Thrombosis, Embolism and Infarction
Thrombus formation (called Virchow's triad):
(1) endothelial injury,
(2) stasis or turbulent blood flow
(3) hypercoagulability of the blood
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.
Physical loss of endothelium can lead to exposure of the subendothelial ECM, adhesion of platelets, release of tissue factor, and local depletion of PGI2 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, PGI2, 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 hypercholesterolemia.
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:

![Image: Alterations in Normal Blood Flow](http://www.oocities.org/venkatej/mech/fluid_mechanics/LaminarFlowProfile.gif)

**Wall shear stress** $\tau_w$

**Flow**

**Linear shear stress distribution**

**Parabolic velocity profile**

**Shear stress and Velocity distributions in pipe, fully developed flow of Newtonian fluid, for Laminar flow**

http://www.oocities.org/venkatej/mech/fluid_mechanics/LaminarFlowProfile.gif
Acetylcholine
Bradykinin

K+

COX

NOS

Endothelium

NOS

Endothelium

Angiotensin II

Prostaglandins

L-Arg

L-Cit

BH4

Endothelin-1

Endothelial hyperpolarizing factor

NO

cAMP

cGMP

V

Leukocyte

TNF

IL-6

Adhesion molecules

O2−

Thrombomodulin

Von Willebrand’s factor

Tissue factor

Tissue plasminogen activator

Plasminogen activator inhibitor-1

NO

NO

VASODILATION

VASCULAR TONE

PLATELET ADHESION

FIBRINOLYSIS

CLOTTING CASCADE

LEUKOCYTE

ADHESION

SMOOTH MUSCLE

RELAXATION

HYPERPolarization

ANTI-FIBRINOLYSIS

REGULATION OF CLOTTING

CASCADE

ANTI-INFLAMMATORY

ACTIONS

OXIDATIVE STRESS

Catherine N. Marti et al. JACC 2012;60:1455-1469
Alterations in Normal Blood Flow

Promote endothelial activation, enhancing procoagulant activity and leukocyte adhesion. 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

Ulcerated atherosclerotic plaques 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.

Hyperviscosity (such as is seen with polycythemia vera) increases resistance to flow and causes small vessel stasis; the deformed red cells in sickle cell anemia (Chapter 14) cause vascular occlusions, with the resulting stasis also predisposing to thrombosis.
Hypercoagulability

Red Blood Cells
- Abnormal erythroid cells
- Source of procoagulant phospholipids
- Enhanced cohesiveness

Platelets
- Increased platelet aggregation
- State of oxidative stress (ROS)
- Expression of activation markers (CD62P and CD63)

Iron overload
- Hyperviscosity
- Endothelial damage
- Monocyte activation
- Release of microparticles

Decreased levels of
- Protein C
- Protein S
- Antithrombin III

Genetic mutations
- Factor V Leiden
- Prothrombin G20210
- MTHFR C677T (hyperhomocysteinemia)
- Others

Hypercoagulable State

Cardiac dysfunction
- Liver dysfunction
- Hormonal deficiencies
- Antiphospholipid antibodies
- Intravascular hemolysis

http://ars.els-cdn.com/content/image/1-s2.0-S0268960X08000362-gr1.jpg
PRIMARY (GENETIC)

Common

- Factor V mutation (G1691A mutation; factor V Leiden)
- Prothrombin mutation (G20210A variant) 5,10-Methylenetetrahydrofolate reductase (homozygous C677T mutation)
- Increased levels of factors VIII, IX, XI, or fibrinogen.
In the normal person, **factor V functions as a cofactor to allow factor Xa to activate thrombin**. Thrombin in turn cleaves fibrinogen to form fibrin. Activated protein C (aPC) is a natural anticoagulant that acts to limit the extent of clotting by cleaving and degrading factor V. ([http://en.wikipedia.org/wiki/Factor_V_Leiden](http://en.wikipedia.org/wiki/Factor_V_Leiden))
Normal Factor V: APC binds to factor V and cleaves it into 2 inactive fragments (factor V)

The three pathways that makeup the classical blood coagulation pathway

**Intrinsic**
- XII – Hageman factor, a serine protease
- XI – Plasma thromboplastin, antecedent serine protease
- IX – Christmas factor, serine protease
- VIII – Stable factor, serine protease
- XIII – Fibrin stabilising factor, a transglutaminase
- PL – Platelet membrane phospholipid
- Ca^{2+} – Calcium ions

**Extrinsic**
- IX
- TF – Tissue Factor
- X
- XIIa

**Common**
- prothrombin
- thrombin (serine protease)
- fibrinogen
- fibrin
- stable fibrin clot

---

**Figure 7-2 A, Sites of action of the natural anticoagulants; B, method of inactivation of factor V; and C, demonstration of the inability of activated protein C, to inactivate factor Va when the factor V Leiden mutation is present**


Hypercoagulability

Rare

- Antithrombin III deficiency
- Protein C deficiency
- Protein S deficiency

Very Rare

- Fibrinolysis defects
- Homozygous homocystinuria (deficiency of cystathione β-synthetase)

Gerinnung wird ausgelöst

Die Hemmung durch ATIII

ATIII → Xa
Aktivierter Faktor X (Xa) entsteht

Xa → X
Der Prothrombin-Aktivator Komplex wird gebildet (aus Faktoren X und V, Calcium und Phospholipiden)

ATIII → IIa
Thrombin (=aktivierter Faktor II = IIa) entsteht

IIa → Fibrin
Aus Fibrinogen wird Fibrin

Fibrinogen → Fibrin
Fibrinketten bilden sich

Das Blutgerinnsel entsteht

---

The three pathways that make up the classical blood coagulation pathway:

**Intrinsic**
- XII – Hageman factor, a serine protease
- XI – Plasma thromboplastin, antecedent serine protease
- IX – Christmas factor, serine protease
- VII – Stable factor, serine protease
- XIIa – Fibrin stabilising factor, a transglutaminase
- PL – Platelet membrane phospholipid
- Ca²⁺ – Calcium ions
- TF – Tissue Factor

**Extrinsic**
- IX
- (VIII, PL, Ca²⁺)
- X
- TF-VIIa
- tissue damage

**Common**
- prothrombin
- thrombin (serine protease)
- fibrinogen
- fibrin
- stable fibrin clot

---

https://www.med4you.at/laborbefunde/lbef2/atIII_anim3.gif
Thrombomodulin (TM)

CD141 or BDCA-3 is an integral membrane protein expressed on the surface of endothelial cells and serves as a cofactor for thrombin. It reduces blood coagulation by converting thrombin to an anticoagulant enzyme from a procoagulant enzyme.

FIGURE 4–6 Anti- and procoagulant activities of endothelium. NO, nitric oxide; PGI₂, prostacyclin; t-PA, tissue plasminogen activator; vWF, von Willebrand factor. The thrombin receptor is also called a protease-activated receptor (PAR).

Copyright © 2010 by Saunders, an imprint of Elsevier Inc.
Inactivation of Va and VIIIa

Deceleration of thrombin generation

Thrombin

Fibrin generation

Endothelial cell

http://www.neurology.org/content/78/3/157/F1.large.jpg

APC= activated Protein C
Fig. 1: Activated protein C anticoagulant pathway: 1.

Bloomenthal D et al. CMAJ 2002;167:48-54

©2002 by Canadian Medical Association
Hypercoagulability (secondary)
(Thrombophilia*)

High Risk for Thrombosis
- Prolonged bedrest or immobilization
- Myocardial infarction
- Atrial fibrillation
- Tissue injury (surgery, fracture, burn)
- Cancer
- Prosthetic cardiac valves
- Disseminated intravascular coagulation
- Heparin-induced thrombocytopenia
- Antiphospholipid antibody syndrome

*Thrombophilia is a condition where the blood has an increased tendency to form clots

http://www.patient.co.uk/health/thrombophilia-leaflet
Risk for Thrombosis

Hyperestrogenic states (pregnancy and postpartum)
Oral contraceptive use
Cardiomyopathy
Nephrotic syndrome
Sickle cell anemia
Smoking

Pathophysiology, continued

Pregnancy is considered as a hypercoagulable state by:
- An increase in all coagulation factors except FXI/FXIII. Fibrinogen which increases to 400-650mg/dl in late pregnancy.
- The fibrinolytic system is depressed during normal pregnancy and labor but returns to normal one hour after delivery of the placenta.
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 name).

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.
Heparin-induced thrombocytopenia (HIT)

- Heparin
- PF4
- Anti-heparin/PF4 IgG
- Heparin/PF4 complex
- Anti-heparin/PF4 IgG immune complex
- Fibrinogen, VWF, PF4, Serotonin, ADP, Ca^{2+}
- "heparin-like" molecules
- Subendothelial matrix (collagen, VWF)

Platelet activation
- Positive feedback loop
- Platelet aggregation and removal
- Thrombosis
Antiphospholipid antibody syndrome  
(previously called the lupus anticoagulant syndrome)

Antiphospholipid antibodies are a heterogeneous group of auto-antibodies (IgG, IgM, and IgA)

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.
**Figure 3** Endothelial cell activation by anti-β₂GPI autoantibodies

*Nat. Rev. Rheumatol.* doi:10.1038/nrrheum.2011.52

beta2 Glycoprotein 1
ENDOTHELIAL INJURY → THROMBOSIS → ABNORMAL BLOOD FLOW → HYPERCOAGULABILITY
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.
FIGURE 4–13A Mural thrombi. A, Thrombus in the left and right ventricular apices, overlying white fibrous scar. B, Laminated thrombus in a dilated abdominal aortic aneurysm. Numerous friable mural thrombi are also superimposed on advanced atherosclerotic lesions of the more proximal aorta (left side of picture).

Copyright © 2010 by Saunders, an imprint of Elsevier Inc.
FIGURE 4–13B Mural thrombi. A, Thrombus in the left and right ventricular apices, overlying white fibrous scar. B, Laminated thrombus in a dilated abdominal aortic aneurysm. Numerous friable mural thrombi are also superimposed on advanced atherosclerotic lesions of the more proximal aorta (left side of picture).

Copyright © 2010 by Saunders, an imprint of Elsevier Inc.
Arterial vs venous thrombi

- Grow retrograde to flow
- Begin at site of injury or turbulence
- Frequently occlusive
- Occur in coronary, cerebral, femoral arteries

- Grow with direction of flow
- Begin at site of stasis
- Occlusive
- Occur in lower extremities 90%, also upper extremities, periprostatic plexus, ovarian or periuterine veins
Fate of the Thrombus

- **Propagation.** Thrombi accumulate additional platelets and fibrin.

- **Embolization.** Thrombi dislodge and travel to other sites in the vasculature.

- **Dissolution.** Result of fibrinolysis, which can lead to the rapid shrinkage and total disappearance of recent thrombi. (Extensive fibrin deposition and crosslinking in older thrombi renders them more resistant to lysis.) Natural and Therapeutic.

- **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.
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.

- Propagation
- Embolization
- Dissolution
- Organization and recanalization


http://i48.tinypic.com/2vmvqcj.jpg

Organized arterial thrombus
Recanalization

http://farm3.static.flickr.com/2791/4337748744_3a92ba6583.jpg
Aortic thrombi from electrical injury
Lung hilum thromboembolus with lines of Zahn
Right atrial mural thrombus with lines of Zahn
**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 (see below).

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.
Embolisms

- Detached intravascular solid, liquid, gasous mass carried by the blood

- Pulmonary embolisms
  - Often arise from deep vein thromboses
    - Associated with immobilization, hypercoagulability
  - Frequently small, silent, becoming organized
  - Right heart failure, cor pulmonale, when >60% pulmonary circulation obstructed
  - Rupture of obstructed arteries causes bleeding without infarction due to blood supply
  - Multiple emboli lead to hypertension and right ventricular failure
An embolus is a detached intravascular solid, liquid, or gaseous mass that is carried by the blood to a site distant from its point of origin.

The term embolus was coined by Rudolf Virchow in 1848 to describe objects that lodge in blood vessels and obstruct the flow of blood. Almost all emboli represent some part of a dislodged thrombus, hence the term thromboembolism. Rare forms of emboli include fat droplets, nitrogen bubbles, atherosclerotic debris (cholesterol emboli), tumor fragments, bone marrow, or even foreign bodies. However, unless otherwise specified, emboli should be considered thrombotic in origin. Inevitably, emboli lodge in vessels too small to permit further passage, causing partial or complete vascular occlusion; a major consequence is ischemic necrosis (infarction) of the downstream tissue. Depending on where they originate, emboli can lodge anywhere in the vascular tree; the clinical outcomes are best understood based on whether emboli lodge in the pulmonary or systemic circulations.
FIGURE 4–15 Embolus from a lower extremity deep venous thrombosis, now impacted in a pulmonary artery branch.

Copyright © 2010 by Saunders, an imprint of Elsevier Inc.
Systemic thromboembolism

• Emboli in arterial circulation
• Arise from intracardiac mural thrombi
  ▪ 60% associated with left ventricular wall infarcts
  ▪ 25% associated with atrial dilation or fibrillation
  ▪ Remainder originate from aneurysms, valvular vegetation
• Deposit in lower extremities or brain
• Consequences depend on caliber of occluded vessel, redundant blood supply
An infarct is an area of ischemic necrosis caused by occlusion of either the arterial supply or the venous drainage.

Tissue infarction is a common and extremely important cause of clinical illness.

Roughly 40% of all deaths in the United States are caused by cardiovascular disease, and most of these are attributable to myocardial or cerebral infarction.

Pulmonary infarction is also a common complication in many clinical settings, bowel infarction is frequently fatal, and ischemic necrosis of the extremities (*gangrene*) is a serious problem in the diabetic population.
Nearly all infarcts result from thrombotic or embolic arterial occlusions.

Occasionally infarctions are caused by other mechanisms, including local vasospasm, hemorrhage into an atheromatous plaque, or extrinsic vessel compression (e.g., by tumor).

Rarer causes include torsion of a vessel (e.g., in testicular torsion or bowel volvulus), traumatic rupture, or vascular compromise by edema (e.g., anterior compartment syndrome) or by entrapment in a hernia sac.

Although venous thrombosis can cause infarction, the more common outcome is just congestion; in this setting, bypass channels rapidly open and permit vascular outflow, which then improves arterial inflow. Infarcts caused by venous thrombosis are thus more likely in organs with a single efferent vein (e.g., testis and ovary).
White infarcts occur with arterial occlusions in solid organs with end-arterial circulation (e.g., heart, spleen, and kidney), and where tissue density limits the seepage of blood from adjoining capillary beds into the necrotic area.
**Red infarcts occur**
(1) with venous occlusions (e.g., ovary)
(2) in loose tissues (e.g., lung) where blood can collect in the infarcted zone,
(3) in tissues with dual circulations (e.g., lung and small intestine) that allow blood flow from an unobstructed parallel supply into a necrotic zone,
(4) in tissues previously congested by sluggish venous outflow
(5) when flow is re-established to a site of previous arterial occlusion and necrosis (e.g., following angioplasty of an arterial obstruction).
FIGURE 4–18A Red and white infarcts.

Copyright © 2010 by Saunders, an imprint of Elsevier Inc.
Factors That Influence Development of an Infarct.

The effects of vascular occlusion can range from no or minimal effect to causing the death of a tissue or person.

The major determinants of the eventual outcome are:
(1) the nature of the vascular supply,
(2) the rate at which an occlusion develops,
(3) vulnerability to hypoxia,
(4) the oxygen content of the blood.

Neurons: 3 – 4 minutes
Myocardial cells: 20 – 30 minutes
Fibroblasts, skeletal muscle: hours
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.
Extra Stuff
Nature of the vascular supply. The availability of an alternative blood supply is the most important determinant of whether vessel occlusion will cause damage.

Rate of occlusion development. Slowly developing occlusions are less likely to cause infarction, because they provide time to develop alternate perfusion pathways.

Vulnerability to hypoxia. Neurons undergo irreversible damage when deprived of their blood supply for only 3 to 4 minutes. Myocardial cells, though hardier than neurons, are also quite sensitive and die after only 20 to 30 minutes of ischemia. In contrast, fibroblasts within myocardium remain viable even after many hours of ischemia.

Oxygen content of blood. A partial obstruction of a small vessel that would be without effect in an otherwise normal individual might cause infarction in an anemic or cyanotic patient.
The dominant histologic characteristic of infarction is ischemic coagulative necrosis.

It is important to recall that if the vascular occlusion has occurred shortly (minutes to hours) before the death of the person, no demonstrable histologic changes may be evident; it takes 4 to 12 hours for the tissue to show frank necrosis. Acute inflammation is present along the margins of infarcts within a few hours and is usually well defined within 1 to 2 days.

Most infarcts are ultimately replaced by scar. The brain is an exception to these generalizations, as central nervous system infarction results in liquefactive necrosis.
Fat and marrow embolism

• Release of fatty marrow from broken bones
• Onset of symptoms 1 – 3 days after injury
• Leads to pulmonary insufficiency
  ▪ Tachypnea, dyspnea, tachycardia
• Neurological symptoms
  ▪ Irritability, restlessness
• Thrombocytopenia
  ▪ Platelets adhere to fat globules
  ▪ Diffuse petechial rash
Fat and marrow embolism

• Mechanical obstruction
  - Fat emboli with RBC and platelet aggregates occlude pulmonary and cerebral microvasculature

• Biochemical injury
  - FFA released from fat globules injure endothelium initiating inflammation
  - Platelet aggregation and granulocyte recruitment result in free radicals, proteases, eicosanoids
Fat embolism
Air embolisms

- Iatrogenic consequences of
  - Coronary bypass surgery
  - Neurosurgery
  - Laparoscopic procedures
- Chest wall injury
- Decompression sickness
  - Nitrogen bubbles from blood within muscle, lungs, joints
  - Edema or ischemic necrosis in lungs (emphysema), femoral head, tibia, humerus
Amniotic fluid embolism

- Infusion of amniotic fluid containing fetal components into uterine veins via rupture
- Incidence 1:40K; mortality 80%; morbidity 13% total incidence, 85% survivors
- Pulmonary microcirculation may contain
  - Fetal cells, vernix caseosa fat, fetal respiratory or GI mucin, lanugo hair
- Onset characterized by sudden, severe dyspnea, cyanosis, shock, headache, seizures
- Followed by pulmonary edema
- Diffuse Intravascular Coagulation (DIC)