1. Basic Human Pathology Lecture #9 Vascular Hemodynamics

Basic Human Pathology Lecture #9
Vascular Hemodynamics

2007
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2. Vascular Hemodynamics

Vascular Hemodynamics

- Blood flow - Normal fluid homeostasis
  - Edema
  - Hyperemia
  - Hemorrhage
- Maintainence of blood as a liquid
  - Hemostasis
  - Thrombosis
- Embolism
- Infarction
- Shock

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3. Vascular Hemodynamics

Vascular Hemodynamics

- Normal fluid homeostasis:
  - Intact circulation
    - Maintenance of vessel wall integrity
    - Physiologic ranges of
      - Intravascular pressure
      - Osmolarity
- Altered vascular homeostasis results in:
  - Change in net movement of water across the vascular wall

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4. Edema

Edema

- Excess accumulation of fluid in the interstitial tissue spaces or body cavities
  - Under normal circumstances only a small amount of fluid leaks from vessels to form interstitial fluid which is removed by lymphatic vessels

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5. Edema

Edema

Causes:
- More fluid leaves capillaries than enters:
  1. if the hydrostatic pressure in vessels is increased (e.g., interference with venous drainage, congestive heart failure)
     - Right-side -> peripheral (subcutaneous) edema; left-side -> pulmonary edema
  2. decreased plasma oncotic pressure (hypoproteinemia - albumin)
     - Nephrotic syndrome – loss of protein in kidney
     - Decreased albumin production in liver during cirrhosis
  3. vascular permeability is altered (allergic responses liberate histamine, acute inflammation, burn injury)

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6. Edema

Edema

Causes (cont’d)
- Increased sodium retention
  - Primary – assoc. with renal disorders
  - Secondary – occurs in congestive heart failure
    - Decreased cardiac output -> decreased renal blood flow -> activation of renin-angiotensin system -> aldosterone activated -> retention of sodium and water
- Blockage of lymphatics
  - Results in lymphedema

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7. Causes of Edema

Causes of Edema

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8. Factors Affecting Fluid Transit Across Capillary Walls

Factors Affecting Fluid Transit Across Capillary Walls

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9. Causes of Edema

Causes of Edema

- Increased permeability
- Increased hydrostatic pressure
- Decreased oncotic pressure
- Lymphatic obstruction

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10. Edema

Edema

- Two important types of edema due to cardiac failure
  - Pulmonary edema
    - Accumulation of fluid in the lung alveoli
    - Caused by increased hydrostatic pressure in the pulmonary vascular bed resulting from left-side heart failure
  - Peripheral (subcutaneous) edema
    - Accumulation of fluid in subcutaneous tissues
    - Caused by increased hydrostatic pressure in the systemic venous system resulting from right-side heart failure

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11. Sequence of Events Leading to Systemic Edema

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12. Vascular Hemodynamics: Slide 12

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13. Pulmonary Edema

14. Pitting Edema of the Subcutaneous Tissues
Edema

Types of edema

- Anasarca
  - Generalized edema
- Hydrothorax
  - Accumulation of fluid in the pleural cavity
- Hydropericardium
  - Abnormal accumulation of fluid in the pericardial cavity
    - May result in cardiac tamponade
- Hydroperitoneum (ascites)
  - Abnormal accumulation of fluid in the peritoneal cavity

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Edema

Types of edema (cont’d)

- Transudate
  - Noninflammatory edema fluid that results form altered intravascular hydrostatic pressure or osmotic pressure
    - Low protein content and specific gravity < 1.012

- Exudate
  - Edema fluid from increased vascular permeability as a result of inflammation
    - High protein content and specific gravity > 1.020
    - Contains large number of inflammatory leukocytes which often consume glucose and thus results in glucose content being greatly reduced

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17. Ascites

18. Hyperemia

- Localized increase in the volume of blood in capillaries and small vessels
- Active hyperemia
  - Results from localized arteriolar dilation (blushing, inflammation)
19. Hyperemia

Hyperemia

- Passive congestion (passive hyperemia)
  - Results from obstructed venous return or increased back pressure from CHF
  - Active passive congestion – shock, acute inflammation, sudden right heart failure
  - Chronic passive congestion
    - Lung – left heart failure or mitral stenosis cause; congestion, distention of alveolar capillaries → rupture → heart failure cells (hemosiderin laden macrophages)
    - Liver and lower extremities – right heart failure cause with nutmeg liver (combination of dilated congested central veins, and brown yellow fatty liver cells)

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20. Chronic Passive Congestion – “Heart Failure Cell...”

Chronic Passive Congestion – “Heart Failure Cells”

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21. Nutmeg Liver

Nutmeg Liver

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22. Hemorrhage

Hemorrhage

- Escape of blood from the vasculature into surrounding tissues, hollow organ or body cavity or to the outside
  - Caused by rupture of blood vessels
  - Massive exsanguination usually caused by trauma to a major artery or vein but may also be from bursting of a vessel weakened by disease
  - Bleeding into tissues or body cavities results in several types of hemorrhage

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23. Hemorrhage

Hemorrhage

- Types of hemorrhage:
  - Hematoma
    - Accumulation of blood within soft tissues usually due to trauma of vessels but occasionally follows spontaneous rupture of diseased vessels
  - Petechia and Ecchymosis
    - 1-2 mm and 2-10 mm, respectively tissue hemorrhages of the skin or oral mucosa due to abnormal small vessel fragility, abnormal blood clotting or abrupt increase in pressure within small venules and capillaries
  - Hemopericardium
    - Collection of blood in the pericardial cavity due to rupture of the heart or the aorta
      - May result in cardiac tamponade

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24. Hemorrhage

Hemorrhage

- Types of hemorrhage (cont’d)
  - Hemothorax
    - Collection of blood in the pleural cavities due to trauma or rupture of the aorta
  - Hemoperitoneum
    - Collection of blood in the peritoneum due to rupture of an aortic aneurysm or trauma to liver, spleen, or aorta
  - Hemoarthrosis
    - Collection of blood in a joint space due to trauma or bleeding disorder (e.g., hemophilia)

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25. Purpura = Petechiae and Ecchymoses

Purpura = Petechiae and Ecchymoses

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26. Petechial hemorrhages of the colonic mucosa / Fatal intracer...

Petechial hemorrhages of the colonic mucosa / Fatal intracerebral bleed

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Hemostasis

- Normal hemostasis results from well regulated processes that maintain blood in a fluid, clot-free state in normal vessels while inducing the rapid formation of a localized hemostatic plug at the site of vascular injury
- Dependent on the vascular wall, platelets and the coagulation cascade (as is pathological thrombosis)
- Has a normal general sequence of events

Normal Hemostatic Process Events

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31. Thrombosis

Thrombosis

- Process of thrombus formation due to activation of the normal blood coagulation system
  - An intravascular coagulation of blood often causing significant interruption of blood flow
  - Predisposed by venous stasis, CHF, polycythemia, sickle cell disease, visceral malignancies, oral contraceptives especially when combined with cigarette smoking

- A thrombus is a structured solid mass composed of blood constituents (platelets, insoluble fibrin, embedded RBCs) that forms within the cardiovascular system
  - Not a coagulum = unstructured and forms when blood clots outside the circulatory system

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32. Thrombosis

Thrombosis

Laminated layers of platelets (P) and fibrin / RBCs (F)

- Morphological characteristics
  - Arterial thrombi
    - Formed in areas of active blood flow
    - Mature have dark gray layers of platelets interspersed with lighter layers of fibrin = lines of Zahn
    - Eventually liquefy and disappear or organized with fibrous tissue formation

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33. Thrombosis

Thrombosis

- Morphological characteristics (cont’d)
  - Venous thrombi (phlebothrombosis)
    - Form in areas of less active blood flow, most often veins of the lower extremities and periprostatic or other pelvic veins
    - Predisposed to venous stasis
    - Dark red with higher concentration of RBCs than arterial thrombi so lines of Zahn not present or not prominent
    - Often associated with concurrent venous inflammatory changes

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34. Hemostasis / Thrombosis

Hemostasis / Thrombosis

- Coagulation cascade
  - Ultimate aim is to generate a solid plug of cross linked protein that seals a defect in a blood vessel wall
    - Protein deposited is fibrin generated from its circulating precursor protein fibrinogen
  - To achieve this aim many different protein interact in a cascade
    - Each coagulation factor has a number: I-XIII
    - Nearly all of these are functionally proteases
      - Factors V and VIII are not; act as co-factors

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Hemostasis / Thrombosis

- Compartments of the coagulation cascade
  - Common pathway
    - Results in cross-linked fibrin
    - Thrombin is the key protease
      - Has feedback to activate co-factors, other proteases and thus amplifies the cascade
  - Extrinsic pathway
    - Coagulation initiated by Tissue Factor (generated by damaged tissue) interacting with factor VII
  - Intrinsic pathway
    - Coagulation initiated by contact with surface agents (e.g., collagen, kallikrein) acting through factor XII (Hageman factor)
    - Currently thought to have minor role for in vivo coagulation
    - Activation of factor XI and coagulation stimulation is seen mainly after severe injury (e.g., trauma)

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Hemostasis / Thrombosis

- Details of the intrinsic pathway
  - Coagulation initiated by tissue factor generated on cells’ surface adjacent to vessels and exposed following injury to the vessel wall
    - Tissue factor + VIIIa - - - > activate IX and also X
  - IXa + VIIIa and Ca+ act on platelet phospholipid surface (pps) - - > X - - - > Xa
    - VIII = parts C (coag. pathway and vWF [co-factor activated by thrombin])
  - Xa - - - > complex on pps with Va and Ca+ - - - > prothrombin - - - > thrombin
    - Thrombin cleaves fibrinogen into fibrin and fibrinopeptides A,B
    - Thrombin activates XII - - - > crosslinkage of fibrin - - - > thrombus
    - Thrombin activates XI, VIII, V
    - Thrombin acts on endothelial cells and promotes vasoconstrictive factors and plasminogen activator

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37. Vascular Hemodynamics: Slide 37

![Image](image_url)

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38. Hemostasis / Thrombosis

Hemostasis / Thrombosis

- **Products of the coagulation cascade usually restricted to site of vessel wall damage**
- **Plasma inhibitors limit the cascade**
  - Antithrombin III is most potent especially via action of heparin
  - Protein C
    - Vitamin K dependent
    - Activated by thrombin + thrombomodulin + protein S → destroy Va and VIIIa
    - Allows fibrinolysis
- **Fibrinolysis**
  - Due to formation plasminogen → protease plasmin via plasminogen activators, tPA and uPA [no longer inhibited by plasminogen activator inhibitor 1 but protein C prevents this] → degrades fibrin → fibrinopeptides (fibrin degradation products with anticoagulant activity)

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39. Fibrinolytic System

![Fibrinolytic System Diagram]

Fibrinolytic System

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40. Hemostasis / Thrombosis

Hemostasis / Thrombosis

- Thrombosis events (thrombogenesis) – results from interaction of platelets, damaged endothelial cells and the coagulation cascade
  - Aggregation of platelets held together with a meshwork of fibrin occurs constantly to plug small defects in blood vessel walls
    - Once vessel wall repaired the small platelet/fibrin thrombus is normally removed via fibrinolysis
      - Multienzyme process that destroys fibrin filament meshwork allowing dissolution of the thrombus
  - Excessive thrombosis is prevented by several physiological mechanisms but in pathological thrombosis the thrombus formation proceeds beyond the capacity of the endogenous fibrinolysins to eradicate the thrombus - -> thrombus enlarges by deposition of fresh layers (laminated) of platelets and fibrin until lumen of vessel may be reduced

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41. Vascular Hemodynamics: Slide 41

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42. Vascular Hemodynamics: Slide 42

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43. Platelet Adhesion – Early / Fibrin Deposition - Late...

Platelet Adhesion – Early / Fibrin Deposition - Late

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44. Vascular Hemodynamics: Slide 44

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Thrombosis

**Prevention of thrombosis**
- The normal endothelial cells act to prevent activation of the coagulation cascade generating factors that bring about fibrin lysis
  - **Intact endothelium** prevents platelets from contacting collagen and von Willebrand factor (cause platelet aggregation and degranulation)
  - **Prostacyclin and nitric oxide** prevent adhesion and aggregation of platelets to the endothelium
  - **Thrombomodulin on the endothelial surface** binds to local fibrin formed
    - --→ **thrombomodulin/thrombin complex** initiates anticoagulant effects of vitamin K dependent factor protein C and its cofactor protein S
    - (active protein C destroys factors V and VIII)

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**Normal endothelial cells (cont’d)**
- Produces heparin-like molecules which inhibit elements of the cascade
- Synthesizes plasminogen activators which produce plasmin - - - -→ lyses fibrin and inactivates part of the cascade
- Heparin potentiates antithrombin III a potent inhibitor of coagulation
47. Thrombosis

Thrombosis

3 main factors predispose to thrombus formation
- Endothelial dysfunction
  - Direct injury (trauma and inflammation; atheroma)
- Changes in the flow pattern of blood
  - Stasis allows platelets to come into contact with endothelium and prevents dilution of activated coagulation products
- Changes in the potential blood coagulability
  - Increase in the concentration of fibrinogen in acute phase responses
  - Congenital lack of protein C, protein S, antithrombin III
  - Antiphospholipid antibodies
  - Leiden mutation – factor V

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48. Thrombosis

Thrombosis

- Thrombi in different parts of the circulation have different causative factors and different macroscopic appearances
  - Fast moving blood in arteries and heart chambers have high platelet/fibrin content so are very firm, pale, prominent laminations
  - Slow moving venous blood have a high proportion of entrapped RBCs relative to platelet / fibrin so are red, soft, gelatinous with poor laminations

- Occlusive thrombi
  - Small and medium sized vessels completely occluded

- Mural thrombi
  - In the heart or aorta without complete occlusion
    - Vegetations – thrombi on heart valves

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49. Vascular Hemodynamics: Slide 49

<table>
<thead>
<tr>
<th>Site</th>
<th>Predisposition to Thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artery</td>
<td>Atheroma, aneurysms</td>
</tr>
<tr>
<td>Heart valve</td>
<td>Inflammation caused by infection</td>
</tr>
<tr>
<td>Ventricle</td>
<td>Inflammation following infarction</td>
</tr>
<tr>
<td></td>
<td>Ventricular aneurysm</td>
</tr>
<tr>
<td>Atrium</td>
<td>Atrial fibrillation (→ stasis)</td>
</tr>
<tr>
<td></td>
<td>Mitral valve stenosis</td>
</tr>
<tr>
<td>Vein</td>
<td>Slow flow</td>
</tr>
<tr>
<td></td>
<td>Changes in coagulability of blood</td>
</tr>
<tr>
<td>Cerebral venous sinus</td>
<td>Inflammation following infection</td>
</tr>
<tr>
<td></td>
<td>Change in coagulability of blood</td>
</tr>
</tbody>
</table>

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50. Thrombosed (occlusive) Artery

Thrombosed (occlusive) Artery

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51. Heart Valve Vegetations (thrombi)

Heart Valve Vegetations (thrombi)

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52. Mural Thrombi

Mural Thrombi

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Left ventricle apex  Dilated abdominal aorta

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53. Thrombosis

Thrombosis

4 main outcomes of occlusive thrombi

- Propagation
  - May enlarge along the vessel or undergo lysis by the fibrinolytic system
- Organization
  - Ingrowth of granulation tissue from the vessel wall
- Recanalization
  - Gradual replacement by granulation tissue and new vascular channels develop bridging the site of occlusion and re-establishing flow
- Thromboembolism
  - Fragments break off thrombus and carried by the circulation to impact other vessels

54. Organization and Recanalization of Thrombus

Organization and Recanalization of Thrombus

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Recanalized coronary artery lumen previously blocked by thrombus

Granulation tissue with many small blood vessels completely replace occlusive thrombus

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55. Organization and Recanalization of Thrombus

Organization and Recanalization of Thrombus

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56. Embolism

Embolism

- Occlusion of a vessel by a mass of material (i.e., embolus) that is transported in the bloodstream
  - Most common type due to fragments of circulating thrombus (thromboemboli)
  - Fragments break off site of formation to enter blood circulation where it travels until it meets a blood vessel with a lumen too small to permit further passage
    - If in systemic veins -> heart -> pulmonary thromboembolism
    - If in heart -> aorta -> systemic arterial -> arteries of brain, kidneys, spleen, gut and lower limbs
    - Common carotid arteries -> cerebral arteries
    - Abdominal aorta -> renal arteries and arteries of lower limbs

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57. Embolism

Embolism

- **Pulmonary thromboembolism**
  - Most common preventable cause of sudden death in a hospital patient
  - Most commonly caused by thrombosis of deep leg vein (calf, popliteal, femoral, iliac veins) → pulmonary a. ("saddle embolus" = straddles bifurcation) → hemorrhagic pulmonary infarct

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58. Vascular Hemodynamics: Slide 58

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59. Large Pulmonary Artery Embolus

Large Pulmonary Artery Embolus

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60. Embolism

Embolism

• Pulmonary thromboembolism (cont’d)
  ❖ Other sources of pulmonary thromboemboli:
    • Very rarely peri-prostatic venous plexus in males; small pelvic veins in women
  ❖ Clinical predisposers
    • Immobility and bed rest; postoperative period, pregnancy and post partum, oral contraceptives with high estrogen, nephrotic syndrome, severe burns, trauma, cardiac failure, disseminated malignancy
  ❖ Two main consequences
    • Increase in pulmonary arterial pressure (strains right side of heart)
    • Ischemia of the lungs
61. Embolism

Embolism

- **4 types of pulmonary thromboembolism:**
  - **Massive** pulmonary embolism (5%)
    - If 60% of pulmonary vasculature suddenly blocked then the heart cannot pump blood through the lungs - - -> cardiovascular collapse - - -> beat with no output - - -> rapid death
  - **Major** pulmonary embolism (10%)
    - Blockage of middle-sized pulmonary arteries
    - Breathlessness; infarction of lungs (10%); hemoptysis; pleuritic chest pain; can lead to massive type if untreated

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62. Embolism

Embolism

- **4 types of pulmonary thromboembolism (cont’d)**
  - **Minor** pulmonary embolism (85%)
    - Blockage of small peripheral vessels by small emboli
    - Asymptomatic or breathlessness, pleuritic chest pain; can lead to massive type if untreated
  - **Recurrent minor** pulmonary embolism
    - Very rare; blockage of many small vessels over many months - - -> pulmonary hypertension

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63. Embolism

Embolism

- **Pulmonary embolus – key facts**
  - Usually follows thrombosis in leg veins, often deep calf veins
  - Small pulmonary emboli impact peripheral branches of the pulmonary artery and cause pulmonary infarcts
  - Large pulmonary emboli may impact in and obstruct a major pulmonary artery to cause sudden death
  - A small pulmonary embolus (premonitory embolus) may be followed by a much larger fatal embolus
  - Prevention of leg vein thrombosis is the best way to prevent pulmonary embolus

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64. Embolism

Embolism

- **Arterial emboli**
  - Sites of origin
    - Usually a mural thrombus (adherent to wall of a heart chamber or major artery)
      - Mural thrombus of right atrium associated with mitral stenosis or with atrial fibrillation
      - Mural thrombus of left ventricle caused by MI
      - At junction of internal and external carotid artery
    - Cause thrombotic brain infarcts (ischemic stroke)

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Embolism

- Arterial emboli (cont’d)
  - Sites of arrest
    - Branches of carotid artery - - - > middle cerebral a. - - - > cerebral infarction
    - Branches of mesenteric artery - - - > hemorrhagic infarct of intestine
    - Branches of renal artery - - - > wedge-shaped pale infarct of renal cortex
- Paradoxical emboli
  - Left-sided that originate in venous circulation but gain access to arterial circulation through a left to right shunt (e.g., patent foramen ovale, atrial septal defect)

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Embolism

Bone Marrow Embolus (fat embolism) following skeletal injury

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- Other types (forms) of emboli
  - Malignant tumor
    - Through wall of vein/venule - - - > venous system - - - > distant site
  - Fat and bone marrow
    - Severe fracture to bones and adipocytes enter circulation - - - > venous - - - > right heart - - - > pulm. art. - - - > lungs or - - - > systemic - - - > brain, kidneys - - - > coma and death

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67. Embolism

Embolism

- **Other types (forms) of emboli (cont’d)**
  - **Air**
    - Accidental pumping of air into venous circulation during IV injection or transfusion
    - Decompression sickness when nitrogen bubbles reform and occlude small vessels → musculoskeletal pain (the bends) and small infarcts (caisson disease) of CNS, bones → anoxia, death
  - **Therapeutic**
    - Wire, gelfoam, glue, balloons for inoperable vascular malformations

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68. Embolism

Embolism

- **Other types (forms) of emboli (cont’d)**
  - **Amniotic fluid**
    - During childbirth, some enters maternal circulation through exposed and bleeding placental bed in the uterus → venous → lungs → alveolar wall damage and DIC → maternal death
  - **Miscellaneous**
    - Atherosclerotic plaques
    - Clumps of inflamed infected tissue

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Infarction

- Necrosis resulting from ischemia; infarct = necrotic tissue
  - Failure of adequate blood supply to a tissue causes cell damage through ischemia
  - Tissue necrosis due to interference with local blood flow → coagulative necrosis
  - Major cause of morbidity and mortality
    - Myocardial infarction, cerebral infarction, pulmonary infarction, gangrene of lower limb, bowel infarction

Infarction

- Most occur due to obstruction of arterial supply to a tissue; some due to interference to the venous drainage
  - When caused by artery blockage then shaped according to the territory of supply of the blocked vessel
    - Occlusion of small vessels results in wedge-shaped infarct with the occluded vessel at the apex
  - Two types:
    - Red infarcts
    - White infarcts
71. White Infarcts / Red Infarcts

White Infarcts / Red Infarcts

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72. Infarction

Infarction

- Hemorrhagic infarcts – “red” (RBCs ooze into necrotic tissue)
  - Characteristically occur in the lung and GI tract
    - Loose, well vascularized with redundant arterial blood supplies and hemorrhage into the infarct occurs from the nonobstructed portion of the vasculature

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73. Infarction

Infarction

- **White infarcts**
  - Characteristically occur in heart, brain, kidney and liver
    - Damaged area initially poorly defined, pale and swollen; 48 hrs. better demarcated, pale and yellow - -> acute inflammation with red hyperemic border - - -> at 10 days ingrowth of granulation tissue and organization are advanced - - -> ultimately replaced by collagenous scarring

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74. Infarct Infarct – Red (lung) and Pale (spleen)

Infarct Infarct – Red (lung) and Pale (spleen)

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Renal Infarcts

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Infarction

- Venous infarcts
  - Usual cause is torsion of vascular pedicle of an organ and also in brain (venous sinus occlusion by thrombosis)
  - Blockage of venous drainage because tissue becomes suffused by blood
  - Blood unable to drain from tissues via veins but arterial blood arrives - - -> congestion - - -> rapid rise in pressure - - -> vessel wall rupture - - -> arterial blood cannot enter - - -> necrosis
  - Deeply congested and unoxygenated blood so almost black (hemorrhagic infarction)
77. Venous Infarctions

Venous Infarctions

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78. Slow Occlusion of a Vessel

Slow Occlusion of a Vessel

• Results in:
  ▶ Development of a collateral circulation (but not in areas supplied by a single artery)
  OR
  ▶ Tissue undergoes ischemic atrophy (not infarction)
    • Specialized cells shrink - - -> hyaline pink-staining amorphous support tissue

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79. **Infarction**

**Infarction**

- **Infarction key facts**
  - Infarction is death of tissue due to anoxia following abrupt interference with the blood supply
  - Arterial infarction
    - Sudden obstruction to the arterial supply to a tissue or organ
  - Venous infarction
    - Sudden and persistent obstruction to venous drainage of an organ or tissue

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80. **Vascular Hemodynamics**

- **Shock**
  - Clinical state associated with generalized (systemic) failure of tissue perfusion due to reduction in tissue blood flow and manifested by hypotension
  - Circulatory collapse with decreased oxygenation of tissues

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Vascular Hemodynamics

• Shock – cont’d
  ❖ Causes
  • Severe failure of pumping mechanism of heart
    (cardiogenic shock)
    – Decreased cardiac output (left ventr. failure)
  • Blockage of major arteries (obstructive shock)
  • Lack of blood to pump (hypovolemic shock) - hemorrhage
  • Abnormal dilatation of peripheral vessels causing lack of
    venous return of blood (septic shock/endotoxic shock,
    anaphylactic shock, neurogenic shock)

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Vascular Hemodynamics

• Types of shock
  ❖ Cardiogenic
    • Circulatory collapse from pump failure of the left
      ventricle most often caused by massive myocardial
      infarction
  ❖ Hypovolemic
    • Acute reduction in circulating blood volume caused
      by severe hemorrhage or massive loss of fluid from
      the skin from extensive burns or from severe trauma
      OR
    • Loss of fluid from GI tract through severe vomiting or
       diarrhea

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• Types of shock – cont’d
  ❖ Septic
  • Most often associated with gram (-) infections - - - - - - gram (-) endotoxemia
    – Lipopolysaccharide endotoxin - - - cytokines - - - direct toxic injury to vessels - - - coagulation pathway and DIC OR
    – Superantigens - - - toxic shock syndrome (esp. Staph aureus)
  • Initial vasodilation - - - increased blood flow - - - signif. peripheral pooling - - - relative hypovolemia and impaired perfusion

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Stages of shock
  – Nonprogressive (early) stage
    • Compensatory mechanisms maintain perfusion of vital organs
      – Increased heart rate and increased peripheral resistance
  – Progressive stage
    • Tissue hypoperfusion and onset of circulatory and metabolic imbalance, including metabolic acidosis
    • Compensatory mechanisms are no longer adequate
  – Irreversible stage
    • Severe organ damage and metabolic disturbances --- - survival not possible

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Events

– At first, protective mechanisms operate to maintain perfusion of vital organs
  • Renin-angiotensin-aldosterone system
    – ADH secretion increased → sodium and water retention increases blood volume
  • Increased catecholamine production by adrenals
  • Increased sympathetic activity → tachycardia and vasoconstriction

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Events – cont’d

– With persistence, systemic acidosis develops → dilatation of previously constricted vessels → blood pressure falls → blood diverted from gut and kidneys to maintain perfusion of heart and brain → urine output falls → damage to renal epi cells and gut stasis with epithelial lining necrosis → necrosis of liver, heart, brain → death with multiple organ failure

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- **Morphologic manifestations**
  - Acute tubular necrosis of kidney – most imp't.
    - Potentially reversible with appropriate medical management
  - Areas of brain necrosis
  - Centrilobular necrosis of the liver
  - Fatty changes of heart or liver
  - Patchy mucosal hemorrhages in the colon
  - Depletion of lipid in the adrenal cortex
  - Pulmonary edema

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Clinical

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Early shock</th>
<th>Late shock</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Pale and cold</td>
<td>Cyanosed</td>
</tr>
<tr>
<td>Kidneys</td>
<td>Low urine production</td>
<td>Necrosis of tubular epithelium</td>
</tr>
<tr>
<td>Gut</td>
<td>Bowel stasis</td>
<td>Necrosis of lining epithelium</td>
</tr>
<tr>
<td>Lung</td>
<td>Tachypnea</td>
<td>Necrosis of alveolar epithelium</td>
</tr>
<tr>
<td>Liver</td>
<td>Fatty change</td>
<td>Necrosis of centrilobular cells</td>
</tr>
<tr>
<td>Brain</td>
<td>Reduced conscious level</td>
<td>Necrosis of neurons, coma</td>
</tr>
<tr>
<td>Heart</td>
<td>Tachycardia</td>
<td>Myocardial necrosis</td>
</tr>
</tbody>
</table>

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Symptoms of Shock

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