Arteriosclerosis
Atherosclerosis
Aneurysms and Dissection

By: Shefaa’ Alqa’qa’, MD
Arteriosclerosis

• **Arteriosclerosis** literally means “hardening of the arteries”; it is a generic term for arterial wall thickening and loss of elasticity. There are three general patterns, with different clinical and pathologic consequences:
1- Arteriolosclerosis affects small arteries and arterioles, and may cause downstream ischemic injury. The two anatomic variants, hyaline and hyperplastic.
• **Hyaline arteriolosclerosis:**
  - Arterioles show homogeneous, pink hyaline thickening with associated luminal narrowing.
  - These changes reflect both *plasma protein leakage* across injured endothelial cells, as well as increased smooth muscle cell matrix synthesis in response to the chronic hemodynamic stresses of **hypertension**.
  - Although the vessels of **older** patients (either normotensive or hypertensive) also frequently exhibit hyaline arteriosclerosis, it is more generalized and severe in patients with hypertension.
  - The same lesions are also a common feature of **diabetic** microangiography; in that case, the underlying etiology is hyperglycemia-induced endothelial cell dysfunction.
  - In **nephrosclerosis** due to chronic hypertension, the arteriolar narrowing of hyaline arteriosclerosis causes diffuse impairment of renal blood supply and glomerular scarring.
• Hyperplastic Arteriolosclerosis.
  - This lesion occurs in severe (malignant) hypertension.
  - Vessels exhibit concentric, laminated ("onion-skin") thickening of the walls with luminal narrowing. The laminations consist of smooth muscle cells with thickened, reduplicated basement membrane; in malignant hypertension, they are accompanied by fibrinoid deposits and vessel wall necrosis (necrotizing arteriolitis), particularly in the kidney.
Figure 11-6 Vascular pathology in hypertension. A, Hyaline arteriolosclerosis. The arteriolar wall is thickened with increased protein deposition (hyalinized), and the lumen is markedly narrowed. B, Hyperplastic arteriolosclerosis (onion-skinning) causing luminal obliteration (periodic acid–Schiff [PAS] stain). (Courtesy Helmut Rennke, MD, Brigham and Women’s Hospital, Boston, Mass.)
2- **Mönckeberg medial sclerosis**
- It is characterized by **calcification** of the walls of muscular arteries, typically involving the **internal elastic membrane**.
- Persons **older than age 50** are most commonly affected.
- The calcifications do not encroach on the vessel lumen and are usually **not clinically significant**.

3- **Atherosclerosis**, from Greek root words for “gruel” and **hardening,”** is the **most frequent and clinically important** Pattern.
Atherosclerosis

- Atherosclerosis is characterized by *initimal* lesions called *atheromas* (also called atheromatous or atherosclerotic *plaques*) that protrude into vessel lumens.
Epidemiology:

Although atherosclerosis-associated ischemic heart disease is ubiquitous among most developed nations, risk reduction and improved therapies have combined to moderate the associated mortality.

At the same time, reduced mortality from infectious diseases and the adoption of Western lifestyles has led to increased prevalence of ischemic heart disease in developing nations.

As a result, the death rate for coronary artery disease in the United States now lags behind the death rates in most of Africa, India, and Southeast Asia.

The countries of the former Soviet Union hold the dubious distinction of having the highest ischemic heart disease-associated mortality rates, three to five times higher than the United States, and seven to 12 times greater than Japan.
• The prevalence and severity of atherosclerosis and ischemic heart disease among individuals and groups are related to a number of **risk factors**. Some of these factors are **constitutional** (and therefore less controllable), but others are **acquired** or related to specific behaviors and potentially amenable to intervention.

• These risk factors have roughly **multiplicative effect**
Table 11-2 Major Risk Factors for Atherosclerosis

<table>
<thead>
<tr>
<th>Nonmodifiable (Constitutional)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic abnormalities</td>
</tr>
<tr>
<td>Family history</td>
</tr>
<tr>
<td>Increasing age</td>
</tr>
<tr>
<td>Male gender</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Modifiable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Cigarette smoking</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Inflammation</td>
</tr>
</tbody>
</table>
• Constitutional Risk Factors:
  - **Genetics**: Family history is the most important independent risk factor for atherosclerosis. Certain Mendelian disorders are strongly associated with atherosclerosis (e.g., familial hypercholesterolemia), but these account for only a small percentage of cases.
  - **Age** is a dominant influence, middle age or later.
  - **Gender**: premenopausal women are relatively protected against atherosclerosis and its consequences compared to age-matched men.
Modifiable Major Risk Factors:

- **Hyperlipidemia**—and more specifically **hypercholesterolemia**— is a major risk factor for atherosclerosis; even in the absence of other risk factors, hypercholesterolemia is sufficient to initiate lesion development. Low-density lipoprotein (LDL) (“bad cholesterol”) is the complex that delivers cholesterol to peripheral tissues; in contrast, high-density lipoprotein (HDL) is the complex that mobilizes cholesterol from the periphery (including atheromas) and transports it to the liver for excretion in the bile. High dietary intake of cholesterol and **saturated fats** (present in egg yolks, animal fats, and butter, for example) raises plasma cholesterol levels.

- **Hypertension**
- **Cigarette smoking**
- **Diabetes mellitus** induces hypercholesterolemia and markedly increases the risk of atherosclerosis
• Additional Risk Factors:
  - Inflammation, CRP
  - Hyperhomocystinemia (rare inborn errors of metabolism, results in elevated circulating homocysteine (>100 μmol/L))
  - Metabolic syndrome (dyslipidemia, hyperglycemia, hypertension)
  - Lipoprotein a [Lp(a)] is an altered form of LDL that contains the apolipoprotein B-100 portion of LDL linked to apolipoprotein A (apo A)
  - Factors affecting hemostasis. Several markers of hemostatic and/or fibrinolytic function (e.g., elevated plasminogen activator inhibitor 1)
    - stressful life style
    - obesity
Pathogenesis of Atherosclerosis:

“response to injury” hypothesis. This model views atherosclerosis as a chronic inflammatory and healing response of the arterial wall to endothelial injury. Lesion progression occurs through interaction of modified lipoproteins, monocyte-derived macrophages, and T lymphocytes with endothelial cells and smooth muscle cells of the arterial wall.

According to this schema, atherosclerosis progresses in the following sequence:
- **Endothelial injury** and dysfunction, causing increased vascular permeability, leukocyte adhesion, and thrombosis
- **Accumulation of lipoproteins** (mainly LDL and its oxidized forms) in the vessel wall
- **Monocyte adhesion** to the endothelium, followed by migration into the intima and transformation into macrophages and foam cells
- **Platelet adhesion**
- Factor release from **activated platelets**, macrophages, and vascular wall cells, inducing **smooth muscle cell recruitment**, either from the media or from circulating precursors
- **Smooth muscle cell proliferation**, **extracellular matrix production**, and **recruitment of T cells**.
- **Lipid accumulation** both extracellularly and within cells (macrophages and smooth muscle cell)
1. Chronic endothelial "injury":
   - Hyperlipidemia
   - Hypertension
   - Smoking
   - Homocysteine
   - Hemodynamic factors
   - Toxins
   - Viruses
   - Immune reactions

2. Endothelial dysfunction (e.g., increased permeability, leukocyte adhesion), monocyte adhesion and emigration

3. Macrophage activation, smooth muscle recruitment

4. Macrophages and smooth muscle cells engulf lipid

5. Smooth muscle proliferation, collagen and other extracellular matrix deposition, extracellular lipid
• Endothelial Injury:
Endothelial loss due to any kind of injury—induced experimentally by mechanical denudation, hemodynamic forces, immune complex deposition, irradiation, or chemicals—results in intimal thickening. However, early human lesions begin at sites of morphologically intact endothelium. Thus, nondenuding endothelial dysfunction underlies most human atherosclerosis; the intact but dysfunctional endothelial cells exhibit increased endothelial permeability, enhanced leukocyte adhesion, and altered gene expression.

Etiologic culprits include toxins from cigarette smoke, homocysteine, and even infectious agents.

Inflammatory cytokines (e.g., tumor necrosis factor [TNF]) can also stimulate pro-atherogenic endothelial gene expression. However, the two most important causes of endothelial dysfunction are hemodynamic disturbances and hypercholesterolemia.
• Hemodynamic Disturbances.

The importance of hemodynamic turbulence in atherogenesis is illustrated by the observation that plaques tend to occur at ostia of exiting vessels, branch points, and along the posterior wall of the abdominal aorta, where there are disturbed flow patterns. In vitro studies have demonstrated that nonturbulent laminar flow leads to the induction of endothelial genes whose products (e.g., the antioxidant superoxide dismutase) actually protect against atherosclerosis.
Lipids.
Lipids are transported in the bloodstream bound to specific apoproteins (forming lipoprotein complexes). Dyslipoproteinemias are lipoprotein abnormalities include:
(1) increased LDL cholesterol levels
(2) decreased HDL cholesterol levels
(3) increased levels of the abnormal lipoprotein (a).
These may result from mutations that lead to defects in apoproteins or lipoprotein receptors, or arise from other underlying disorders that affect circulating lipid levels, such as nephrotic syndrome, alcoholism, hypothyroidism, or diabetes mellitus.
The mechanisms by which hyperlipidemia contributes to atherogenesis include the following:

- Chronic hyperlipidemia, particularly hypercholesterolemia, can directly impair endothelial cell function by increasing local reactive oxygen species production; besides causing membrane and mitochondrial damage, oxygen free radicals accelerate nitric oxide decay, damping its vasodilator activity.

- With chronic hyperlipidemia, lipoproteins accumulate within the intima, where they may aggregate or become oxidized by free radicals produced by inflammatory cells. Such modified LDL is then accumulated by macrophages through a variety of scavenger receptors. Because the modified lipoproteins cannot be completely degraded, chronic ingestion leads to the formation of lipid-filled macrophages called foam cells; smooth muscle cells can similarly transform into lipid-laden foam cells by ingesting modified lipids through LDL-receptor related proteins. Not only are the modified lipoproteins toxic to endothelial cells, smooth muscle cells, and macrophages, but their binding and uptake also stimulates the release of growth factors, cytokines, and chemokines that create a vicious cycle of monocyte recruitment and activation.
• Inflammation:
Chronic inflammation contributes to the **initiation and progression** of atherosclerotic lesions. It is believed that inflammation is **triggered by the accumulation of cholesterol crystals and free fatty acids** in macrophages and other cells. The net result of macrophage and T cell activation is the local production of cytokines and chemokines that recruit and activate more inflammatory cells. Activated **macrophages** produce **reactive oxygen species** that enhance LDL oxidation, and elaborate **growth factors** that drive smooth muscle cell proliferation. Activated **T cells** in the growing intimal lesions elaborate inflammatory **cytokines**, e.g., interferon-γ, which, in turn, can activate macrophages as well as endothelial cells and smooth muscle cells. These leukocytes and vascular wall cells release growth factors that promote smooth muscle cell proliferation and synthesis of extracellular matrix proteins.
• Infection:
Although circumstantial evidence has been presented linking atherosclerosis to herpesvirus, cytomegalovirus, and Chlamydophila pneumoniae, there is no established causal role for infection
• Smooth Muscle Proliferation and Matrix Synthesis:

Intimal smooth muscle cell proliferation and extracellular matrix deposition convert a fatty streak into a mature atheroma and contribute to the **progressive growth** of atherosclerotic lesions.

Intimal smooth muscle cells have a **proliferative and synthetic phenotype** distinct from the underlying medial smooth muscle cells. Several growth factors are implicated in smooth muscle cell proliferation, including platelet-derived growth factor (PDGF, released by locally adherent platelets, as well as macrophages, endothelial cells, and smooth muscle cells), fibroblast growth factor, and transforming growth factor-α. These factors also stimulate smooth muscle cells to synthesize extracellular matrix (notably collagen), which **stabilizes atherosclerotic plaques**. In contrast, activated inflammatory cells in atheromas may increase the breakdown of extracellular matrix components, resulting in unstable plaques.
Figure 11-11 Sequence of cellular interactions in atherosclerosis. Hyperlipidemia, hyperglycemia, hypertension, and other influences cause endothelial dysfunction. This results in platelet adhesion and recruitment of circulating monocytes and T cells, with subsequent cytokine and growth factor release from inflammatory cells leading to smooth muscle cell migration and proliferation as well as further macrophage activation. Foam cells in atheromatous plaques derive from macrophages and smooth muscle cells that have accumulated modified lipids (e.g., oxidized and aggregated low density lipoprotein [LDL]) via scavenger and LDL-receptor-related proteins. Extracellular lipid is derived from insudation from the vessel lumen, particularly in the presence of hypercholesterolemia, as well as from degenerating foam cells. Cholesterol accumulation in the plaque reflects an imbalance between influx and efflux; high-density lipoprotein (HDL) likely helps clear cholesterol from these accumulations. In response to the elaborated cytokines and chemokines, smooth muscle cells migrate to the intima, proliferate, and produce extracellular matrix, including collagen and proteoglycans. IL-1, interleukin-1; MCP-1, monocyte chemoattractant protein-1.
• Atheromas are dynamic lesions consisting of dysfunctional endothelial cells, proliferating smooth muscle cells, and admixed T lymphocytes and macrophages. All four cell types are capable of liberating mediators that can influence atherogenesis, death of these cells releases lipids and necrotic debris. With progression, the atheroma is modified by extracellular matrix synthesized by smooth muscle cells; connective tissue is particularly prominent on the intimal aspect forming a fibrous cap, although lesions also typically retain a central core of lipid-laden cells and fatty debris that can become calcified.

• The intimal plaque may progressively encroach on the vessel lumen, or may compress the underlying media, leading to its degeneration; this in turn may expose thrombogenic factors such as tissue factor, resulting in thrombus formation and acute vascular occlusion.
Figure 11-7 Basic structure of an atherosclerotic plaque. Note that atherosclerosis is an intimal-based process.
• MORPHOLOGY:

Fatty streaks:
composed of lipid-filled foamy macrophages.
Beginning as multiple minute flat yellow spots, they eventually coalesce into elongated streaks 1 cm long or longer.
These lesions are not sufficiently raised to cause any significant flow disturbances.
Although fatty streaks can evolve into plaques, not all are destined to become advanced lesions.
Aortas of infants can exhibit fatty streaks, and such lesions are present in virtually all adolescents, even those without known risk factors.
The observation that coronary fatty streaks begin to form in adolescence, at the same anatomic sites that later tend to develop plaques, suggests a temporal evolution of these lesions.
Figure 11-12 Fatty streak, a collection of foamy macrophages in the intima. A, Aorta with fatty streaks (arrows), associated largely with the ostia of branch vessels. B, Photomicrograph of fatty streak in an experimental hypercholesterolemic rabbit, demonstrating intimal, macrophage-derived foam cells (arrows). (B, Courtesy Myron I. Cybulsky, MD, University of Toronto, Canada.)
Atherosclerotic Plaque:
Atheromatous plaques are white-yellow and encroach on the lumen of the artery; superimposed thrombus over ulcerated plaques is red-brown. Plaques vary in size but can coalesce to form larger masses. Atherosclerotic lesions are patchy, usually involving only a portion of any given arterial wall and are rarely circumferential; on cross-section, the lesions therefore appear “eccentric”. This attributable to the vagaries of vascular hemodynamics. Local flow disturbances, such as turbulence at branch points, make certain portions of a vessel wall more susceptible to plaque formation. Although focal and sparsely distributed at first, with time atherosclerotic lesions can become larger, more numerous, and more broadly distributed. Moreover, in any given vessel, lesions at various stages often coexist.
Figure 11-13 Gross views of atherosclerosis in the aorta. A, Mild atherosclerosis composed of fibrous plaques, one of which is denoted by the arrow. B, Severe disease with diffuse and complicated lesions including an ulcerated plaque (open arrow), and a lesion with overlying thrombus (closed arrow).
• In descending order, the most extensively involved vessels are the lower abdominal aorta, the coronary arteries, the popliteal arteries, the internal carotid arteries, and the vessels of the circle of Willis.

• abdominal aorta is typically involved to a much greater degree than the thoracic aorta.

• Vessels of the upper extremities are usually spared, as are the mesenteric and renal arteries, except at their ostia.
Atherosclerotic plaques have three principal components:

1. smooth muscle cells, macrophages, and T Cells
2. extracellular matrix, including collagen, elastic fibers, and proteoglycans
3. intracellular and extracellular lipid

There is a **superficial fibrous cap** composed of smooth muscle cells and relatively dense collagen. Beneath and to the side of the cap (the “shoulder”) is a more cellular area containing macrophages, T cells, and smooth muscle cells. Deep to the fibrous cap is a **necrotic core**, containing lipid (primarily **cholesterol and cholesterol esters**), debris from dead cells, foam cells (lipid laden macrophages and smooth muscle cells), fibrin, variably organized thrombus, and other plasma proteins; the cholesterol content is frequently present as crystalline aggregates that are washed out during routine tissue processing and leave behind only empty “clefts.” The periphery of the lesions demonstrate **neovascularization** (proliferating small blood vessels).

Most atheromas contain abundant lipid, but some plaques ("**fibrous plaques**") are composed almost exclusively of smooth muscle cells and fibrous tissue.

Plaques generally continue to change and progressively enlarge through cell death and degeneration, synthesis and degradation (**remodeling**) of extracellular matrix, and organization of any superimposed thrombus. Moreover, atheromas often undergo **calcification**
Figure 11-14 Histologic features of atheromatous plaque in the coronary artery. A, Overall architecture demonstrating fibrous cap (F) and a central necrotic core (C) containing cholesterol and other lipids. The lumen (L) has been moderately compromised. Note that a segment of the wall is plaque free (arrow); the lesion is therefore “eccentric.” In this section, collagen has been stained blue (Masson trichrome stain). B, Higher-power photograph of a section of the plaque shown in A, stained for elastin (black), demonstrating that the internal and external elastic laminae are attenuated and the media of the artery is thinned under the most advanced plaque (arrow). C, Higher magnification photomicrograph at the junction of the fibrous cap and core, showing scattered inflammatory cells, calcification (arrowhead), and neovascularization (small arrows).
- Atherosclerotic plaques develop and grow slowly over decades.
- Atherosclerotic plaques are susceptible to the following clinically important pathologic changes:
  - **Rupture**, ulceration, or erosion of the surface of atheromatous plaques exposes highly thrombogenic substances and leads to thrombosis, which may partially or completely occlude the vessel lumen. If the patient survives, the clot may become organized and incorporated into the growing plaque.
  - Hemorrhage into a plaque. Rupture of the overlying fibrous cap, or of the thin-walled vessels in the areas of neovascularization, can cause intraplaque hemorrhage; a contained hematoma may expand the plaque or induce plaque rupture.
  - **Atheroembolism**. Plaque rupture can discharge atherosclerotic debris into the bloodstream, producing microemboli.
  - **Aneurysm formation**. Atherosclerosis-induced pressure or ischemic atrophy of the underlying media, with loss of elastic tissue, causes weakness and potential rupture.
Consequences of Atherosclerotic Disease

• Large elastic arteries (e.g., aorta, carotid, and iliac arteries) and large and medium-sized muscular arteries (e.g., coronary and popliteal arteries) are the major targets of atherosclerosis.

• Symptomatic atherosclerotic disease most often involves the arteries supplying the heart, brain, kidneys, and lower extremities. Myocardial infarction (heart attack), cerebral infarction (stroke), aortic aneurysms, and peripheral vascular disease (gangrene of the legs) are the major consequences of atherosclerosis.
- **Atherosclerotic Stenosis.** In small arteries, atherosclerotic plaques can gradually occlude vessel lumina, compromising blood flow and causing ischemic injury. At early stages of stenosis, outward remodeling of the vessel media tends to preserve the size of the lumen. However, there are limits on the extent of remodeling, and eventually the expanding atheroma impinges on the lumen to such a degree that blood flow is compromised. **Critical stenosis** is the stage at which the occlusion is sufficiently severe to produce tissue ischemia. In the coronary (and other) circulations, this typically occurs at when the occlusion produces a **70% decrease** in luminal cross-sectional area; with this degree of stenosis, chest pain may develop with exertion (so-called stable angina). Although acute plaque rupture is the most dangerous consequence, atherosclerosis also takes a toll through chronically diminished arterial perfusion: **mesenteric occlusion** and **bowel ischemia**, **sudden cardiac death**, **chronic ischemic heart disease**, **ischemic encephalopathy**, and **intermittent claudication** (diminished perfusion of the extremities) are all consequences of flow-limiting stenoses.
• Acute Plaque Change.

Plaque changes fall into three general categories:

1. **Rupture/fissuring**, exposing highly thrombogenic plaque constituents
2. **Erosion/ulceration**, exposing the thrombogenic subendothelial basement membrane to blood
3. **Hemorrhage** into the atheroma, expanding its volume

Plaque erosion or rupture is typically promptly followed by partial or complete vascular **thrombosis**, resulting in acute tissue infarction (e.g., myocardial or cerebral infarction).

Plaques rupture when they are unable to withstand **mechanical stresses** generated by vascular shear forces. The events that trigger abrupt changes in plaques and subsequent thrombosis are complex and include both **intrinsic factors** (e.g., plaque structure and composition) and **extrinsic elements** (e.g., blood pressure, platelet reactivity, vessel spasm).

Plaques that contain large areas of foam cells and extracellular lipid, and those in which the fibrous caps are thin or contain few smooth muscle cells or have clusters of inflammatory cells, are more likely to rupture; these are referred to as **“vulnerable plaques”**.
• The fibrous cap undergoes continuous remodeling that can stabilize the plaque, or conversely, render it more susceptible to rupture. Collagen is the major structural component of the fibrous cap, and accounts for its mechanical strength and stability. Thus, the balance of collagen synthesis versus degradation affects cap integrity. Collagen in atherosclerotic plaque is produced primarily by smooth muscle cells so that loss of these cells results in a less sturdy cap. Moreover, collagen turnover is controlled by metalloproteinases (MMPs), enzymes elaborated largely by macrophages and smooth muscle cells within the atheromatous plaque; conversely, tissue inhibitors of metalloproteinases (TIMPs) produced by endothelial cells, smooth muscle cells, and macrophages modulate MMP activity. In general, plaque inflammation results in a net increase in collagen degradation and reduced collagen synthesis, thereby destabilizing the mechanical integrity of the fibrous cap.

• Influences extrinsic to plaques also contribute to acute plaque changes. Thus, adrenergic stimulation can increase systemic blood pressure or induce local vasoconstriction, thereby increasing the physical stresses on a given plaque. Indeed, the adrenergic stimulation associated with wakening and rising can cause blood pressure spikes (followed by heightened platelet reactivity) that have been causally linked to the pronounced circadian periodicity for onset of acute MI (peaking between 6 AM and noon). Intense emotional stress can also contribute to plaque disruption.
Stable plaques can produce symptoms related to chronic ischemia by narrowing vessel lumens, whereas unstable plaques can cause dramatic and potentially fatal
It is now recognized that plaques that are responsible for myocardial infarction and other acute coronary syndromes are often asymptomatic before the acute change. Thus, pathologic and clinical studies show that the majority of plaques that undergo abrupt disruption and coronary occlusion previously showed only mild to moderate noncritical luminal stenosis.
It is also important to note that not all plaque ruptures result in occlusive thromboses with catastrophic consequences. Indeed, plaque disruption and an ensuing superficial platelet aggregation and thrombosis are probably common, repetitive, and often clinically silent complications of atheroma. Healing of these subclinical plaque disruptions—and resorption of their overlying thrombi— is an important mechanism in the growth of atherosclerotic lesions.
Thrombosis:
partial or total thrombosis superimposed on a disrupted plaque is a central factor in **acute coronary syndromes**. In its most serious form, thrombosis leads to **total occlusion** of the affected vessel. In contrast, in other coronary syndromes, luminal obstruction by the thrombus is **incomplete**, and may even wax and wane with time. Mural thrombi in a coronary artery can also **embolize**.

Vasoconstriction:
Vasoconstriction compromises lumen size, and, by increasing the local mechanical forces, can potentiate **plaque disruption**. Vasoconstriction at sites of atheroma may be stimulated by (1) circulating adrenergic agonists, (2) locally released platelet contents, (3) endothelial cell dysfunction with impaired secretion of endothelial derived relaxing factors (nitric oxide) relative to contracting factors (endothelin), and (4) mediators released from perivascular inflammatory cells.
Figure 11-16 The natural history, morphologic features, main pathogenic events, and clinical complications of atherosclerosis.
Embolism

- An embolus is a detached intravascular **solid**, **liquid**, or **gaseous** mass that is carried by the blood from its point of origin to a distant site, where it often causes tissue dysfunction or infarction.
- **The vast majority of emboli are dislodged thrombi**, hence the term **thromboembolism**.
- Other rare emboli are composed of fat droplets, nitrogen bubbles, atherosclerotic debris (cholesterol emboli), tumor fragments, bone marrow, or even foreign bodies.
- Emboli travel through the blood until they encounter vessels too small to permit further passage, causing partial or complete vascular occlusion. Depending on where they originate, emboli can lodge anywhere in the vascular tree; as discussed later, the clinical consequences vary widely depending on the size and the position of the lodged embolus, as well as the vascular bed that is impacted.
Pulmonary Embolism:
Pulmonary emboli originate from deep venous thromboses and are the **most common form of thromboembolic disease**. In more than 95% of cases, PEs originate from leg DVTs. Fragmented thrombi from DVTs are carried through progressively larger veins and the right side of the heart before slamming into the pulmonary arterial vasculature. Depending on the size of the embolus, it can occlude the main pulmonary artery, straddle the pulmonary artery bifurcation (**saddle embolus**), or pass out into the smaller, branching arteries. Frequently there are multiple emboli, occurring either sequentially or simultaneously as a shower of smaller emboli from a single large mass; in general, the patient who has had one PE is at high risk for more. Rarely, a venous embolus passes through an interatrial or interventricular defect and gains access to the systemic arterial circulation (**paradoxical embolism**).
Figure 4-15 Embolus from a lower extremity deep venous thrombosis, lodged at a pulmonary artery branchpoint.
the major functional consequences of pulmonary emboli.
- Most pulmonary emboli (60% to 80%) are clinically silent because they are small.
- **Sudden death**, right heart failure (cor pulmonale), or cardiovascular collapse occurs when emboli **obstruct 60% or more** of the pulmonary circulation.
- Embolic obstruction of medium-sized arteries with subsequent vascular rupture can result in **pulmonary hemorrhage** but usually does not cause pulmonary infarction. This is because the lung is supplied by both the pulmonary arteries and the bronchial arteries, and the intact bronchial circulation is usually sufficient to perfuse the affected area. Understandably, if the bronchial arterial flow is compromised (e.g., by left-sided cardiac failure), infarction may occur.
- Embolic obstruction of small end-arteriolar pulmonary branches often does produce hemorrhage or infarction.
- Multiple emboli over time may cause **pulmonary hypertension** and right ventricular failure.
Systemic Thromboembolism:

Most systemic emboli (80%) arise from intracardiac mural thrombi, two thirds of which are associated with left ventricular wall infarcts and another one fourth with left atrial dilation and fibrillation. The remainder originates from aortic aneurysms, atherosclerotic plaques, valvular vegetations, or venous thrombi (paradoxical emboli); 10% to 15% are of unknown origin. In contrast to venous emboli, the vast majority of which lodge in the lung, arterial emboli can travel to a wide variety of sites; the point of arrest depends on the source and the relative amount of blood flow that downstream tissues receive. Most come to rest in the lower extremities (75%) or the brain (10%), but other tissues, including the intestines, kidneys, spleen, and upper extremities, may be involved on occasion. The consequences of systemic emboli depend on the vulnerability of the affected tissues to ischemia, the caliber of the occluded vessel, and whether a collateral blood supply exists; in general, however, the outcome is tissue infarction.
• Fat and Marrow Embolism:

Microscopic fat globules—sometimes with associated hematopoietic bone marrow—can be found in the pulmonary vasculature after fractures of long bones or, rarely, in the setting of soft tissue trauma and burns. Fat embolism occurs in some 90% of individuals with severe skeletal injuries, but less than 10% of such patients have any clinical findings.

Fat embolism syndrome is the term applied to the minority of patients who become symptomatic. It is characterized by pulmonary insufficiency, neurologic symptoms, anemia, and thrombocytopenia, and is fatal in about 5% to 15% of cases. Typically, 1 to 3 days after injury there is a sudden onset of tachypnea, dyspnea, and tachycardia; irritability and restlessness can progress to delirium or coma. Thrombocytopenia is attributed to platelet adhesion to fat globules and subsequent aggregation or splenic sequestration; anemia can result from similar red cell aggregation and/or hemolysis. A diffuse petechial rash (seen in 20% to 50% of cases) is related to rapid onset of thrombocytopenia and can be a useful diagnostic feature. The pathogenesis of fat emboli syndrome probably involves both mechanical obstruction and biochemical injury. Fat microemboli and associated red cell and platelet aggregates can occlude the pulmonary and cerebral microvasculature. Release of free fatty acids from the fat globules exacerbates the situation by causing local toxic injury to endothelium, and platelet activation and granulocyte recruitment (with free radical, protease, and eicosanoid release) complete the vascular assault.
Figure 4-16 Bone marrow embolus in the pulmonary circulation. The cellular elements on the left side of the embolus are hematopoietic cells, while the cleared vacuoles represent marrow fat. The relatively uniform red area on the right of the embolus is an early organizing thrombus.
Air Embolism:

Gas bubbles within the circulation can coalesce to form frothy masses that obstruct vascular flow and cause distal ischemic injury. For example, a very small volume of air trapped in a coronary artery during bypass surgery, or introduced into the cerebral circulation by neurosurgery in the “sitting position,” can occlude flow with dire consequences. A larger volume of air, generally more than 100 cc, is necessary to produce a clinical effect in the pulmonary circulation; unless care is taken, this volume of air can be inadvertently introduced during obstetric or laparoscopic procedures, or as a consequence of chest wall injury.

A particular form of gas embolism, called decompression sickness, occurs when individuals experience sudden decreases in atmospheric pressure. Scuba and deep sea divers, underwater construction workers, and individuals in unpressurized aircraft in rapid ascent are all at risk. When air is breathed at high pressure (e.g., during a deep sea dive), increased amounts of gas (particularly nitrogen) are dissolved in the blood and tissues. If the diver then ascends (depressurizes) too rapidly, the nitrogen comes out of solution in the tissues and the blood. The rapid formation of gas bubbles within skeletal muscles and supporting tissues in and about joints is responsible for the painful condition called the bends. In the lungs, gas bubbles in the vasculature cause edema, hemorrhage, and focal atelectasis or emphysema, leading to a form of respiratory distress called the chokes. A more chronic form of decompression sickness is called caisson disease. In caisson disease, persistence of gas emboli in the skeletal system leads to multiple foci of ischemic necrosis; the more common sites are the femoral heads, tibia, and humeri.

Individuals affected by acute decompression sickness are treated by being placed in a chamber under sufficiently high pressure to force the gas bubbles back into solution. Subsequent slow decompression permits gradual resorption and exhalation of the gases, which prevents the obstructive bubbles from reforming.
• Amniotic Fluid Embolism: Amniotic fluid embolism is the fifth most common cause of maternal mortality worldwide; it accounts for roughly 10% of maternal deaths in the United States and results in **permanent neurologic deficit in as many as 85% of survivors**. Amniotic fluid embolism is an ominous complication of labor and the immediate postpartum period. **The mortality rate is up to 80%.** The onset is characterized by sudden severe dyspnea, cyanosis, and shock, followed by **neurologic impairment** ranging from headache to seizures and coma. If the patient survives the initial crisis, **pulmonary edema** typically develops, frequently accompanied by **disseminated intravascular coagulation**. The morbidity and mortality in amniotic fluid embolism may stem from **the biochemical activation** of coagulation factors and components of the innate immune system by substances in the amniotic fluid, rather than the mechanical obstruction of pulmonary vessels by amniotic debris.

The underlying cause is the infusion of amniotic fluid or fetal tissue into the maternal circulation via a **tear** in the placental membranes or rupture of uterine veins.

Classic findings at autopsy include the presence of squamous cells shed from fetal skin, lanugo hair, fat from vernix caseosa, and mucin derived from the fetal respiratory or gastrointestinal tract in the maternal pulmonary microvasculature. Other findings include marked pulmonary edema, diffuse alveolar damage, and the presence of fibrin thrombi in many vascular beds due to disseminated intravascular coagulation.
Figure 4-17 Amniotic fluid embolism. Two small pulmonary arterioles are packed with laminated swirls of fetal squamous cells. There is marked edema and congestion. Elsewhere the lung contained small organizing thrombi consistent with disseminated intravascular coagulation. (Courtesy Dr. Beth Schwartz, Baltimore, Md.)
Aneurysms and Dissection

- An aneurysm is a localized abnormal dilation of a blood vessel or the heart that may be congenital or acquired, and involve the entire thickness of the wall.
- “True” aneurysm: when an aneurysm involves an attenuated but intact arterial wall or thinned ventricular wall of the heart. Atherosclerotic, syphilitic, and congenital vascular aneurysms, as well as ventricular aneurysms that follow transmural myocardial infarctions are of this type.
- False aneurysm: (also called pseudo-aneurysm) is a defect in the vascular wall leading to an extravascular hematoma that freely communicates with the intravascular space (“pulsating hematoma”). Examples include a ventricular rupture after myocardial infarction that is contained by a pericardial adhesion, or a leak at the sutured junction of a vascular graft with a natural artery.

Aneurysms are classified by macroscopic shape and size:

Saccular aneurysms are spherical outpouchings involving only a portion of the vessel wall; they vary from 5 to 20 cm in diameter and often contain thrombus.

Fusiform aneurysms are diffuse, circumferential dilations of a long vascular segment; they vary in diameter (up to 20 cm) and in length and can involve extensive portions of the aortic arch, abdominal aorta, or even the iliacs.

These types are not specific for any disease or clinical manifestations.

- An arterial dissection: arises when blood enters a defect in the arterial wall and tunnels between its layers. Dissections are often but not always aneurysmal.
Figure 11-18 Aneurysms. A, Normal vessel. B, True aneurysm, saccular type. The wall focally bulges outward and may be attenuated but is otherwise intact. C, True aneurysm, fusiform type. There is circumferential dilation of the vessel, without rupture. D, False aneurysm. The wall is ruptured, and there is a collection of blood (hematoma) that is bounded externally by adherent extravascular tissues. E, Dissection. Blood has entered (dissected) the wall of the vessel and separated the layers. Although this is shown as occurring through a tear in the lumen, dissections can also occur by rupture of the vessels of the vasa vasorum within the media.
• Pathogenesis of Aneurysms:
Aneurysms can occur when the structure or function of the connective tissue within the vascular wall is compromised:
- **The intrinsic quality of the vascular wall connective tissue is poor:**
  * In Marfan syndrome: defective synthesis of the scaffolding protein **fibrillin** leads to aberrant TGF-β activity and weakening of elastic tissue.
  * Loeys-Dietz syndrome: mutations in **TGF-β receptors** lead to defective synthesis of elastin and collagens I and III.
Aneurysms in such individuals can rupture fairly easily (even at small size) and are thus considered to follow an “**aggressive**” course.
  * Vascular forms of Ehlers-Danlos syndrome: defective **type III collagen** synthesis
  * Vitamin C deficiency (scurvy): altered **collagen cross-linking**
The balance of collagen degradation and synthesis is altered by inflammation and associated proteases: increased matrix metalloprotease (MMP) expression, these enzymes have the capacity to degrade virtually all components of the extracellular matrix in the arterial wall (collagens, elastin, proteoglycans, laminin, fibronectin). Decreased expression of tissue inhibitors of metalloproteases (TIMPs) can also contribute to the extracellular matrix degradation. may be associated with MMP and/or TIMP polymorphisms, or altered by the nature of the local inflammatory response.
- The vascular wall is weakened through loss of smooth muscle cells or the synthesis of noncollagenous or nonelastic extracellular matrix. Ischemia of the inner media occurs when there is atherosclerotic thickening of the intima, which increases the distance that oxygen and nutrients must diffuse. Systemic hypertension can also cause significant narrowing of arterioles of the vasa vasorum, which causes outer medial ischemia.

Medial ischemia may lead to “degenerative changes” of the aorta, whereby smooth muscle cell loss—or change in synthetic phenotype—leads to scarring (and loss of elastic fibers), inadequate extracellular matrix synthesis, and production of increasing amounts of amorphous ground substance (glycosaminoglycan). Histologically, these changes are collectively recognized as cystic medial degeneration, which can be seen in a variety of settings, including Marfan syndrome and scurvy.

Tertiary syphilis is another rare cause of aortic aneurysms. The obliterative endarteritis characteristic of late stage syphilis shows a predilection for small vessels including those of the vasa vasorum of the thoracic aorta. This leads to ischemic injury of the aortic media and aneurysmal dilation, which sometimes involves the aortic valve annulus.
Figure 11-19 Cystic medial degeneration. **A**, Cross-section of aortic media from a patient with Marfan syndrome, showing elastin fragmentation and areas devoid of elastin that resemble cystic spaces but are actually filled with proteoglycans (asterisks). **B**, Normal media for comparison, showing the regular layered pattern of elastic tissue. In both **A** and **B**, elastin is stained.
• The two most important causes of aortic aneurysms are atherosclerosis and hypertension; atherosclerosis is a greater factor in AAAs, while hypertension is the most common etiology associated with ascending aortic aneurysms.

• Other factors that weaken vessel walls and lead to aneurysms include trauma, vasculitis, congenital defects (e.g., fibromuscular dysplasia and berry aneurysms typically in the circle of Willis, and infections (mycotic aneurysms).
Abdominal Aortic Aneurysm (AAA)

- AAAs occur more frequently in men and in smokers, rarely developing before age 50.
- Atherosclerosis is a major cause of AAA, but other factors clearly contribute.
• MORPHOLOGY:
  - Usually positioned **below the renal arteries and above the bifurcation of the aorta**
  - AAA can be saccular or fusiform,
  - up to 15 cm in diameter, and up to 25 cm in length.
  - There is severe complicated **atherosclerosis** with destruction and thinning of the underlying aortic media
  - the aneurysm frequently contains a bland, laminated, poorly organized mural **thrombus**.
• three AAA variants:

1- Inflammatory AAA:
account for 5% to 10% of all AAA; these typically occur in younger patients, who often present with back pain and elevated inflammatory markers (e.g., elevation of C-reactive protein). Characterized by abundant lymphoplasmacytic inflammation with many macrophages (and even giant cells) associated with dense periaortic scarring that can extend into the anterior retroperitoneum. The cause is a presumed localized immune response to the abdominal aortic wall.

2- A subset of inflammatory AAA may be a vascular manifestation of a recently recognized entity called immunoglobulin G4 (IgG4)-related disease. This is a disorder marked by (in most cases) high plasma levels of IgG4 and tissue fibrosis associated with frequent infiltrating IgG4-expressing plasma cells. It may affect a variety of tissues, including pancreas, biliary system, and salivary gland. The affected individuals have aortitis and periaortitis that weaken the wall sufficiently in some cases to give rise to aneurysms. Recognition of this entity is important since it responds well to steroid therapy.

3- Mycotic AAA are lesions that have become infected by the lodging of circulating microorganisms in the wall. In such cases, suppuration further destroys the media, potentiating rapid dilation and rupture.
Figure 11-20 Abdominal aortic aneurysm. A, External view, gross photograph of a large aortic aneurysm that ruptured (rupture site is indicated by the arrow). B, Opened view, with the location of the rupture tract indicated by a probe. The wall of the aneurysm is exceedingly thin, and the lumen is filled by a large quantity of layered but largely unorganized thrombus.
• Clinical Features:
- Most cases of AAA are asymptomatic.
- Rupture into the peritoneal cavity or retroperitoneal tissues with massive, potentially fatal hemorrhage.
- Obstruction of a vessel branching off from the aorta, resulting in ischemic injury to the supplied tissue; for example, iliac (leg), renal (kidney), mesenteric (gastrointestinal tract), or vertebral arteries (spinal cord).
- Embolism from atheroma or mural thrombus.
- Impingement on an adjacent structure, for example, compression of a ureter or erosion of vertebrae.

The risk of rupture is directly related to the size of the aneurysm, varying from nil for AAA 4 cm or less in diameter, to 1% per year for AAA between 4 and 5 cm, 11% per year for AAA between 5 and 6 cm, and 25% per year for aneurysms larger than 6 cm. Most aneurysms expand at a rate of 0.2 to 0.3 cm/year, but 20% expand more rapidly.

operative mortality for unruptured aneurysms is approximately 5%, whereas emergency surgery after rupture carries a mortality rate of more than 50%.
Thoracic Aortic Aneurysm

- most commonly associated with hypertension, although other causes such as Marfan syndrome and Loeys-Dietz syndrome are increasingly recognized.
- These can present with signs and symptoms referable to:
  1. respiratory difficulties due to encroachment on the lungs and airways
  2. difficulty in swallowing due to compression of the esophagus
  3. persistent cough due to compression of the recurrent laryngeal nerves
  4. pain caused by erosion of bone (i.e., ribs and vertebral bodies),
  5. cardiac disease as the aortic aneurysm leads to aortic valve dilation with valvular insufficiency or narrowing of the coronary ostia causing myocardial ischemia
  6. rupture.

Most patients with syphilitic aneurysms die of heart failure secondary to aortic valvular incompetence.
Cardiovascular syphilis, in the form of syphilitic aortitis, accounts for more than 80% of cases of tertiary disease. The pathogenesis of this vascular lesion is not known, but the scarcity of treponemes and the intense inflammatory infiltrate suggest that the immune response plays a role. The aortitis leads to slowly progressive dilation of the aortic root and arch, which causes aortic valve insufficiency and aneurysms of the proximal aorta.
STAGE | PATHOLOGY
---|---
Primary | Chancre
Secondary | Palmar rash
 | Lymphadenopathy
 | Condyloma latum
 | Neurosyphilis (usually asymptomatic)
Latent | Neurosyphilis: Asymptomatic (CSF abnormalities)
 | Meningovascular
 | Tabes dorsalis
 | General paresis
Aortitis: Aneurysms
 | Aortic regurgitation
Gummas: Hepar lobatum
 | Skin, bone, others
Tertiary | Late abortion or stillbirth
 | Congenital
 | Infantile: Rash
 | Osteochondritis
 | Periostitis
 | Liver and lung fibrosis
Childhood: Interstitial keratitis
 | Hutchinson teeth
Aortic Dissection

- Aortic dissection occurs when blood separates the laminar planes of the media to form a blood-filled channel within the aortic wall; this can be catastrophic if the dissection then ruptures through the adventitia and hemorrhages into adjacent spaces.

- Aortic dissection occurs principally in two groups of patients:
  1. men aged 40 to 60 years with antecedent hypertension (more than 90% of cases)
  2. younger adults with systemic or localized abnormalities of connective tissue affecting the aorta (e.g., Marfan syndrome).

- Dissections can be iatrogenic, for example, following arterial cannulations during coronary catheterization procedures or cardiopulmonary bypass.

- Rarely, pregnancy is associated with aortic (or other vessel) dissection. This typically occurs during or after the third trimester, and may be related to hormone-induced vascular remodeling and the hemodynamic stresses of the perinatal period.

- Dissection is unusual in the presence of substantial atherosclerosis or other cause of medial scarring such as syphilis, presumably because the medial fibrosis inhibits propagation of the dissecting hematoma.
Pathogenesis:
- Hypertension is the major risk factor for aortic dissection. Ischemic injury (due to diminished flow through the vasa vasorum, possibly exacerbated by high wall pressures) is contributory.

- Other dissections occur in the setting of inherited or acquired connective tissue disorders with defective vascular extracellular matrix (e.g., Marfan syndrome, Ehlers-Danlos syndrome, defects in copper metabolism).

- Regardless of the underlying etiology, the trigger for the intimal tear and initial intramural aortic hemorrhage is not known in most cases. Once a tear has occurred, blood flow under systemic pressure dissect through the media, leading to progression of the hematoma.

- In some cases, disruption of penetrating vessels of the vasa vasorum can give rise to an intramural hematoma without an intimal tear.
• MORPHOLOGY:
The most frequent preexisting histologically detectable lesion is **cystic medial degeneration**. Inflammation is characteristically absent.

In the vast majority of spontaneous dissections, the tear occurs in the **ascending aorta**, usually within 10 cm of the aortic valve. Tears are typically **transverse** with sharp, jagged edges up to **1 to 5 cm** in length, separates the various layers. The dissection can extend **retrograde** toward the heart as well as **distally**, sometimes into the iliac and femoral arteries. The dissecting hematoma spreads characteristically along the laminar planes of the aorta, usually between the **middle and outer thirds**.

It can rupture through the adventitia causing massive hemorrhage (e.g., into the thoracic or abdominal cavities) or **cardiac tamponade** (hemorrhage into the pericardial sac). In some (lucky) instances, the dissecting hematoma reenters the lumen of the aorta through a second distal intimal tear, creating a new false vascular channel (**double-barreled aorta**). This averts a fatal extraaortic hemorrhage, and over time, such false channels can be endothelialized to become recognizable **chronic dissections**.
Figure 11-21 Aortic dissection. A, Gross photograph of an opened aorta with proximal dissection originating from a small, oblique intimal tear (probe), allowing blood to enter the media and creating a retrograde intramural hematoma (narrow arrows). Note that the intimal tear has occurred in a region largely free of atherosclerotic plaque and that propagation of the intramural hematoma distally is arrested where atherosclerosis begins (broad arrow). B, Histologic view of the dissection demonstrating an aortic intramural hematoma (asterisk). Aortic elastic layers are black and blood is red (Movat stain).
Clinical Features:
The morbidity and mortality associated with dissections depend on which part of the aorta is involved; the most serious complications occur with dissections between the aortic valve and the distal arch. Accordingly, aortic dissections are generally classified into two types:

1- **type A** dissections: The more common (and dangerous) proximal lesions, involving either both the ascending and descending aorta or just the ascending aorta only (types I and II of the DeBakey classification)

2- **type B** dissections: Distal lesions not involving the ascending part and usually beginning distal to the subclavian artery (DeBakey type III).
Figure 11-22 Classification of dissections. Type A (proximal) involves the ascending aorta, either as part of a more extensive dissection (DeBakey I) or in isolation (DeBakey II). Type B (distal or DeBakey III) dissections arise after the take-off of the great vessels. Type A dissections typically have the most serious complications and greatest associated mortality.
• The classic clinical symptoms of aortic dissection are the sudden onset of excruciating pain, usually beginning in the anterior chest, radiating to the back between the scapulae, and moving downward as the dissection progresses; the pain can be confused with that of myocardial infarction.
• The most common cause of death is rupture of the dissection into the pericardial, pleural, or peritoneal cavities.
• Retrograde dissection into the aortic root can also disrupt the aortic valve annulus. Common clinical manifestations include cardiac tamponade and aortic insufficiency.
• Dissections can also extend into the great arteries of the neck, or into the coronary, renal, mesenteric, or iliac arteries, causing vascular obstruction and ischemic consequences such as myocardial infarction.
• In type A dissections, rapid diagnosis and institution of intensive antihypertensive therapy coupled with surgical plication of the aortic intimal tear can save 65% to 85% of patients. However, mortality approaches 70% in those who present with hemorrhage or symptoms related to distal ischemia, and the overall 10-year survival is only 40% to 60%.
• Most type B dissections can be managed conservatively; patients have a 75% survival rate whether they are treated with surgery or antihypertensive medication only.