Hemodynamic Disorders, Thrombosis, Shock 2/2/07 11:33 AM

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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
    - transudate, 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

TABLE 4–1 Pathophysiologic Categories of Edema

Increased Hydrostatic Pressure
Impaired venous return
Congestive heart failure
Constrictive pericarditis
Ascites (liver cirrhosis)
Venous obstruction or compression
Thrombosis
External pressure (e.g., mass)
Lower extremity inactivity with prolonged dependency
Arteriolar dilation
Heat
Neurohumoral dysregulation
Reduced Plasma Osmotic Pressure (Hypoproteinemia)
Protein-losing glomerulopathies (nephrotic syndrome)
Liver cirrhosis (ascites)
Malnutrition
Protein-losing gastroenteropathy
Lymphatic Obstruction
Inflammatory
Neoplastic
Postsurgical
Postirradiation
Sodium Retention
Excessive salt intake with renal insufficiency
Increased tubular reabsorption of sodium
Renal hypoperfusion
Increased renin-angiotensin-aldosterone secretion
Inflammation
Acute inflammation
Chronic inflammation
Angiogenesis

Modified from Leaf A, Cotran RS: Renal Pathophysiology, 3rd ed., New York, Oxford University Press, 1985, p 146. Used by permission of Oxford Press, Inc.

- know the bigger headings not necessarily the smaller details

flow chart of edema causes – picture

- not nephrotic syndrome

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)

Catergories of hemmorhage

- ***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
    - recruitment of more platelets
- ***secondary hemostasis – picture***
    - tissue factor
    - coagulation cascade is activated
- ***THROMBOSIS – picture***
    - t-PA/fibrinolysis
    - thrombodulin
- ***favor/inhibit thrombosis - picture***
    - antithrombin III
    - throbin
    - activation of protein C
- ***high maginification of clotting – picture***
    - Gp1b receptors used to connect platelets to von Willebrand's factor which in turn attaches to collagen
    - 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*
    - the endothelium may still be intact, but thrombis formation occurs anyway due to interurpion 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*
    - (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 4–2 Hypercoagulable States

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

- 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

- Hyperhomocystenemia
    - 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 *)
    - cardiolipin is also used to diagnose syphilis
    - 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
    - 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*
    - 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
    - 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
    - chicken broth like appearance
    - red center

	THROMBUS	POSTMORTEM CLOT
CONSISTENCY	Dry and Friable	Moist and Jelly-like
SURFACE	Granular and rough	Smooth and glistening
COLOR	White or Buff	Intense red or yellow
ATTACHMENT	Attached to vessel wall	Not attached to vessel wall
ENDOTHELIUM	Damaged/injured	Undamaged
COMPOSITION	Platelets primarily	Fibrin Primarily
RAPIDITY OF BLOOD FLOW	Formed in flowing stream of blood	Formed in stagnant column of blood
ANIMAL	Formed in living animal	Formed in dead animal
ORGANIZATION	May be partially organized	No organization

- 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*
    - *Trousseau* typically seen in pancreatic cancer due to production of abnormal clotting factors

Fate of the Thrombus - picture

- Older thrombi tend to become *organized.*
    - thrombus is replaced by fibrosis, endothelial cells, smooth muscle, etc.
    - 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
    - diagnosed via PT PTT FDP (extrinsic) are high and (intrinsic) pathways

process of disseminated intravascular coagulation - picture

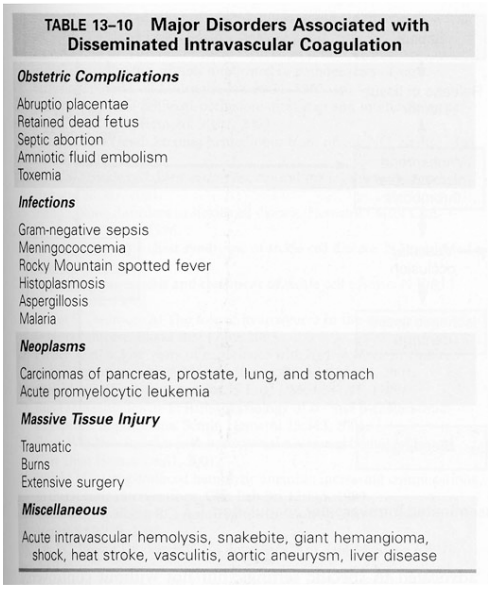

TABLE 13–10 Major Disorders Associated with Disseminated Intravascular Coagulation

Obstetric Complications
Abruptio placentae
Retained dead fetus
Septic abortion
Amniotic fluid embolism
Toxemia
Infections
Gram-negative sepsis
Meningococcemia
Rocky Mountain spotted fever
Histoplasmosis
Aspergillosis
Malaria
Neoplasms
Carcinomas of pancreas, prostate, lung, and stomach
Acute promyelocytic leukemia
Massive Tissue Injury
Traumatic
Burns
Extensive surgery
Miscellaneous
Acute intravascular hemolysis, snakebite, giant hemangioma, shock, heat stroke, vasculitis, aortic aneurysm, liver disease

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
    - 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
    - rhematic heart disease can cause vegetation

FAT EMBOLISM

- *Fat embolism syndrome is characterized by pulmonary insufficiency, neurologic symptoms, anemia, and thrombocytopenia*
    - 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 – picure (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 scaring – picture

- eosinophilia
- no nucleus
- *constriction band necrosis*
  - a feature of MI

more heart scaring - picture

liquefctive 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*
    - 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 4–3 Three Major Types of Shock

Type of Shock	Clinical Examples	Principal Mechanisms
Cardiogenic	Myocardial infarction Ventricular rupture Arrhythmia Cardiac tamponade Pulmonary embolism	Failure of myocardial pump owing to intrinsic myocardial damage, extrinsic pressure, or obstruction to outflow
Hypovolemic	Hemorrhage Fluid loss, e.g., vomiting, diarrhea, burns, or trauma	Inadequate blood or plasma volume
Septic	Overwhelming microbial infections Endotoxic shock Gram-positive septicemia Fungal sepsis Superantigens	Peripheral vasodilation and pooling of blood; endothelial activation/injury; leukocyte-induced damage; disseminated intravascular coagulation; activation of cytokine cascades

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