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1. Edema
   - increased fluid in the interstitial tissue spaces
   - hydrothorax, hydropericardium, and hydroperitoneum/ascites
   - Anasarca is a severe and generalized edema with profound subcutaneous tissue swelling.
   - Exudate vs transudate
     - exudates is protein rich, cellular contents, and is cloudy, high specific gravity
     - transude, clear, watery, low protein and cells, low specific gravity

edema mechanism capillary bed - picture
   - venous end
     - high plasma colloid osmotic pressure
   - arterial end
     - high hydrostatic pressure
   - increased interstitial fluid pressure pushes fluid into the lymphatics to the thoracic duct
2. Hyperemia and Congestion

- local increased volume of blood in a particular tissue
- *Hyperemia* is an *active process* resulting from augmented tissue inflow because of *arteriolar dilation*
- *Congestion* is a *passive process* resulting from impaired outflow from a tissue *cyanosis*
  - something is preventing blood flow from the venous end
  - blood pools in the body pushing fluid into the tissues and causing edema
- Congestion and edema
- *chronic passive congestion*
  - lack of blood flow causes death of tissue, fibrosis and scar formation
chronic passive congestion of the liver - picture
- called “nutmeg” liver
- cell death can be seen

pathogenesis of hyperemia and congestion - picture

3. Hemorrhage
- vessel rupture
- chronic congestion
- hemorrhagic diatheses (bleeding disorders)
  - problem with coagulation factors or platelets
  - occurs without trauma
- blood within tissue is referred to as a hematoma
- hemothorax, hemopericardium, hemoperitoneum, or hemarthrosis (blood in joint)

Categories of hemorrhage
- petechiae – picture
- purpura – picture
- ecchymoses – picture
  - bigger than 2 cm is called a hematoma

Clinical Significance
- volume and rate of bleeding
- site
  - petechiae – picture
  - interperichymal hematoma - picture

Clotting
- NORMAL HEMOSTASIS – picture
  - endothelin
    - responsible for transient vasoconstriction
    - reduces blood flow to a portion of a vessel that is hemmorhaging
- primary hemostasis – picture
  - von Willebrand Factor forms a bridge
  - platelet adhesion to collagen
• degranulation
  o recruitment of more platelets

• secondary hemostasis – picture
  o tissue factor
  o coagulation cascade is activated

• THROMBOSIS – picture
  o t-PA/fibrinolysis
  o thrombodulin

• favor/inhibit thrombosis - picture
  o antithrombin III
  o thrombin
  o activation of protein C

• high magnification of clotting – picture
  o Gp1b receptors used to connect platelets to von Willebrand’s factor
    which in turn attaches to collagen
  o Know the 3 diseases on this page

• PIC? - picture

Endothelial Injury – picture
  • Virchow’s triad
  • heart or the arterial circulation
  • endothelium need not be denuded or physically disrupted to contribute to the development of thrombosis
    o the endothelium may still be intact, but thrombosis formation occurs anyway due to interrupion in antithrombotic process
  • any perturbation in the dynamic balance of the pro- and antithrombotic effects of endothelium can influence local clotting events

Alterations in Normal Blood Flow
  • Turbulence, arterial and cardiac thrombosis by causing endothelial injury or dysfunction by forming countercurrents in atherosclerotic plaques and aneurysms
  • stasis is a major factor in the development of venous thrombi
    o (1) disrupt laminar flow and bring platelets into contact with the endothelium
(2) prevent dilution of activated clotting factors by fresh flowing blood
(3) retard the inflow of clotting factor inhibitors and permit the build-up of thrombi
(4) promote endothelial cell activation, predisposing to local thrombosis, leukocyte adhesion, and a variety of other endothelial cell effects.
  - endothelial cells produce nitric oxide, prostaglandins etc.

<table>
<thead>
<tr>
<th>TABLE 4-2 Hypercoagulable States</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary (Genetic)</strong></td>
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<tr>
<td>Common</td>
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<tr>
<td>Mutation in factor V gene (factor V Leiden)</td>
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<tr>
<td>Mutation in prothrombin gene</td>
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<tr>
<td>Mutation in methyltetrahydrofolate gene</td>
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<tr>
<td>Rare</td>
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<tr>
<td>Antithrombin III deficiency</td>
</tr>
<tr>
<td>Protein C deficiency</td>
</tr>
<tr>
<td>Protein S deficiency</td>
</tr>
<tr>
<td>Very rare</td>
</tr>
<tr>
<td>Fibrinolysis defects</td>
</tr>
<tr>
<td><strong>Secondary (Acquired)</strong></td>
</tr>
<tr>
<td>High risk for thrombosis</td>
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<tr>
<td>Prolonged bed rest or immobilization</td>
</tr>
<tr>
<td>Myocardial infarction</td>
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<tr>
<td>Atrial fibrillation</td>
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<tr>
<td>Tissue damage (surgery, fracture, burns)</td>
</tr>
<tr>
<td>Cancer</td>
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<tr>
<td>Prosthetic cardiac valves</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation</td>
</tr>
<tr>
<td>Heparin-induced thrombocytopenia</td>
</tr>
<tr>
<td>Antiphospholipid antibody syndrome (lupus anticoagulant syndrome)</td>
</tr>
<tr>
<td>Lower risk for thrombosis</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Hyperestrogenic states (pregnancy)</td>
</tr>
<tr>
<td>Oral contraceptive use</td>
</tr>
<tr>
<td>Sickle cell anemia</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
</tbody>
</table>

- definitely know the primary (genetic) causes

**Factor V mutation (called the Leiden mutation)**
- substituting a glutamine for the normal arginine residue at position 506 and rendering the protein resistant to cleavage by protein C
  - mutation to factor V causes it to not bind with protein C
- A single nucleotide change (G to A transition) in the 3'-untranslated region of the prothrombin gene is a fairly common allele (1% to 2% of the population) that is associated with elevated prothrombin levels and an almost three-fold increased risk of venous thromboses
• Hyperhomocysteinemia
  o inhibition of antithrombin III and endothelial thrombomodulin

Heparin-induced thrombocytopenia (HIT) syndrome.
formation of antibodies that bind to molecular complexes of heparin and platelet factor 4 membrane protein
the result is platelet activation, endothelial injury, and a prothrombotic state
To reduce this problem, specially manufactured low-molecular-weight heparin preparations—which retain anticoagulant activity but do not interact with platelets—are used.

Antiphospholipid antibody syndrome
• associated with high titers of circulating antibodies directed against anionic phospholipids (e.g., cardiolipin *)
  o cardiolipin is also used to diagnose syphilis
  o there can be a false positive in some patients due to ....?
• In vitro these antibodies interfere with the assembly of phospholipid complexes and thus inhibit coagulation.
• In vivo, the antibodies induce a hypercoagulable state. possible explanations include direct platelet activation, inhibition of PGI2 production by endothelial cells, or interference with protein C synthesis or activity
  o paradoxical since antiphospholipids in the body would normally imply bleeding instead of thrombosis
• Primary/ secondary antiphospholipid syndrome
• venous or arterial thrombi but also include repeated miscarriages, cardiac valvular vegetations, or thrombocytopenia
  o always get an antiphospholipid antibody titer on a young women who has had multiple miscarriages
• When formed in the heart or aorta, thrombi may have grossly (and microscopically) apparent laminations, called lines of Zahn
• When arterial thrombi arise in heart chambers or in the aortic lumen, they usually adhere to the wall of the underlying structure and are termed mural thrombi

lines of zahn - picture
• composed of platelets and red cells alternating in a thrombus
• blood clots don’t have lines of zahn
  o they are just an aggregate of platelets

**mural thrombi - picture**
• attached to heart wall

**thrombus in aortic aneurysm - picture**

**Arterial thrombi**
• occlusive
• coronary, cerebral, and femoral arteries
• superimposed on an atherosclerotic plaque
• firmly adherent to the injured arterial wall and are gray-white and friable

**Cardiac Thrombosis**
• Cardiac mural thrombi can arise in the setting of myocardial infarction related to dyskinetic contraction of the myocardium as well as damage to the adjacent endocardium
• *Rheumatic heart disease* may result in atrial mural thrombi due to mitral valve stenosis, followed by left atrial dilation; concurrent atrial fibrillation augments atrial blood stasis

(Other picture before this)

**coronary artery thrombosis – picture**

**Venous thrombosis, or phlebothrombosis**
• invariably occlusive
• red, or stasis, thrombi
• lower extremities (90% of cases)
• Postmortem clots
  o chicken broth like appearance
  o red center
• important that thrombus is attached to the vessel wall while a postmortem clot is not
• usually there is no evidence of damage to the vessel wall in a PMC
• know this chart pretty well

Superficial venous thrombi
  • varicose ulcers
  • Deep venous thrombosis
  • reduced physical activity, injury to vessels, release of procoagulant substances from tissues, and/or reduced t-PA activity
  • Tumor-associated procoagulant release is largely responsible for the increased risk of thromboembolic phenomena seen in disseminated cancers, so-called migratory thrombophlebitis or Trousseau syndrome
    o Trousseau typically seen in pancreatic cancer due to production of abnormal clotting factors

Fate of the Thrombus - picture
  • Older thrombi tend to become organized.
    o thrombus is replaced by fibrosis, endothelial cells, smooth muscle, etc.
    o lines of zahn dissapear

DISSEMINATED INTRAVASCULAR COAGULATION (DIC)
  • sudden or insidious onset of widespread fibrin thrombi in the microcirculation
  • diffuse circulatory insufficiency
• consumption coagulopathy
• fibrinolytic mechanisms are activated, and as a result an initially thrombotic disorder can evolve into a serious bleeding disorder
  o diagnosed via PT  PTT  FDP (extrinsic) are high and (intrinsic) pathways

process of disseminated intravascular coagulation - picture

<table>
<thead>
<tr>
<th>TABLE 15-10 Major Disorders Associated with Disseminated Intravascular Coagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstetric Complications</td>
</tr>
<tr>
<td>Abruptio placenta  · Retarded dead fetus  · Amniotic fluid embolism  · Trauma</td>
</tr>
<tr>
<td>Infections</td>
</tr>
<tr>
<td>Gram-negative sepsis  · Meningococcemia  · Rocky Mountain spotted fever  · Malaria</td>
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<tr>
<td>Neoplasms</td>
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<tr>
<td>Carcinoma of pancreas, prostate, lung, and stomach  · Acute promyelocytic leukemia</td>
</tr>
<tr>
<td>Massive Tissue Injury</td>
</tr>
<tr>
<td>Traumatic  · Burns  · Extensive surgery</td>
</tr>
<tr>
<td>Miscellaneous</td>
</tr>
<tr>
<td>Acute intravascular hemolysis, snakebite, giant hemangioma, shock, heat stroke, vasculitis, aortic aneurysm, liver disease</td>
</tr>
</tbody>
</table>

Clinical Diagnosis of DIC
• Elevated PTT
• Thrombocytopenia (decreased platelets)
• Elevated fibrin split products (fibrin degradation products) or elevated D-dimer

Embolism
• detached intravascular solid, liquid, or gaseous mass that is carried by the blood to a site distant from its point of origin
• potential consequence of such thrombo-embolic events is the ischemic necrosis of distal tissue, known as infarction

PULMONARY THROMBOEMBOLISM
• 20 to 25 per 100,000 hospitalized patients
• In more than 95% of instances, venous emboli originate from deep leg vein thrombi
• paradoxical embolism
  o if there is a right to left shunt in the heart, the thrombus will travel to the left side of heart to the systemic circulation and then to the central nervous system

Saddle embolus – picture
(2 more pictures)
• vased shape infarct of the lung?

SYSTEMIC THROMBOEMBOLISM
• Most (80%) arise from intracardiac mural thrombi, two thirds of which are associated with left ventricular wall infarcts
• aortic aneurysms, thrombi on ulcerated atherosclerotic plaques, or fragmentation of a valvular vegetation
  o rheumatic heart disease can cause vegetation

FAT EMBOLISM
• Fat embolism syndrome is characterized by pulmonary insufficiency, neurologic symptoms, anemia, and thrombocytopenia
  o fat gets into the blood via fracture of the femur

AIR EMBOLISM
• decompression sickness, exposure to sudden changes 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) become dissolved in the blood and tissues
• If the diver then ascends (depressurizes) too rapidly, the nitrogen expands in the tissues and bubbles out of solution in the blood to form gas emboli.

Air embolism in brain vessel - picture
AMNIOTIC FLUID EMBOLISM – picture (note squamous cells)

- mortality rate of 20% to 40%
- sudden severe dyspnea, cyanosis, and hypotensive shock, followed by seizures and coma
- infusion of amniotic fluid or fetal tissue into the maternal circulation via a tear in the placental membranes or rupture of uterine veins

Infarction

- an area of ischemic necrosis caused by occlusion of either the arterial supply or the venous drainage
- myocardial or cerebral infarction
- 99% of all infarcts result from thrombotic or embolic events, and almost all result from arterial occlusion
- local vasospasm
  - expansion of an atheroma owing to hemorrhage within a plaque
  - extrinsic compression of a vessel (e.g., by tumor)
  - other uncommon causes include twisting of the vessels, compression of the blood supply by edema or by entrapment in a hernia sac, or traumatic rupture of the blood supply
- infarcts caused by venous thrombosis are more likely in organs with a single venous outflow channel, such as the testis and ovary
  - other organs are protected due to collateral circulation

Morphology

- Red (hemorrhagic) infarcts
  - with venous occlusions (such as in ovarian torsion)
  - in loose tissues (such as lung)
  - in tissues with dual circulations (e.g., lung and small intestine)
  - in tissues that were previously congested because of sluggish venous outflow
  - when flow is re-established to a site of previous arterial occlusion and necrosis
  - cause compromise to the venous drainage

- White (anemic) infarcts
arterial occlusions in solid organs with end-arterial circulation (such as heart, spleen, and kidney
causes compromise in the arterial drainage

*Kidney white infarcts – picture*

**Ischemic coagulative necrosis**
- An inflammatory response begins to develop along the margins of infarcts within a few hours and is usually well defined within 1 or 2 days
- Inflammation at these sites is incited by the necrotic material
- most infarcts are ultimately replaced by *scar tissue*
- *central nervous system* results in *liquefactive necrosis*
- *Septic infarctions* may develop when embolization occurs by fragmentation of a bacterial vegetation from a heart valve

*Kidney scarring – picture*

*Heart tissue scarring – picture*
- eosinophilia
- no nucleus
- *constriction band necrosis*
  - a feature of MI

*More heart scarring – picture*

*Liquefactive necrosis of brain – picture*
- all cells are liquefied
- there is a blod of necrotic tissue that does not even vaguely resemble the healthy tissue

**Factors That Influence Development of an Infarct**
- *Nature of the vascular supply*
  - *dual blood supply*, lungs, liver, hand and forearm
  - *end-arterial blood supply*, renal and splenic
- *Rate of development of occlusion*
- *Vulnerability to hypoxia*
  - Neurons (3 to 4 minutes)
  - Myocardial cells (20 to 30 minutes)
  - Fibroblasts within myocardium (many hours)
• Oxygen content of blood
  o anemic patience develop infarct damage faster due to low oxygen in the blood

Shock

• shock gives rise to systemic hypoperfusion caused by reduction either in cardiac output or in the effective circulating blood volume

• The end results are hypotension, followed by impaired tissue perfusion and cellular hypoxia

• initially cause only reversible cellular injury, persistence of shock eventually causes irreversible tissue injury and can culminate in the death of the patient.

<table>
<thead>
<tr>
<th>TABLE 4-3  Three Major Types of Shock</th>
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<tbody>
<tr>
<td>Type of Shock</td>
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<tr>
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<tr>
<td>Cardiogenic</td>
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<tr>
<td>Hypovolemic</td>
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<tr>
<td>Septic</td>
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Stages of Shock

• An initial nonprogressive phase during which reflex compensatory mechanisms are activated and perfusion of vital organs is maintained

• A progressive stage characterized by tissue hypoperfusion and onset of worsening circulatory and metabolic imbalances, including acidosis

• An irreversible stage that sets in after the body has incurred cellular and tissue injury so severe that even if the hemodynamic defects are corrected, survival is not possible