 was used. ANSYS is a general-purpose finite element software for numerically solving a variety of mechanical properties. The finite element solution may be broken into three stages of preprocessing, solution, and postprocessing. In preprocessing stage, the ideal coronary plaque was designed. Atherosclerosis plaques with different cap thicknesses, lipid pool percentage, and calcification are modeled. First, atherosclerotic plaques with different fibrous cap thicknesses were modeled. Then, groups of atherosclerotic plaque with different lipid core percentage were modeled. Similarly, plaques with the different distribution of calcium were designed. For modeling each group, only one parameter was changed while keeping others constant. In this two-dimensional modeling, tetra type mesh was used with dimensions of 0.00004 mm. Mechanical properties, including Young’s Modulus and Poisson’s ratio, are assigned to the plaque segments according to the Table 1. In the solution stage, the plaque geometry was constrained in two dimensional, and the blood pressure of 120 mmHg was applied to the plaque. In post-processing stage, maximum stresses and strains were found.

| Material       | Young’s modulus (KPa) | Poisson’s ratio |
|----------------|----------------------|----------------|
| Fibrous cap    | 800                  | 0.49           |
| Lipid core     | 5                    | 0.49           |
| Artery wall    | 150                  | 0.49           |
| Calcium        | 5000                 | 0.49           |

Table 1: Mechanical properties of plaque components
Results and Discussion

Relationship between fibrous cap thickness and plaque maximum stress

By increasing cap thickness from 40 to 250 μm, and keeping stenosis and lipid percentage constant, the relationship between maximum plaque stress and fibrous cap thickness is found. According to Figure 1, maximum peripheral stress is reduced exponentially as it thickens. Furthermore, maximum peripheral stress occurs at the shoulders of atherosclerosis plaque. Maximum peripheral strain, maximum radial stress, and maximum radial strain are shown in Tables 2-8.

Relationship between lipid percentage and maximum plaque stress

By increasing lipid percentage and keeping stenosis and fibrous cap thickness constant, the relationship between maximum plaque stress and lipid percentage was found.

According to Figure 2 by increasing lipid percentage, maximum peripheral stress enhances. Therefore, more lipid leads to more vulnerable atherosclerosis plaque. Maximum peripheral strain, maximum radial stress, and maximum radial strain are shown in Tables 9 and 10.

Relationship between calcium and maximum plaque stress

To investigate the role of calcium in plaque stress, calcium was considered in both agglomerate and microcalcium forms.

A. Examining agglomerate calcium formed near lumen: according to Figure 3, when calcium is formed near the lumen, maximum peripheral stress increases as compared with noncalcified plaque. However, Table 11 shows plaque stress decreases as calcium percentage increases. Hence, calcium presence enhances maximum plaque stress significantly, but fully calcified plaque is less vulnerable than fully lipid plaque.

B. Examining agglomerate calcium formed far from the lumen: according to Table 12, increasing calcium leads to a continuous decline in plaque stress. Thus, calcium formed far from the lumen contributes to plaque stability. Comparison between maximum stress when calcium is agglomerated near and far from the lumen shows that atherosclerosis plaque is exposed to higher stress when calcium is agglomerated near the lumen.

Relationship between size of microcalciums and maximum plaque stress

For finding the relationship between size and maximum stress, microcalciums with radii of 2.5, 5, 10, 15, 20,

Table 2: Maximum stress and strain in arteries with constant lipid core of 10% and stenosis of 50% (S1) and stenosis of 70% (S2)

| Fibrous cap thickness (mm) | Stenosis | 40     | 65     | 100    | 150    | 200    | 250    |
|---------------------------|----------|--------|--------|--------|--------|--------|--------|
| Maximum peripheral stress (KPa) | S1        | 283.79 | 201.66 | 173.9  | 171.54 | 174.24 | 173.17 |
|                           | S2        | 261.00 | 197.06 | 138.48 | 99.178 | 97.097 | 97.306 |
| Maximum peripheral strain (m/m) | S1        | 1.9157 | 1.3262 | 1.0528 | 0.8626 | 0.6966 | 0.5673 |
|                           | S2        | 1.329  | 0.9179 | 0.7394 | 0.5894 | 0.4932 | 0.4169 |
| Maximum radial stress (KPa)  | S1        | -201.51| -96.93 | -121.51| -110.23| -88.375| -70.975|
|                           | S2        | -157.95| -116.62| -93.849| -69.773| -51.078| -41.781|
| Maximum radial strain (mm)   | S1        | -2.1813| -1.182 | -1.7015| -1.1552| -0.934 | -0.762 |
|                           | S2        | -1.571 | -1.125 | -0.8893| -0.7002| -0.5709| -0.4811|
and 30 were modeled. According to Table 13, maximum peripheral stress increases by increasing of microcalcium size, so there is more probability of plaque rupture.

**Validation**

To validate the numerical solution, calculated strains of the current research were compared with the analysis of Baldewsing et al.\[21\] In Baldewsing study, cap thickness is considered 50 μm and Young’s modulus is between 500 and 2500 kpa. In this section, geometry, boundary conditions, and blood flow were exactly modeled the same as Baldewsing’s work. In Figure 4, Young’s modulus-strain curve below compares the present study with Baldewsing results.
Table 7: Maximum stress and strain in arteries with constant lipid core of 60% and stenosis of 50% (S1) and stenosis of 70% (S2)

| Fibrous cap thickness (mm) | Stenosis | 40    | 65    | 100   | 150   | 200   |
|---------------------------|----------|-------|-------|-------|-------|-------|
|                           |          |       |       |       |       |       |
| Maximum peripheral stress (KPa) | S1      | 418.64| 281.98| 206.47| 173.72| 174.66|
|                           | S2      | 386.21| 256.04| 171.74| 116.77| 97.278|
| Maximum peripheral strain (m/m) | S1      | 0.6328| 0.5616| 0.3698| 0.2545| 0.2085|
|                           | S2      | 0.4942| 0.3136| 0.2121| 0.1465| 0.1235|
| Maximum radial stress (KPa) | S1      | −130.03| −117.5| −78.472| −46.921| −66.870|
|                           | S2      | −90.719| −71.737| −49.254| −35.966| −25.360|
| Maximum radial strain (mm)  | S1      | −1.098| −0.8031| −0.5506| −0.2561| −0.3099|
|                           | S2      | −0.9349| −0.5333| −0.3600| −0.2241| −0.1526|

Table 8: Maximum stress and strain in arteries with constant lipid core of 70% and stenosis of 50% (S1) and stenosis of 70% (S2)

| Fibrous cap thickness (mm) | Stenosis | 40    | 65    | 100   | 150   | 200   |
|---------------------------|----------|-------|-------|-------|-------|-------|
|                           |          |       |       |       |       |       |
| Maximum peripheral stress (KPa) | S1      | 429.53| 280.94| 222.11| 190.26| 190.26|
|                           | S2      | 387.23| 227.3 | 211.36| 137.95| 137.95|
| Maximum peripheral strain (m/m) | S1      | 0.6204| 0.5640| 0.4247| 0.2287| 0.2287|
|                           | S2      | 0.5026| 0.2995| 0.2327| 0.1611| 0.1611|
| Maximum radial stress (KPa) | S1      | −130.06| −116.85| −78.472| −46.921| −88.056|
|                           | S2      | −93.45| −75.848| −59.226| −46.031| −46.031|
| Maximum radial strain (mm)  | S1      | −1.092| −0.897| −0.5506| −0.2561| −0.4825|
|                           | S2      | −0.8623| −0.5136| −0.3385| −0.1694| −0.1694|

Table 9: Maximum stress and strain in arteries with constant fibrous cap of 40 mm and stenosis of 50% (S1) and stenosis of 70% (S2)

| Lipid percentage of plaque | Stenosis | 10    | 20    | 30    | 40    | 50    | 60    | 70    | 80    | 90    |
|---------------------------|----------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
|                           |          |       |       |       |       |       |       |       |       |       |
| Maximum peripheral stress (KPa) | S1      | 283.79| 320.35| 357.94| 362.49| 390.08| 418.64| 429.53| 371.11| 383.79|
|                           | S2      | 261   | 300.25| 314.14| 343.36| 364.33| 386.21| 387.23| 394.23| 380.33|
| Maximum peripheral strain (m/m) | S1      | 1.916 | 1.296 | 1.016 | 0.872 | 0.8193| 0.638 | 0.620 | 0.6886| 0.7129|
|                           | S2      | 1.329 | 0.835 | 0.6469| 0.5377| 0.4888| 0.4942| 0.5026| 0.4450| 0.4517|
| Maximum radial stress (KPa) | S1      | −201.5| −167.4| −155.6| −144.3| −127.2| −130.0| −156.2| −224.6|         |
|                           | S2      | −157.9| −128.7| −111.9| −99.31| −92.86| −90.72| −93.45| −118.5| −135.2|
| Maximum radial strain (mm)  | S1      | −2.181| −1.654| −1.411| −1.291| −1.224| −1.098| −1.122| −1.118|         |
|                           | S2      | −1.571| −1.178| −1.007| −0.918| −0.895| −0.935| −0.862| −0.715 | −0.747|

In summary, in this project, ideal atherosclerotic plaque geometry was modeled, and analysis was done based on mechanical properties of each component. The results of the analysis are collected in Table 14.
Table 10: Maximum stress and strain in arteries with constant fibrous cap of 65 mm and stenosis of 50% (S1) and stenosis of 70% (S2)

| Lipid percentage of plaque | Stenosis | 10   | 20   | 30   | 40   | 50   | 60   | 70   | 80   | 90   |
|----------------------------|----------|------|------|------|------|------|------|------|------|------|
| Maximum peripheral stress (KPa) | S1       | 283.79 | 320.35 | 357.94 | 362.49 | 390.08 | 418.64 | 429.53 | 371.11 | 383.79 |
| Maximum peripheral strain (m/m) | S1       | 1.916 | 1.296 | 1.016 | 0.872 | 0.8193 | 0.638 | 0.620 | 0.6886 | 0.7129 |
| Maximum radial stress (KPa) | S1       | -201.5 | -167.4 | -155.6 | -144.3 | -127.2 | -130.0 | -156.2 | -224.6 |
| Maximum radial strain (mm) | S1       | -2.181 | -1.654 | -1.411 | -1.291 | -1.224 | -1.098 | -1.122 | -1.118 |

Table 11: Relation between plaque stress and calcium percentage when calcium is agglomerated near the lumen

| Calcium percentage | 10   | 20   | 30   | 40   | 50   | 60   |
|--------------------|------|------|------|------|------|------|
| Maximum peripheral stress (KPa) | 1713.4 | 814.1 | 482.6 | 249.3 | 169.6 | 169.1 |
| Maximum peripheral strain (m/m) | 1.2325 | 0.9361 | 0.5345 | 0.3294 | 0.2186 | 0.2177 |
| Maximum radial stress (KPa) | -156.12 | -116.13 | -188.49 | -62.316 | -35.112 | -25.624 |
| Maximum radial strain (mm) | -0.9136 | -0.7476 | -0.4101 | -0.2830 | -0.1760 | -0.1409 |

Table 12: Relation between plaque stress and calcium percentage when calcium is agglomerated far from the lumen

| Calcium percentage | 10   | 20   | 30   | 40   | 50   | 60   |
|--------------------|------|------|------|------|------|------|
| Maximum peripheral stress (KPa) | 250.99 | 226.1 | 216.00 | 169.95 | 169.56 | 169.16 |
| Maximum peripheral strain (m/m) | 0.5296 | 0.4536 | 0.3114 | 1.26 | 0.2896 | 0.2177 |
| Maximum radial stress (KPa) | -111.41 | -103.89 | -97.109 | -61.507 | -47.83 | -25.624 |
| Maximum radial strain (mm) | -0.8079 | -0.7491 | -0.6124 | -1.4027 | -0.2287 | -0.1409 |

Table 13: Relation between size of microcalcium and the maximum stress

| Radius (mm) | 2.5 | 5   | 10   | 15   | 20   | 30   |
|-------------|-----|-----|------|------|------|------|
| Maximum peripheral stress (KPa) | 296.38 | 292.24 | 313.89 | 334.33 | 400.91 | 530.39 |
| Maximum peripheral strain (m/m) | 0.3470 | 0.3411 | 0.3602 | 0.3560 | 0.3548 | 0.3593 |
| Maximum radial stress (KPa) | -104.66 | -181.86 | -152.1 | -155.3 | -111.29 | -106.92 |
| Maximum radial strain (mm) | -0.6347 | -0.6429 | -0.6684 | -0.6678 | -0.6659 | -0.6677 |

Table 14: Summary of results

| Parameter       | Description                                                                 |
|-----------------|------------------------------------------------------------------------------|
| Cap thickness   | Maximum plaque stress increases exponentially as cap thickness decreases      |
| Lipid core      | Maximum plaque stress increases as lipid pool is enlarged                    |
| Calcium         | Maximum plaque stress increases as calcium deposits. However, calcium burdens more stress as compared with plaque due to greater Young’s modulus. On the other hand, maximum plaque stress decreases as calcium percentage increases. As calcium accumulates, plaque stress decreases. Therefore, influence of calcium is determined by its percentage. |
| Agglomerate calcium | Maximum plaque stress increases dramatically as calcium agglomerates near the lumen. However, calcium accumulated behind the lipid pool does not change plaque stress significantly |
| Microcalcium    | Maximum plaque stress increases as size of microcalcium enhances              |

Figure 3: Schematic of atherosclerosis plaque when calcium is agglomerated near the lumen

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**Conflicts of interest**

There are no conflicts of interest.
Babaniamansour, et al.: The relationship between atherosclerosis plaque composition and plaque rupture

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