Atherosclerosis is not a disease unique to modern civilization. Mummies from 1500 BC showed evidence of atherosclerotic lesions, yet our understanding of this complex process is still evolving. Advances in our understanding of atherogenesis and processes that lead to plaque rupture – the pathophysiologic hallmark of acute coronary syndromes (ACS) – allow for more precise identification, risk stratification and treatment in the future.1, 2

This section will focus on evolving concepts of atherosclerosis and the pathophysiology of ACS. Pivotal to this discussion is the understanding that the atherosclerotic plaque occurs as a “response to injury” and that factors effecting the vessel wall, blood flow and thrombogenicity are critically interrelated. Response to plaque rupture is determined by local and systemic factors, with inflammation and thrombosis playing central roles.

**Atherosclerosis**

Atherosclerosis as a “response to injury” was first suggested by Russell Ross in 1973. There are four steps in his model; 1) endothelial damage, 2) migration of LDL particles across the endothelial layer into the intima where they are modified, 3) inflammatory response, 4) formation of a fibrous cap. The endothelium can be damaged by a variety of factors such as hypertension, diabetes, tobacco, infections, or oxidative and shear stress.4 These insults lead to the expression of surface adhesion molecules [P-selectin, Vascular Cell Adhesion Molecule -1 (VCAM-1)] and chemokines encouraging more sustained leukocyte adhesion and interaction within the endothelium. This results in increased endothelial permeability with transmigration of low-density lipoprotein (LDL) and

**Atherothrombosis**

Localized thrombus formation and vasoconstriction are homeostatic responses to microvascular damage. Atherothrombosis, defined as atherosclerotic plaque disruption with superimposed thrombus, is the leading cause of mortality in the Western world. It is clinically manifested as coronary artery disease, stroke, transient ischemic attacks (TIA) and peripheral artery disease. A recent analysis of the data from the Framingham Heart Study was conducted to determine the impact of cardiovascular disease on life expectancy. According to this analysis, more than 60% of men and women over 40 years of age will develop atherothrombotic disease at some point in their lives. For patients greater than 50 years of age, the development of atherothrombotic disease reduces life expectancy by 8 to 12 years.3

**OBJECTIVES:**

1. Describe the role of inflammation in the development of atherosclerosis and vulnerable plaques
2. Discuss the role of thrombosis associated with a ruptured plaque in the development of acute coronary syndrome
monocytes into the intima and decrease in vascular response to nitric oxide. The monocytes mature into macrophages and express scavenger receptors. The LDL particles are then modified by oxidative stress or enzymatic degradation and subsequently taken up by macrophages producing foam cells which accumulate into intimal “fatty streaks”. Macrophage activity is a potent stimulus for the production and release of various cytokines (granulocyte-macrophage colony stimulating factor (GCSF), IL-1, IL-6, tumor necrosis factor (TNF), CD40 and C-reactive protein) as well as cytotoxic substances. Locally acting cytokines within the inflamed intima recruit more macrophages, T-cells and smooth muscle cells, and in addition, further up-regulate endothelial adhesion molecules and increase endothelial permeability. Trapped foam cells aggregate into lipid pools forming the core of the atherosclerotic lesion. Smooth muscle cells migrate from the media into the intima, where they lay down collagen, forming a fibrous cap which stabilizes the plaque by walling off the lipid core from the blood stream. This is a self-perpetuating process as endothelial permeability to LDL is influenced by local and systemic inflammation. Modified LDL leads to amplification of the inflammatory response by macrophages. The local inflammation feeds back, promoting further transmigration of LDL into the intima and subsequent modification. Stimulated macrophages produce matrix metalloproteinases (MMPs) which degrade collagen. Intimal smooth muscle cells appear to be subject to apoptosis (programmed cell death). The fibrous cap thins, it is more likely to rupture, exposing the thrombogenic contents of the plaque to the bloodstream, resulting in clots formation. These proinflammatory forces drive plaque growth and instability, but there are also anti-inflammatory forces striving to limit growth and promote stability. Cytokines such as IL-4 and TGF-β as well as the actions of smooth muscle cells, act to decrease the amount of inflammation present in the plaques. A balance of forces, similar to that seen in wound healing develops. The balance can be tipped in either direction. If it leans towards progression, ongoing growth begins to impinge on the vessel lumen and the plaque becomes vulnerable to erosion and rupture.

**Vulnerable Plaques**

The stability of the atherosclerotic plaque and the risk for development of an ACS are variable. It is now appreciated that the risk of developing ACS relates more to the composition and “vulnerability” of the plaque than to the degree of vessel stenosis. Risk factors can be categorized as abnormalities of the vessel wall, blood flow or thrombogenicity, or as local versus systemic effects.

The process of initiation, progression and complications of acute coronary arterial thrombosis can be related to Virchow’s triad for thrombogenesis, first described in 1856. Complex lesion morphology (vessel wall) is the angiographic hallmark of ACS. Two percent of patients with acute myocardial infarction are found to have “normal” coronary angiograms. Perhaps these patients have significant atherosclerotic lesions that may not be apparent in the catheterization lab. Angiography however, doesn’t provide information about the remodeling process the atheroma is undergoing. Vulnerability to disruption appears to be determined by the presence of a large lipid-rich core and thin fibrous cap with eccentric morphology, heavily infiltrated by inflammatory cells and acted upon by numerous cytokines, rather than the size of the plaque or severity of the stenosis before disruption. The thinner fibrous cap is less likely to withstand the mechanical stresses of hemodynamic changes, particularly at the shoulders of the cap where there is diminished collagen and smooth muscle. The external physical forces that expose the vessel wall to blood flow at different shear rates also influence the occurrence and progression of plaque disruption, thrombosis and atherosclerosis. A tight stenosis of the vessel...
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does not precipitate ACS, rather it is the physical disruption of the plaque that causes occlusive thrombi. Endothelial dysfunction initiates plaque formation at arterial bifurcations and sites of disturbed flow. Blood flow and vessel wall stress (mechanical and hydrostatic) are key external factors that trigger disruption of plaques. “Cap fatigue” is due to stresses from fluctuations in pressure or motion of the vessel such as bending, compression (vasoconstriction) stretching, and shear – resulting from blood flow within the vessel (laminar and oscillatory). Although plaque rupture is thought to be the main cause of ACS, frank rupture with thrombus-lipid core communication is seen in only 60% of cases. Thrombus associated with superficial plaque erosion devoid of endothelial cells is seen in the rest. These lesions are more common in women, smokers and those with systemic risk factors for a hypercoagulable state. A fracture of the fibrous cap would not likely have significant consequence was it not for the ensuing thrombus. Factors such as lipid and hormonal metabolism, hyperglycemia, fibrinolysis, platelet and leukocyte function are associated with increased blood thrombogenicity. Many plasma hemostatic indices such as fibrinogen, factor VII, von Willebrand factor (VWF), D-dimer have been identified as independent predictors of subsequent cardiovascular events.13

Plaque rupture is thought to occur because of changes in the plaque itself (local) and systemic changes in the patient. Interestingly, contributing factors seem to overlap to a great extent and might even be inter-related.14 From a local perspective, plaque rupture is attributed to changes that occur in the atherosclerotic plaque. The most well understood mechanisms are inflammation and matrix turnover in plaque progression. The degree of plaque disruption (ulceration, fissure or erosion) or substrate exposure is the key factor for determining thrombogenicity at the local site. From a systemic perspective, plaque rupture doesn’t occur as an isolated phenomenon but rather as a systemic disease. In this view, it is the “vulnerable patient” instead of a patient with a localized, vulnerable atherosclerotic plaque. Vulnerable patients often present with multiple ruptured plaques. In one angiographic study of patients with ACS, 39% had multiple complex plaques that were associated with an increased incidence of recurrent ischemia. Rioufol et al., using intravascular ultrasound found 79% of patients presenting with ACS had multiple ruptured plaques at sites other than the culprit lesion that caused the clinical symptoms.15 The occluding thrombus determines the clinical presentation but it is only a focal manifestation of an underlying systemic disease process that includes many rupture-prone or vulnerable lesions. Systemic factors that correlate with plaque rupture are altered increased coagulability, increased systemic inflammation and recurrent infections. These unfavorable systemic changes often interact synergistically with the risk factors of atherosclerosis and plaque rupture, such as hyperlipidemia, smoking and diabetes.16 Systemic contributing factors may explain discrepancies in terms of atherogenesis, lipid accumulation, cell proliferation and extracellular matrix synthesis between patients. As Theroux noted, the progression of atherosclerotic disease is neither linear nor predictable.17

In a minority of cases fatal coronary thrombosis results from superficial erosion of the intima without frank rupture through the plaque fibrous cap. Erosion occurs when inflammatory mediators cause apoptosis of endothelial cells and activate proteases, with the consequence of endothelial cells separating from their underlying substrate, portions of which are thrombogenic. Endothelial cells can also express proteinases regulated by inflammatory cytokines and oxidized lipoproteins. Activation of the proteases in response to inflammatory stimuli can sever the tethers that hold the endothelial cell to its underlying matrix promoting desquamative injury to the intima thus initiating a thrombotic process. If the disruption of the plaque leads to a significant thrombus it may impinge the vessel lumen and manifest itself clinically.18
When the plaque is disrupted all three components of Virchow’s triad come into play simultaneously. Highly thrombogenic material (especially tissue factor) is released from the lipid core and activates the extrinsic clotting cascade. Tissue factor forms high affinity complexes with factors VII/VIIa which activate factor IX and factor X, leading to formation of the prothrombinase complex and ultimately to the generation of thrombin and fibrinogen conversion to fibrin. The exposure of platelets to collagen or von Wildenbrand’s Factor (VWF) on the subendothelial surface leads to platelet adhesion with multiple receptors. Platelet adhesion is followed by activation and aggregation with concomitant release of thrombogenic constituents. With the activation of platelets, the glycoprotein (GP) receptors are activated. Glycoproteins, VWF and fibrinogen bind together linking platelets. Many local and systemic factors coexist to increase the thrombogenicity around the injured plaque, including increased turbulence and stasis around disrupted region, leading to propagation of the thrombus in the coronary artery.

Ischemic Presentations
Plaque disruption with a subsequent change in plaque geometry and thrombosis results in complicated lesions. A rapid change may result in acute occlusion or subocclusion with clinical manifestations of unstable angina or other ACS. More frequently however, the rapid changes seem to result in mural thrombus without evident clinical symptoms. Such thrombus may be the main contributor to the progression of atherosclerosis. Local and systemic circulating factors influence the degree and duration of thrombus deposition. Acute coronary syndromes are a continuum. Symptoms occur when there is an abrupt imbalance between oxygen supply and demand influenced by extrinsic (exercise) and intrinsic (flow) factors.

Stable angina is characterized by atherosclerotic plaques with fixed stenosis. Clinical symptoms occur when oxygen demand exceed supply (exercise, stress). There is often significant vascular collaterals if the problem is long standing. Unstable angina usually results from decreased perfusions (plaque disruption resulting in thrombus and reduced flow) or increased oxygen demand (oxygen mismatch). The thrombus is often labile with obstruction or transient occlusion. Here the myocardium is stressed by ischemia but recovers. Non ST-segment elevation myocardial infarction (NSTEMI) occurs when myocardial perfusion is disrupted due to persistent thrombotic occlusion or vasospasm. Spontaneous thrombolysis, resolution of vasoconstriction or flow from collateral sources limit the resulting ischemic injury. Plaque disruption and thrombosis that result in complete coronary artery occlusion leads to transmural ischemia and necrosis, the hallmark of ST-segment elevation myocardial infarction (STEMI).

While NSTEMI and STEMI are felt to share a common underlying pathophysiology it is unclear why they behave differently in terms of therapeutic response. It has been postulated that the thrombus differ in cellular composition. Variations in clinical manifestations in “vulnerable patients” are likely impacted by multiple systemic factors.

Therapeutic Implications
Recognizing the role of inflammation in atherothrombosis opens the window for new diagnostic strategies and therapies. Inflammatory markers are making their way into real-time clinical practice. Patients with ACS who have high levels of inflammatory markers (CRP), are at higher risk for developing ACS and require evaluation for anti-inflammatory therapy. Elevated markers at the time of percutaneous coronary intervention (PCI) predict adverse outcomes. We are entering a period when many new biomarkers for inflammation and cellular ischemia – not just necrosis, are becoming available. It is too early to tell which ones will be added to our armamentarium, but it is likely that in the future we will approach risk stratification of ACS patients differently.
also someday follow inflammatory marker levels to assess the effectiveness of interventions such as diet, statins, and ASA. Our understanding of “vulnerable patients”, not just vulnerable atherosclerotic plaques, highlights the importance of systemic factors on cardiovascular outcomes. The role of proteomics in assessing population-based therapeutic efforts is also on the horizon for EP’s.

In most situations therapy is based on pathophysiology. In atherosclerosis, treatment has evolved from epidemiologic outcome correlations, including statins for hyperlipidemia, diabetic glucose control, diet and weight control, and exercise. Investigations suggest that many of the approaches embraced over the last few decades addressing cardiovascular health modify atherothrombosis in part by reducing inflammation. The level of physical activity was independently associated with a lower odds ratio for an elevated CRP, WBC or fibrinogen levels. Healthy subjects undergoing a 6-month exercise program saw reductions in atherogenic cytokines (IL-1, TNF) by as much as 58% and atheroprotective cytokines (IL-4, TGF-beta) increased by 35%. Some have suggested that obesity is proinflammatory. Weight loss, on average 14 kg/14 months, reduced CRP levels by 32%. Low fat diets appear to improve endothelial function and lower adhesion molecules such as P-selectin. Aspirin remains of the most effective therapies for primary and secondary prevention of coronary disease. Given its modest antiplatelet effect, aspirin’s anti-inflammatory properties are probably just as important. Thienopyridines bind to platelets through an adenosine diphosphate (ADP) receptor. The beneficial effects were thought to be related to their ability to decrease clot formation but recent evidence suggest they could also have anti-inflammatory effects. Clopidogrel inhibits platelet expression of CD40 ligand. Platelet activation leads to expression of CD40 ligand, and these agents may block the pathway. Angiotensin-converting enzyme (ACE) inhibitors and 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors (statins) have been shown to significantly reduce cardiovascular events. The degree of benefit is greater than would be expected from blood pressure reduction or lipid lowering alone. The renin-angiotensin system plays a direct role in inflammation. In animal studies statins have been found to significantly reduce leukocyte adherence to endothelial cells and transmigration, hence decreasing inflammation.

Ross noted that atherosclerosis resulted from a “response to injury” three decades ago. It has become very clear that inflammation plays a central role in this process. Future therapeutic modalities are likely to target the inflammatory system. Therapies that interfere or block the actions of adhesion molecules, cytokines, T cells and macrophages and other inflammatory mediators may one day become important adjuncts in preventing and managing ACS.

**SUMMARY**

Assessment, risk stratification and treatment of patients with ACS demand that emergency physicians have a working understanding of the pathophysiology of atherothrombosis. The risk of plaque disruption and thrombus formation is related to aberrations in the coronary vessel wall, blood flow and underlying degree of thrombogenicity. Inflammation plays a key role in determining coronary vessel response to injury. Atherothrombosis results from both local and systemic effects; the importance of recognizing the vulnerable patient is gaining acceptance. The complexity of the pathways involved offer a wide array of future diagnostic and therapeutic approaches.
REFERENCES


