UNDERSTANDING ATHEROSCLEROSIS AND PLAQUE RUPTURE VULNERABILITY

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Abstract

Atherosclerosis is considered to be the leading cause of cardiovascular disease resulting in acute coronary syndromes. It is pathologically defined as the accumulation of large lipid-rich core, blood clots and calcification forming lesions called plaques. If the atherosclerotic plaque ruptures, it could potentially lead to serious clinical events such as a heart attack and stroke. The pathology of atherosclerosis is well understood; however, there is limited information on the material properties of plaque rupture and its vulnerability. The main objective of this report is to perform a literature review of atherosclerosis. This review will mainly cover the underlying pathology of the disease and its vulnerability to plaque rupture, treatments in use, and an overview of the current investigative research in the progression of the disease.
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1. Introduction

Cardiovascular diseases (CVD) are responsible for claiming the lives of 17.1 million people worldwide, making them the number one cause of death [11]. By 2030, it is expected that this number will increase to 23.6 million people keeping CVD the most prevalent disease. In Canada, 30% of deaths are caused from cardiovascular diseases costing the Government of Canada a staggering $22.2 billion every year in physician services, hospital costs and decreased productivity [14]. Nevertheless, there has been tremendous clinical progress in reducing the number of fatalities leading to CVD deaths.

Atherosclerosis is considered to be the most common cardiovascular disease resulting in acute coronary syndromes. It is a disease affecting the medium to large size arteries such as the coronary, iliac and femoral arteries, and the largest artery in the human body, the aorta. Atherosclerosis is pathologically defined as the accumulation of large lipid-rich core, blood clots and calcification forming lesions called plaques. If the atherosclerotic plaque ruptures, a blood clot may form and block the blood flow to the heart leading to fatal clinical events. Individuals who have high blood pressure, high blood cholesterol level and diabetes are at a higher risk of developing atherosclerosis.

The objective of this report is to write a literature review on the scientific research progress on atherosclerosis with a focus on the mechanical behavior of atherosclerotic plaque rupture. Furthermore, an overview of the clinical implications of coronary artery atherosclerosis will be discussed.
2. Heart Anatomy

In order to understand the pathophysiology of atherosclerosis, it is critical to comprehend the basic anatomy and functioning of the heart muscle. The heart, as seen in figure 1, is a muscular organ responsible for pumping blood received from the veins into the arteries, supplying oxygenated blood to different tissues in the body for energy and proper functioning. The following is a brief overview of the blood flow pathway in the circulatory system:

1. The superior and inferior vena cava are veins that empty de-oxygenated blood from the upper and lower body into the right atrium.
2. By a sinoatrial impulse, the right atrium contracts and empties the blood into the right ventricle. Followed by pumping blood into the pulmonary artery where it is transported to the lungs.
3. After inspiration, and by several transport mechanisms, the rich-oxygenated blood is then driven from the lungs by the pulmonary veins into the left atrium and ventricle.
4. From the left ventricle, the blood is pumped into the aorta where blood is transported into the upper and lower body and a partial amount into the coronary arteries in order to supply oxygen to the heart.
2.1 The coronary arteries

The heart requires oxygen and nutrients for contraction and to provide oxygenated blood to the rest of the body. As seen in figure 2, the coronary artery system is characterized by a network of arteries found in the epicardial layer enclosing the heart and fulfills that role. The left coronary artery, which supplies blood to the left atrium and ventricle, branches out into the left circumflex coronary artery and the left anterior descending coronary artery. In contrast, the right coronary artery supplies oxygen to the right atrium and ventricle. The function of coronary arteries are critical to the life of an individual, a lack of blood flow to the heart reduces the oxygen supply to the muscle resulting in a deadly cardiac event. In atherosclerosis, the potential plaque build-up in the coronary arteries could potentially block oxygen supply to the heart leading to severe health conditions.

Figure 2 Front view of the heart [16]
2.2 Pathophysiology of Atherosclerosis

Atherosclerosis is defined as a chronic inflammatory, fibroproliferative disease fuelled by the accumulation of lipids, blood clots and calcification in the inner artery wall known as plaques. If the plaque ruptures, there is a high risk of a serious clinical event. Plaque rupture is characterized by the accumulation of a lipid rich core, a thin fibrous cap that contains smooth muscle, angiogenesis and inflammation [4]. It is a complex process that starts as early as childhood, symptoms become more apparent in the mid to late adulthood. Falk focused his work on the cellular components that play a major role in the development in atherosclerosis. His research determined that endothelial cells, leukocytes and intimal smooth muscle cells are major players that activate the pathogenesis of the disease [4]. Many researchers have indicated that the atherosclerotic lesions begin to develop at areas where the endothelium has been damaged. Consequently, plasma molecules, lipoprotein particles, fatty substances, cholesterol and other constituents penetrate the damaged wall and become cytotoxic, proinflammatory, and proatherogenic. Progressively, the endothelial damage stimulates the immune system to attract more cytotoxic substances to the damage site further promoting pathogenesis. Gradually, the atherosclerotic plaque hardens and thickens hence reducing the artery’s diameter and oxygen supply to the heart. It’s important to mention that atherosclerotic lesions alone are not critical, rather thrombosis that occurs on the ruptured plaque that is potentially dangerous to the individual. In other words, when the fibrous cap is damaged and the plaque ruptures, the thrombogenic lipid-rich core is exposed to the blood flow potentially causing a blood clot. If the blood clot blocks blood flow to the heart, it is considered a heart attack. However, if the blood flow is blocked to the brain, it is called a stroke.
2.2.1 Normal arteries

As seen in Figure 3, arteries are structured into three layers: the intima, the media, and the adventitia. Each layer has its own characteristics that influence the mechanical behavior of the artery. The intima is the innermost layer of the artery and is composed of endothelial cells that are in direct contact with the blood flow. The intima’s thickness increases with age, progressing from a size of 60μm at 5 years of age to 250μm at 40 years of age [17]. In coronary arteries, the media is composed of smooth muscle allowing for a stretch and recoil behavior. Media thickness varies from 125μm to 350μm and becomes thinner with atherosclerosis and age. In coronary arteries, the adventitia is the thickest of all three layers, and is composed of mainly connective tissue and smooth muscle.

![Figure 3 Structure of arterial wall (17)](image-url)
2.2.3 Atherosclerotic arteries

Unlike healthy arteries, atherosclerotic arteries exhibit different characteristics due to the constituents that have diseased the different wall layers. As previously mentioned, atherosclerosis begins at early stage of life but prevail at a later age. In order to better characterize the disease, the American Heart Association has been able to classify the different stages of artherogenesis based on histology. Their objective was to be able to characterize the composition of atherosclerotic lesions as they develop over the course of a person’s lifetime. As seen in Figure 4, type I to type III lesions, we notice the beginning of the endothelium damage and leakage of macrophages into the artery wall to an accumulation of intracellular small lipid pools. The risk factor of a serious clinical outcomes becomes more prevalent at lesion of type IV (atheromas), where vascular remodeling and obstruction of blood flow occurs. Lesions of type IV and V contain a lipidic core but differ in the integrity of the fibrous cap. The cap composition of a type IV lesion has a thickness comparable to a normal intima. This enables the vascular remodeling to occur outwards, however, if lipid accumulation reaches a certain limit, the lipid accumulation will force an inward and create a narrowing of the blood vessel resulting in obstruction. In addition, type V plaques also contain a single or multiple layer lipid cores and are classified into lipidic, calcified or fibrous plaques (18). Type VI lesions are characterized by a surface defect such as thrombosis.
2.2.4 Vulnerable Plaques

When a plaque becomes vulnerable, its likelihood of plaque rupture increases potentially leading to a high risk of a clinical event. There are several determinants that characterize plaque vulnerability such as a) the size of the atheromatous core b) the thickness of the fibrous cap c) inflammation and repair within the cap [18].

The size of the atheromatous core plays a key role in the stability of the plaque. In fact, Virmani et al. showed that the mean necrotic core size in coronary arteries was the greatest in rupture plaques [19]. Davies and al. found a particular relationship between plaques rupture and core size, he found that a core occupying more than 40% of the plaque area is much more vulnerable to thrombosis and plaque rupture [2]. The core is dependent on the composition and the
temperature. From postmortem analysis, it was found that the core exhibits toothpaste like behavior; whereas, \textit{in vivo} the core becomes softer when the temperature is increased. Furthermore, a thin fibrous cap and decrease collagen content increase plaque vulnerability [28]. Collagen is important in upholding the integrity of biological tissues. When macrophages penetrate the fibrous cap, they may secrete enzymes that stimulate and activate more macrophages to attack the fibrous cap and predispose it to rupture.

\textbf{2.2.5 Rupture Triggers}

A vulnerable plaque is critical when it comes to preventing a fatal accident. However, there are other factors involved in plaque rupture. The fibrous cap is constantly being affected by different biomechanical and hemodynamic forces that may trigger plaque rupture such as blood pressure and pulse pressure. The blood pressure exhibits a circumferential tension and radial compression on the wall. If a fibrous cap is thin and contains a soft core, it will be unable to bear the load from these forces and likely result in plaque rupture. On the other hand, the pulse pressure creates a pulsatile motion of the artery wall creating a cyclic pulse wave that causes deformation in lumen size and shape and possible change in the plaque cap structure. Over time, these stresses will likely cause the plaque to rupture due to cyclic fatigue, especially in areas when there is a difference in stiffness between the adjacent healthy plaque-free wall and the plaque cap.

\begin{figure}[h]
\centering
\includegraphics[width=0.3\textwidth]{lipid_plaqueHistology.png}
\caption{Histology of a lipid rich coronary plaque. The thin fibrous cap (arrows) and lipid core (LC)[4]}
\end{figure}
2.2.6 Hemodynamics forces

The entire vascular system is exposed to risk factors that accelerate atherogenesis. However, atherosclerotic lesions form at specific regions in the arterial tree where flow is disturbed specifically surrounding branch points, the outer wall of bifurcations, and the inner wall of curvatures (13). Chatzizisis et al. determined that hemodynamic forces such as flow-generated endothelial shear stress (ESS) and tensile stress play a major role in the localization of atherosclerotic lesions (13). Endothelial shear stress is defined as the tangential stress from the friction of the blood flow on the endothelial wall and is expressed in N/m$^2$ or Pa or dyne/cm$^2$ [1 Pa = 10 dyne/cm$^2$]. ESS could also be formulated by, \[ ESS = \mu \frac{dv}{dy} \]

The irregular geometry of the coronary arteries combined with the instability of the blood flow due to its pulsatile behavior determines the endothelial shear stress profile. In his work, Chatzizisis highlights several points on the role of low ESS on atherosclerosis. He summarizes his points by mentioning that low ESS:

1) Attenuates nitric oxide (NO)- dependent atheroprotection
2) Promotes low density lipoprotein cholesterol (LDL) uptake
3) Promotes oxidative stress and inflammation
4) Promotes vascular smooth muscle cell migration, differentiation and proliferation.
5) Promotes extracellular matrix (ECM) degradation in vascular wall and plaque fibrous cap.

6) Attenuates ECM synthesis in vascular wall and plaque fibrous cap.

Nitric oxide is known to possess strong anti-inflammatory, anti-mitogenic and anti-thrombotic properties [13]. Several studies have shown that in the arterial regions with disturbed flow, a low ESS reduces the production of NO, hence increasing the risk of exposure of the endothelium to atherogenic effects.

Vascular remodeling response to atherosclerosis is also a significant clinical factor in the progression of the disease. The integrity of the arterial wall is primarily maintained by a matrix protein synthesis [13]. As explained in figure 10, early atherosclerotic lesions are initiated by a low ESS leading to a formation of early fibroatheroma. If compensatory expansive remodeling takes place, the local ESS is normalized and the plaque stabilizes with limited inflammation. When local, systematic or genetic factors are present, the artery wall might undergo excessive expansive remodeling with a persistence of local low ESS and further plaque progression and vessel expansion. Furthermore, when fibroproliferative processes dominate against inflammation and matrix breakdown, the vascular structure undergoes constrictive remodeling and narrowing of the artery. Several studies have shown that this remodeling occurs in 20% of minimally diseased coronary arteries and that it might occur in response to plaque growth [13]. It is important to mention that local ESS does not appear to play a role in constrictive remodeling.
3. Imaging Modalities

Advancements in technology have surpassed expectations in the field of medicine. Biomedical imaging has taken a great leap in the acquisition of highly sophisticated and accurate medical imaging to help in correct diagnosis. Equipments such as X-ray, CT scan, PET scan and MRi have all contributed immensely in helping narrow down a specific disease. Each of the latter presents their advantages and disadvantages. However, this report will not cover the details of these equipments due to their rather complicated nature. The following paragraphs will highlight some of the invasive and non-invasive imaging modalities used today to diagnose and treat atherosclerosis. One of the most difficult challenges in assessing atherosclerosis is the small size of the artery. In addition, the heart palpitations distort the image making difficult for radiologist to diagnose the patient.
3.1 Non-invasive modalities

*X-ray angiography* is a non-invasive imaging method used to detect, diagnose and treat heart diseases. A catheter is inserted into the femoral or brachial artery and guided through to the affected area where a contrast material (iodine) is injected so that the arteries can be visualized on the image. As seen in Figure 6, the X-ray allows physicians to determine the exact location of a blocked artery, and determine the appropriate method for treatment. However, this technique is limited in its capabilities to study the atherosclerotic plaque. It allows the determination of stenosis rather than provide information on the properties of the wall and plaque. Therefore, it is difficult to determine the vulnerability of an atherosclerotic plaque and the likelihood of a cardiac coronary event.

![Angiogram of a coronary artery blockage](image)

*Figure 8 Angiogram of a coronary artery blockage [6]*

Computed Tomography (CT) is another imaging technique that allows the reproduction of 2D or 3D cross-sectional images of the internal structures of human organs. Some studies have shown that CT is capable of determining calcified coronary plaques (18). Nevertheless, the ionizing radiation is a major concern when it comes to using the CT scans and there have been some concerns about the accurate reconstruction of small arteries.
The most non-invasive technique to assess coronary atherosclerosis is the magnetic resonance imaging (MRI). It allows the reconstruction of 3D images of cross sectional areas of certain organs. MRI does not use ionizing radiation, hence making safe to use and giving it an upper hand on the other proposed methods.

3.2 Invasive Modalities

Intravascular ultrasound (IVUS) is a powerful imaging modality for the assessment of the arterial wall and to help identify atherosclerotic plaques. IVUS involves a miniaturized high frequency ultrasound transducer placed on the distal end of the catheter, where images are transmitted to ultrasound equipment for analysis. IVUS produces high frequency tomographic cross-sectional images of the arterial wall, plaque and lumen [20]. As seen in figure 7, the resulting image allows physicians to examine the condition and composition of the atherosclerotic plaque. The plaque area could be calculated from the difference between the external elastic lamina and the lumen. The main advantage of IVUS over angiography is the ability to image the entire wall and accurately assess the plaque vulnerability. The inability for IVUS to properly distinguish between different plaque components such as fibrous, lipids and calcific poses a common disadvantage. However, there have been recent developments that allow for good histopathological correlation. The combination between virtual histology and IVUS (VH-IVUS) uses spectral analysis of radiofrequency backscatter to characterize between different plaque components.
Optical coherence tomography (OCT) is a method used in conjunction with IVUS to measure reflected light. It has proven to image high resolution atheroma showing macrophage activity. The major drawback of this technique is the use of invasive cardiac catheterization.

Current research is in progress for new emerging non-invasive technologies for assessing the composition of atherosclerotic plaque. There is interest in combining methods such as Raman and Near-Infrared Spectroscopy with IVUS, this will allow for an assessment of the chemical composition of the atherosclerotic tissue [18].

4. Treatments

Atherosclerosis is a silent but a killer of a disease. Unfortunately, it does not exhibit symptoms until severe damage has been done to the artery wall and blood flow is restricted. Restriction of blood flow to the heart may cause a myocardial infarction where as narrowing of arteries leading to the brain may eventually lead to a stroke. There are several treatments available to reduce the effects of atherosclerosis and help prevent serious clinical events. General treatments include lifestyle changes (exercise, healthy eating habits), drugs to help lower cholesterol level or anticoagulants to reduce the formation of blood clots. When aggressive vessel narrowing occurs,
there is a call to minimally invasive surgery such as angioplasty procedures to deploy stents to
expand the artery and promote blood supply. Also, a major bypass surgery, where the blood is
rerouted away from clogged arteries to improve blood flow and oxygen supply to the heart.
There are also other pharmaceutical products in the marketplace that help reduce trigger events
that would lead to a cardiac event.

The most common minimally invasive procedure to restore the shape of the artery is balloon
angioplasty. The procedure consists of inserting a catheter into the stenotic location where a
balloon is inflated to reopen the artery. In order to keep the artery open when the balloon is
deflated, a metallic stent is deployed in that location. In some cases, the stent experiences
restenosis and additional surgical intervention is needed.

Figure 10 Balloon Angioplasty [21]
5. Conclusion

Cardiovascular diseases affect millions of people worldwide and are the leading cause of death. Atherosclerosis is by far the most frequent underlying cause of coronary artery disease. The accumulation of fatty substances, cholesterol and calcium deposits in the artery wall form lesions called plaques. The atherosclerotic plaque may rupture without warning and cause acute coronary syndromes such as heart attack and stroke. Plaque structure properties have been poorly understood but it is believed that plaque morphology, mechanical forces, vessel modeling, blood conditions and endothelium surface condition to be related to plaque vulnerability. In addition, research has shown that the presence of low endothelial shear stress be a local stimulus in initiating atherogenesis risk factors. Several imagining modalities are currently being used to study the vulnerability of the plaque but most of them have little capabilities in determining the material properties of the plaque constituents. The most common non invasive method of treatment of atherosclerosis is balloon angioplasty. If the atherosclerotic plaque has reached a critical stage, a major invasive bypass surgery would be necessary. Current research trends have shown that there is limited knowledge about plaque properties due to their size and complexity. The use of finite element modeling is currently being investigated by several researchers to study the plaque vulnerability under physiological loading and the plaque response under mechanical loading.

The current and future advancement in technology in the field of medicine will allow us to further our limited knowledge of the mechanical properties affecting plaque rupture and in the near future help us determine methods and procedures to help improve the quality of human life.
References


[16] Cleveland Clinic http://www.clevelandclinic.org downloaded in April 2011)


[21] Image is retrieved from http://www.heart.org.in/diseases/angioplasty.html, April 2011