**Atheroma**

*Classification and external resources*

<table>
<thead>
<tr>
<th>Atherosclerotic plaque from a <a href="https://www.healthoracle.org">carotid endarterectomy</a> specimen. This shows the <a href="https://www.healthoracle.org">bifurcation</a> of the <strong>common</strong> into the <strong>internal</strong> and <strong>external</strong> carotid arteries.</th>
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<td><strong>ICD-10</strong></td>
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<td><strong>ICD-9</strong></td>
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<td><strong>DiseasesDB</strong></td>
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MeSH  C14.907.137.126.307

In pathology, an atheroma (plural: atheromata) is an accumulation and swelling (-oma) in artery walls that is made up of cells (mostly macrophage cells), or cell debris, that contain lipids (cholesterol and fatty acids), calcium and a variable amount of fibrous connective tissue. In the context of heart or artery matters, atheromata are commonly referred to as atheromatous plaques. It is an unhealthy condition, but is found in most humans.

These anatomic lesions usually begin in some children younger than age 1 year and all children older than age 10 regardless of geography, race, sex or environment.

Veins do not develop atheromata, unless surgically moved to function as an artery, as in bypass surgery.

The accumulation (swelling) is always between the endothelium lining and the smooth muscle wall central region (media) of the arterial tube. While the early stages, based on gross appearance, have traditionally been termed fatty streaks by pathologists, they are not composed of fat cells, i.e. adipose cells, but of accumulations of white blood cells, especially macrophages that have taken up oxidized low-density lipoprotein (LDL).

After they accumulate large amounts of cytoplasmic membranes (with associated high cholesterol content) they are called foam cells. When foam cells die, their contents are released, which attracts more macrophages and creates an extra-cellular lipid core near the center to inner surface of each atherosclerotic plaque.

Conversely, the outer, older portions of the plaque become more calcific, less metabolically active and more physically stiff over time.
Collectively, the process of atheroma development within an individual is called atherogenesis and the overall result of the disease process is termed atherosclerosis.

For most people the first clinical symptoms result from atheroma progression within the heart arteries, most commonly resulting in a heart attack and ensuing debility.

However, because

(a) They are small (from about 5 mm down to invisible),
(b) They are hidden deep within the chest
(c) They never stop moving,

The heart arteries have been a difficult target organ to track, especially clinically in individuals who are still asymptomatic. Additionally all mass applied clinical strategies focus on both

(a) Minimal cost
(b) The overall safety of the procedure.

Therefore existing diagnostic strategies for detecting atheroma and tracking response to treatment have been extremely limited. The methods most commonly relied upon, patient symptoms and cardiac stress testing, do not detect any symptoms of the problem until atheromatous disease is very advanced.

Atheroma continues to be the number one underlying basis for disability and death, despite a trend for gradual improvement since the early 1960s (adjusted for patient age). Thus, increasing efforts towards better understanding, treating and preventing the problem are continuing to evolve.
For about 65% of men and 47% of women, the first symptom of cardiovascular disease is heart attack or sudden death (death within one hour of symptom onset.)

Most artery flow disrupting events occur at locations with less than 50% lumen narrowing. From clinical studies published in the late 1990s to IVUS (in-the-artery-ultrasound) to visualize disease status, the typical heart attack occurs at locations with about 20% stenosis (narrowing), prior to sudden lumen closure and resulting heart attack.¹ Cardiac stress testing, traditionally the most commonly performed non-invasive testing method for blood flow limitations generally only detects lumen narrowing of ~75% or greater, although some physicians advocate that nuclear stress methods can sometimes detect as little as 50%.

Artery and atheroma behavior

Atheroma and changes in the artery wall usually result in small aneurysms (enlargements) just large enough to compensate for the extra wall thickness with no change in the lumen diameter. However, eventually, typically as a result of rupture of vulnerable plaques and clots within the lumen over the plaque, stenosis (narrowing) of the vessel develops in some areas. Less frequently, the artery enlarges so much that a gross aneurysmal enlargement of the artery results. All three results are often observed, at different locations, with the same individual.

Stenosis and closure

Over time, atheromata usually progress in size and thickness and induce the surrounding muscular central region (the media) of the artery to stretch out, termed remodeling, typically just enough to compensate for their size such that the caliber of the artery opening (lumen) remains unchanged until typically over 50% of the artery wall cross sectional area consists of atheromatous tissue.
If the muscular wall enlargement eventually fails to keep up with the enlargement of the atheroma volume, or a clot forms and organized over the plaque, then the lumen of the artery begins to narrow, commonly as a result of repeated ruptures of the covering tissues separating the atheroma from the blood stream. This becomes a more common event after decades of living, increasingly more common after people are in their 30s to 40s.

The endothelium (the cell monolayer on the inside of the vessel) and covering tissue, termed fibrous cap, separate atheroma from the blood in the lumen. If a rupture occurs of the endothelium and fibrous cap, then a platelet and clotting response over the rupture rapidly develops. Additionally, the rupture may result in a shower of debris. Platelet and clot accumulation over the rupture may produce narrowing/closure of the lumen and tissue damage may occur due to either closure of the lumen and loss of blood flow beyond the ruptured atheroma and/or by occlusion of smaller downstream vessels by debris.

This is the principal mechanism of heart attack, stroke or other related cardiovascular disease problems. As research has shown, this process is not a result of stenosis. Prior to the rupture, there may have been no lumen narrowing, even aneurysmal enlargement, at the atheroma. On average, by clinical research using IVUS, there is a minor stenosis, about 20%, present over that unstable atheroma which ruptures and results in major disability or death. Comparatively, stenosis of about 75% is required to produce detectable abnormalities during cardiac stress tests.

**Artery enlargement**

If the muscular wall enlargement is overdone over time, then a gross enlargement of the artery results, usually over decades of living. This is a less common outcome. Atheroma within aneurysmal enlargement (vessel bulging) can also rupture and shower debris of atheroma and clot downstream. If the arterial enlargement continues to 2 to 3 times
the usual diameter, the walls often become weak enough that with just the stress of the pulse, a loss of wall integrity may occur leading to sudden hemorrhage (bleeding), major symptoms and debility; often rapid death. The main stimulus for aneurysm formation is pressure atrophy of the structural support of the muscle layers. The main structural proteins are collagen and elastin. This causes thinning and the wall balloons allowing gross enlargement to occur, as is common in the abdominal region of the aorta.

**Evolution of strategies and changing focus**

The sudden nature of the complications of pre-existing atheroma, vulnerable plaque, has led, since the 1950s, to the development of intensive care units and complex medical and surgical interventions. Angiography and later cardiac stress testing was begun to either visualize or indirectly detect stenosis.

Next came bypass surgery, to plumb transplanted veins, sometimes arteries, around the stenosis and more recently angioplasty, now including stents, most recently drug coated stents, to stretch the stenosis more open.

Yet despite these medical advances, with success in reducing the symptoms of angina and reduced blood flow, atheroma rupture events remain the major problem and still sometimes result in sudden disability and death despite even the most rapid, massive and skilled medical and surgical intervention available anywhere today. According to some clinical trials, bypass surgery and angioplasty procedures have had at best a minimal effect, if any, on improving overall survival. Typically mortality of by-pass operations is from 1-4%, of angioplasty about 1-1.5%.¹

Additionally, these vascular interventions are often done only after an individual is symptomatic, often already partially disabled, as a result of the disease. It is also clear that both angioplasty and by-pass interventions do not prevent future heart attack.
The older methods for understanding atheroma, dating to before World War II, relied on autopsy data. Autopsy data has long shown initiation of fatty streaks in later childhood with slow asymptomatic progression over decades.

One way to see atheroma is the very invasive and costly IVUS ultrasound technology; it gives us the precise volume of the inside intima plus the central media layers of about 2.5 cm of artery length. Unfortunately, it gives no information about the structural strength of the artery. Angiography does not visualize atheroma; it only makes the blood flow within blood vessels visible.

Alternative methods that are non or less physically invasive and less expensive per individual test have been used and are continuing to be developed, such as those using computed tomography (CT; lead by the Electron Beam Tomography form, given its greater speed) and magnetic resonance imaging (MRI).

The most promising since the early 1990s has been EBT, detecting calcification within the atheroma before most individuals start having clinically recognized symptoms and debility.

Interestingly, statin therapy (to lower cholesterol) does not slow the speed of calcification as determined by CT scan. Most visualization techniques are used in research; they are not widely available to most patients, have significant technical limitations, have not been widely accepted and generally are not covered by medical insurance carriers.

From human clinical trials, it has become increasingly evident that a more effective focus of treatment is slowing, stopping and even partially reversing the atheroma growth process. However, this effort has been slow, partly because the asymptomatic nature of atheromata makes them especially difficult to study.

Promising results are found using B-vitamins that reduce a protein corrosive homocysteine and that reduce neck carotid artery plaque volume and thickness, and stroke, even in late-stage disease.
Additionally, understanding what drives atheroma development is complex with multiple factors involved, only some of which, such as lipoproteins, more importantly lipoprotein subclass analysis, blood sugar levels and hypertension are best known and researched. More recently, some of the complex immune system patterns that promote, or inhibit, the inherent inflammatory macrophage triggering processes involved in atheroma progression is slowly being better elucidated in animal models of atherosclerosis.

**Diagnosis**

*Arterial wall fixation, staining and thin section:* historically this has been the gold standard for detection and description of atheroma, though only done after autopsy. With special stains and examination, microcalcifications can be detected, typically with smooth muscle cells of the arterial media near the fatty streaks within a year or two of fatty streaks forming.

*IVUS* is the current most sensitive method detecting and measuring more advanced atheroma within living individuals, though it is typically not used until decades after atheroma begin forming due to cost and body invasiveness.

*CT Scans* using state of the art higher resolution spiral or the higher speed EBT, machines have been the most effective method for detecting calcification present in plaque. However, the atheroma have to be advanced enough to have relatively large areas of calcification within them to create large enough regions of ~130 Hounsfield units which the CT scanner software can recognize as distinct from the other surrounding tissues.

Typically, such regions start occurring within the heart arteries about 2-3 decades after atheroma start developing. Hence the detection of much smaller plaques then previously possible is being developed. The presence of smaller, spotty plaques may actually be the more dangerous culprit for progressing to acute myocardial infarction.
Arterial ultrasound, especially of the carotid arteries, with measurement of the thickness of the artery wall, offers a way to partially track the disease progression.

As of 2006, the thickness, commonly referred to as IMT for intimal-medial thickness, is not measured clinically though it has used by some researchers since the mid 1990s to track changes in arterial walls.

Traditionally, clinical carotid ultrasounds have only estimated the degree of blood lumen restriction, stenosis, a result of very advanced disease. More progressive clinicians have begun using IMT measurement as a way to quantify and track disease progression or stability within individual patients.

Angiography, since the 1960s, has been the traditional way of evaluating for atheroma. However, angiography is only motion or still images of dye mixed with the blood with the arterial lumen and never show atheroma; the wall of arteries, including atheroma with the arterial wall remain invisible. The limited exception to this rule is that with very advance atheroma, with extensive calcification within the wall, a halo-like ring of radio-density can be seen in older humans, especially when arterial lumens are visualized end-on. On cine-floro, cardiologists and radiologists typically look for these calcification shadows to recognize arteries before they inject any contrast agent during angiograms.

Treatment

Many approaches have been promoted as methods to reduce atheroma progression:

(a) Food choices (such as consuming fish and fish derived omega-3 containing fats),

(b) Abdominal fat reduction,
(c) Aerobic exercise,

(d) Inhibitors of the cholesterol synthesis (known as statins),

(e) Lowering normal blood glucose levels (glycosylated hemoglobin, also called HbA1c), values to < 5.0)

(f) Micronutrient (multivitamin and magnesium) supplements, etc.

However, in spite of popular belief, cholesterol is not the villain that causes atherosclerosis, just like aluminium is not the clear villain in Alzheimer disease. From clinical treatment trials, changing lipoprotein physiology, as measured from the MESA trial participants, and lowering blood sugar levels have proven to have the most dramatic impacts on reducing cardiovascular events and death rate from atherosclerotic disease.

However, in spite of great progress, there are many interacting factors and currently we do not possess a complete systemic understanding of atherosclerosis. The Hemorheologic-Hemodynamic Theory of Atherosclerosis was advanced in recognition that the atherogenesis requires factors in addition to hypercholesterolemia.