THROMBOSIS

Three primary abnormalities that lead to thrombus formation (called Virchow's triad):
(1) endothelial injury,
(2) stasis or turbulent blood flow,
(3) hypercoagulability of the blood

Endothelial Injury.

Endothelial injury is particularly important for thrombus formation in the heart or the arterial circulation, where the normally high flow rates might otherwise impede clotting by preventing platelet adhesion and washing out activated coagulation factors. Thus, thrombus formation within cardiac chambers (e.g., after endocardial injury due to myocardial infarction), over ulcerated plaques in atherosclerotic arteries, or at sites of traumatic or inflammatory vascular injury (vasculitis) is largely a consequence of endothelial cell injury. Clearly, physical loss of endothelium can lead to exposure of the subendothelial ECM, adhesion of platelets, release of tissue factor, and local depletion of PGI$_2$ and plasminogen activators.

However, it should be emphasized that endothelium need not be denuded or physically disrupted to contribute to the development of thrombosis; any perturbation in the dynamic balance of the prothrombotic and antithrombotic activities of endothelium can influence local clotting events

Thus, dysfunctional endothelial cells can produce more procoagulant factors (e.g., platelet adhesion molecules, tissue factor, PAIs) or may synthesize less anticoagulant effectors (e.g., thrombomodulin, PGI$_2$, t-PA). Endothelial dysfunction can be induced by a wide variety of insults, including hypertension, turbulent blood flow, bacterial endotoxins, radiation injury, metabolic abnormalities such as homocystinemia or hypercholesterolemia, and toxins absorbed from cigarette smoke.

Alterations in Normal Blood Flow.

Turbulence contributes to arterial and cardiac thrombosis by causing endothelial injury or dysfunction, as well as by forming countercurrents and local pockets of stasis; stasis is a major contributor in the development of venous thrombi.

Normal blood flow is laminar such that the platelets (and other blood cellular elements) flow centrally in the vessel lumen, separated from endothelium by a slower moving layer of plasma.

Stasis and turbulence therefore:

- Promote endothelial activation, enhancing procoagulant activity, leukocyte adhesion, etc., in part through flow-induced changes in endothelial cell gene expression.
- Disrupt laminar flow and bring platelets into contact with the endothelium
- Prevent washout and dilution of activated clotting factors by fresh flowing blood and the inflow of clotting factor inhibitors
Turbulence and stasis contribute to thrombosis in several clinical settings. Ulcerated atherosclerotic plaques not only expose subendothelial ECM but also cause turbulence. Aortic and arterial dilations called aneurysms result in local stasis and are therefore fertile sites for thrombosis.

Acute myocardial infarctions result in areas of noncontractile myocardium and sometimes cardiac aneurysms; both are associated with stasis and flow abnormalities that promote the formation of cardiac mural thrombi.

Rheumatic mitral valve stenosis results in left atrial dilation; in conjunction with atrial fibrillation, a dilated atrium is a site of profound stasis and a prime location for developing thrombi.

Hyperviscosity increases resistance to flow and causes small vessel stasis; the deformed red cells in sickle cell anemia cause vascular occlusions, with the resulting stasis also predisposing to thrombosis.

Hypercoagulability.

Hypercoagulability (also called thrombophilia) is a less frequent contributor to thrombotic states but is nevertheless an important component in the equation, and in some situations can predominate.

It is loosely defined as any alteration of the coagulation pathways that predisposes to thrombosis;

it can be divided into primary (genetic) and secondary (acquired) disorders. Of the inherited causes of hypercoagulability, point mutations in the factor V gene and prothrombin gene are the most common.

<table>
<thead>
<tr>
<th>TABLE 4-2-- Hypercoagulable States</th>
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<tbody>
<tr>
<td><strong>PRIMARY (GENETIC)</strong></td>
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<tr>
<td><strong>Common</strong></td>
</tr>
<tr>
<td>Factor V mutation (G1691A mutation; factor V Leiden)</td>
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<tr>
<td>Prothrombin mutation (G20210A variant)</td>
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<tr>
<td>5,10-Methylenetetrahydrofolate reductase (homozygous C677T mutation)</td>
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<tr>
<td>Increased levels of factors VIII, IX, XI, or fibrinogen</td>
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<tr>
<td><strong>Rare</strong></td>
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Among the acquired thrombophilic states, two that are particularly important clinical problems deserve special mention.

Heparin-induced thrombocytopenia (HIT) syndrome.

HIT occurs following the administration of unfractionated heparin, which may induce the appearance of antibodies that recognize complexes of heparin and platelet factor 4 on the surface of platelets, as well as complexes of heparin-like molecules and platelet factor 4-like proteins on endothelial cells. Binding of these antibodies to platelets results in their activation, aggregation, and consumption (hence the thrombocytopenia in the syndrome.)
This effect on platelets and endothelial damage combine to produce a prothrombotic state, even in the face of heparin administration and low platelet counts. Newer low-molecular weight heparin preparations induce antibody formation less frequently, but still cause thrombosis if antibodies have already formed. Other anticoagulants such as fondaparinux (a pentasaccharide inhibitor of factor X) also cause a HIT-like syndrome on rare occasions.

Antiphospholipid antibody syndrome

(previously called the lupus anticoagulant syndrome). This syndrome has protean clinical manifestations, including recurrent thromboses, repeated miscarriages, cardiac valve vegetations, and thrombocytopenia. Depending on the vascular bed involved, the clinical presentations can include pulmonary embolism (following lower extremity venous thrombosis), pulmonary hypertension (from recurrent subclinical pulmonary emboli), stroke, bowel infarction, or renovascular hypertension. Fetal loss is attributable to antibody-mediated inhibition of t-PA activity necessary for trophoblastic invasion of the uterus.

Antiphospholipid antibody syndrome is also a cause of renal microangiopathy, resulting in renal failure associated with multiple capillary and arterial thromboses.

The name antiphospholipid antibody syndrome is a bit of a misnomer, as it is believed that the most important pathologic effects are mediated through binding of the antibodies to epitopes on plasma proteins (e.g., prothrombin) that are somehow induced or “unveiled” by phospholipids. In vivo, these autoantibodies induce a hypercoagulable state by causing endothelial injury, by activating platelets and complement directly, and through interaction with the catalytic domains of certain coagulation factors. However, in vitro (in the absence of platelets and endothelial cells), the autoantibodies interfere with phospholipids and thus inhibit coagulation. The antibodies also frequently give a false-positive serologic test for syphilis because the antigen in the standard assay is embedded in cardiolipin.

Antiphospholipid antibody syndrome has primary and secondary forms. Individuals with a well-defined autoimmune disease, such as systemic lupus erythematosus, are designated as having secondary antiphospholipid syndrome (hence the earlier term lupus anticoagulant syndrome). In primary antiphospholipid syndrome, patients exhibit only the manifestations of a hypercoagulable state and lack evidence of other autoimmune disorders; occasionally this happens in association with certain drugs or infections. A particularly aggressive form (catastrophic antiphospholipid syndrome) characterized by widespread small-vessel thrombi and multi-organ failure has a 50% mortality. The antibodies also make surgical procedures more difficult; for example

Morphology. Thrombi can develop anywhere in the cardiovascular system (e.g., in cardiac chambers, on valves, or in arteries, veins, or capillaries). The size and shape of thrombi depend on the site of origin and the cause. Arterial or cardiac thrombi usually begin at sites of turbulence or endothelial injury; venous thrombi characteristically occur at sites of stasis. Thrombi are focally attached to the underlying vascular surface; arterial thrombi tend to grow retrograde from the point of attachment, while venous thrombi extend in the direction of blood flow (thus both propagate toward the heart). The propagating portion of a thrombus is often poorly attached and therefore prone to fragmentation and embolization.

Thrombi often have grossly and microscopically apparent laminations called lines of Zahn; these represent pale platelet and fibrin deposits alternating with darker red cell–rich layers.
Such laminations signify that a thrombus has formed in flowing blood; their presence can therefore distinguish antemortem thrombosis from the bland nonlaminated clots that occur postmortem.

Thrombi occurring in heart chambers or in the aortic lumen are designated mural thrombi. Abnormal myocardial contraction (arrhythmias, dilated cardiomyopathy, or myocardial infarction) or endomyocardial injury (myocarditis or catheter trauma) promotes cardiac mural thrombi, while ulcerated atherosclerotic plaque and aneurysmal dilation are the precursors of aortic thrombus.

**Arterial thrombi** are frequently occlusive; the most common sites in decreasing order of frequency are the coronary, cerebral, and femoral arteries. They typically consist of a friable meshwork of platelets, fibrin, red cells, and degenerating leukocytes. Although these are usually superimposed on a ruptured atherosclerotic plaque, other vascular injuries (vasculitis, trauma) may be the underlying cause.

**Venous thrombosis (phlebothrombosis)** is almost invariably occlusive, with the thrombus forming a long cast of the lumen. Because these thrombi form in the sluggish venous circulation, they tend to contain more enmeshed red cells (and relatively few platelets) and are therefore known as red, or stasis, thrombi. The veins of the lower extremities are most commonly involved (90% of cases); however, upper extremities, periprosthetic plexus, or the ovarian and perihilar veins can also develop venous thrombi. Under special circumstances, they can also occur in the dural sinuses, portal vein, or hepatic vein.

**Postmortem clots** can sometimes be mistaken for antemortem venous thrombi. However, postmortem clots are gelatinous with a dark red dependent portion where red cells have settled by gravity and a yellow “chicken fat” upper portion; they are usually not attached to the underlying wall. In comparison, red thrombi are firmer and are focally attached, and sectioning typically reveals gross and/or microscopic lines of Zahn.

Thrombi on heart valves are called vegetations. Blood-borne bacteria or fungi can adhere to previously damaged valves (e.g., due to rheumatic heart disease) or can directly cause valve damage; in both cases, endothelial injury and disturbed blood flow can induce the formation of large thrombotic masses (infective endocarditis); Sterile vegetations can also develop on noninfected valves in persons with hypercoagulable states, so-called nonbacterial thrombotic endocarditis. Less commonly, sterile, verrucous endocarditis (Libman-Sacks endocarditis) can occur in the setting of systemic lupus erythematosus.

**Fate of the Thrombus.**

If a patient survives the initial thrombosis, in the ensuing days to weeks thrombi undergo some combination of the following four events:
• *Propagation.* Thrombi accumulate additional platelets and fibrin.
• *Embolization.* Thrombi dislodge and travel to other sites in the vasculature.
• *Dissolution.* Dissolution is the result of fibrinolysis, which can lead to the rapid shrinkage and total disappearance of recent thrombi. In contrast, the extensive fibrin deposition and crosslinking in older thrombi renders them more resistant to lysis. This distinction explains why therapeutic administration of fibrinolytic agents such as t-PA (e.g., in the setting of acute coronary thrombosis) is generally effective only when given in the first few hours of a thrombotic episode.
• *Organization and recanalization.* Older thrombi become organized by the ingrowth of endothelial cells, smooth muscle cells, and fibroblasts. Capillary channels eventually form that re-establish the continuity of the original lumen, albeit to a variable degree.

Although the earliest capillary channels may not restore significant flow to obstructed vessels, continued recanalization may convert a thrombus into a smaller mass of connective tissue that becomes incorporated into the vessel wall. Eventually, with remodeling and contraction of the mesenchymal elements, only a fibrous lump may remain to mark the original thrombus. Occasionally the centers of thrombi undergo enzymatic digestion, presumably as a result of the release of lysosomal enzymes from trapped leukocytes and platelets. In the setting of bacteremia such thrombi may become infected, producing an inflammatory mass that erodes and weakens the vessel wall. If unchecked, this may result in a mycotic aneurysm.

**Clinical Consequences.**

Thrombi are significant because they cause obstruction of arteries and veins, and are sources of emboli. Which effect predominates depends on the site of the thrombosis. Venous thrombi can cause congestion and edema in vascular beds distal to an obstruction, but they are far more worrisome for their capacity to embolize to the lungs and cause death. Conversely, although arterial thrombi can embolize and cause downstream infarctions, a thrombotic occlusion at a critical site (e.g., a coronary artery) can have more serious clinical consequences.

**Venous Thrombosis (Phlebothrombosis).**

Most venous thrombi occur in the superficial or deep veins of the leg. Superficial venous thrombi typically occur in the saphenous veins in the setting of varicosities. Although such thrombi can cause local congestion, swelling, pain, and tenderness, they rarely embolize. Nevertheless, the local edema and impaired venous drainage do predispose the overlying skin to infections from slight trauma and to the development of varicose ulcers. Deep venous thrombosis (DVT) in the larger leg veins—at or above the knee (e.g., popliteal, femoral, and iliac veins)—is more serious because such thrombi more often embolize to the lungs and give
rise to pulmonary infarction. Although they can cause local pain and edema, venous obstructions from DVTs can be rapidly offset by collateral channels.

Lower extremity DVTs are associated with hypercoagulable states, as described earlier. Common predisposing factors include bed rest and immobilization (because they reduce the milking action of the leg muscles, resulting in reduced venous return), and congestive heart failure (also a cause of impaired venous return). Trauma, surgery, and burns not only immobilize a person but are also associated with vascular insults, procoagulant release from injured tissues, increased hepatic synthesis of coagulation factors, and altered t-PA production. Many elements contribute to the thrombotic diathesis of pregnancy; besides the potential for amniotic fluid infusion into the circulation at the time of delivery, late pregnancy and the postpartum period are also associated with systemic hypercoagulability. Tumor-associated inflammation and coagulation factors (tissue factor, factor VIII) and procoagulants (e.g., mucin) released from tumor cells all contribute to the increased risk of thromboembolism in disseminated cancers, so-called migratory thrombophlebitis or Trousseau syndrome. Regardless of the specific clinical setting, advanced age also increases the risk of DVT.

**Arterial and Cardiac Thrombosis.**

Atherosclerosis is a major cause of arterial thromboses, because it is associated with loss of endothelial integrity and with abnormal vascular flow. Myocardial infarction can predispose to cardiac mural thrombi by causing dyskinetic myocardial contraction as well as damage to the adjacent endocardium, and rheumatic heart disease may engender atrial mural thrombi as discussed above. Besides local obstructive consequences, cardiac and aortic mural thrombi can also embolize peripherally. Although any tissue can be affected, the brain, kidneys, and spleen are particularly likely targets because of their rich blood supply.

**DISSEMINATED INTRAVASCULAR COAGULATION (DIC)**

Disorders ranging from obstetric complications to advanced malignancy can be complicated by DIC, the sudden or insidious onset of widespread fibrin thrombi in the microcirculation. Although these thrombi are not grossly visible, they are readily apparent microscopically and can cause diffuse circulatory insufficiency, particularly in the brain, lungs, heart, and kidneys. To complicate matters, the widespread microvascular thrombosis results in platelet and coagulation protein consumption (hence the synonym consumption coagulopathy), and at the same time, fibrinolytic mechanisms are activated. Thus, an initially thrombotic disorder can evolve into a bleeding catastrophe. *It should be emphasized that DIC is not a primary disease but rather a potential complication of any condition associated with widespread activation of thrombin.*