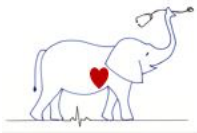
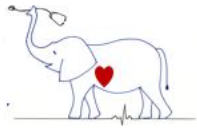




Last Updated 3/27/20

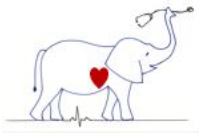
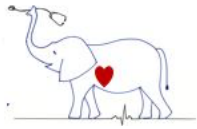
PATHOLOGY OF THE HEART AND BLOOD VESSELS

Created by V'22 Cardio Group modified from Dr. Nicholas Robinson

Pathology of the Heart

Evaluation of the heart at necropsy

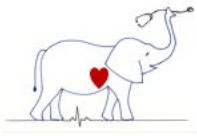
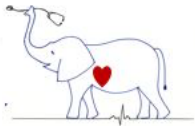
- Position
  - Abnormal position
    - Ectopia cordis – heart located outside of the chest
    - Pericardial diaphragmatic hernia
  - Compression
    - Mediastinal mass
    - Pyothorax
- Pericardium: Parietal layer, pericardial fluid, visceral layer
  - Abnormal pericardium
    - Red and thickened from edema and hyperemia
    - Chronicity (>48-72 hours) to injury – mesothelial cells proliferation → shaggy, roughened appearance
  - Pericardial effusion – excess pericardial fluid
    - Causes: tear of proximal great vessels, neoplasia, myocardial rupture, coagulopathies
    - Cardiac tamponade
      - Affects right ventricle the most during diastole
- Abnormalities of the great vessels
- Removal of the respiratory tract and heart en bloc
  - Cardiac disease often affects the lungs and vice versa
  - Trace pulmonary arteries
    - Look for evidence of thrombosis and/or endoarteritis
- Evaluate cardiac chambers and valves by "following the flow"
- Examine internal and external features/lesions
  - Endothelium: lines chambers of the heart, normally thin and almost invisible
  - Subendocardial tissue: composed of fibroblasts, nerves, collagen, veins, and conduction system
  - **Endocardial thickening**
    - Result of fibrosis from a number of pathological conditions:
      - scarring from "jet lesions"
      - restrictive cardiomyopathy
      - fibroelastosis
  - Valvular structure
    - Dysplasia
      - AV valve most commonly affected
      - Focal or diffuse thickened with fibrosis and abnormal, fibrotic, and shortened chordae attachments
      - Some valve directly fused to the ventricular wall
    - Stenosis
      - Lesions affect the pulmonary valve more often, less in the aortic valve
      - Stenosis may be in the valve or supra/subvalvular

        - Rupture chordae → rapid valvular dysfunction and regurgitation
        - Myxomatous valvular degeneration (Endocardiosis)
            - The most common valvular lesion in dogs, often incidental finding in old dogs
            - Grossly: free edges of valves thickened by 1-2 mm, smooth, shiny opaque white nodules
            - Histologically: valve stroma is expanded by myxomatous materials
            - May see concurrent chordae thickening and rupture
            - in some small dogs → severe changes → marked deformation of the valves → valvular incompetency → secondary atrial enlargement and endocardial fibrosis
        - Valvular endocarditis (vegetation)
            - Fibrinous, yellow to tan to red irregular, roughened deposits on the valves
            - Usually bacterial in origin → large number of pathogens associated with this lesion
            - Histologically: vegetations are composed of fibrin, blood, inflammatory cells, and colonies of bacteria
            - Inflammation can spread down the chordae → rupture
            - Vegetations can break off → embolize into myocardium and lung
- Heart is weighed after blood is removed and the great vessels trimmed off
    - Cardiac diseases typically result in cardiomegaly rather than microcardia
    - Normal heart weight in dogs: < 1% of body weight. Some dog breed (i.e. greyhound) have a higher normal heart:body weight ratio
    - Obese animals → heart weight in the high normal heart to body weight ratio range should be viewed with suspicion for cardiomegaly
    - Cats: absolute weight of the heart → useful indicator of disease
        - Cat hearts should weigh less than 18-20 grams.

Reaction of the heart to altered hemodynamics

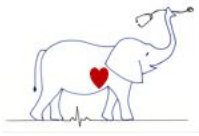
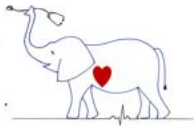
- Increased preload
    - Increase blood volume → increased preload
    - Acutely: stretching and dilation of the ventricle
        - Accommodate end diastolic volume
        - Increased pressure
    - If preload persists → ventricle responds by laying sarcomeres in series
        - “eccentric hypertrophy”
        - Large volume chamber
    - When limit is hit → congestive heart failure
        - Altered conduction
        - Perfusion to the area
        - Morphologic changes to valvular apposition
- Increased afterload
    - Increased resistance to the ejection of blood
    - More force needed to empty the ventricles → sarcomere laid in parallel
        - “concentric hypertrophy”
        - Thickened ventricular wall
    - Acquired disorder (e.g. hypertension)
        - Marked hypertrophy → Increased perfusion distance from capillaries to the

cells (capillaries do not grow with the cells)
        - Hypoxia → abnormal conduction and dysrhythmias
    - Congenital cases (e.g. stenosis)
        - +/- Less severe hypertrophy
        - Cardiac hyperplasia with some matching capillary growth

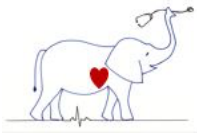
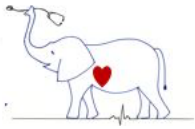
Myocardial Pathology

- Growth Disturbances
    - Myocardial hypertrophy → increased muscle mass due to increase size of myocytes
        - Compensatory response to increased workload/stimulation (reversible if stimulation removed)
        - Primary Idiopathic Hypertrophic Cardiomyopathy → irreversible
        - 2 gross anatomic forms
            - Eccentric: enlarged ventricular chambers with thin-normal walls, result of increased blood volume load (e.g. valvular insufficiency or septal defect)
            - Concentric: small ventricular chambers with thick walls, result of increased pressure load (e.g. valvular stenosis, systemic hypertension, pulmonary disease)
        - 3 stages of hypertrophy
            - Initiation
            - Stable hyperfunction
            - Dysfunction
    - Right ventricular concentric hypertrophy
        - Dirofilariasis → pulmonary hypertension
        - Pulmonic stenosis in dogs
        - Pulmonary hypertension from hypoxia in high altitude (cattle)
        - Chronic alveolar emphysema (horses with heaves)
    - Left ventricular concentric hypertrophy
        - Subaortic stenosis
        - Hyperthyroidism
        - Systemic hypertension
    - Biventricular hypertrophy
        - Idiopathic Cardiomyopathy
        - Some congenital anomalies
        - End stages of heart disease due to other causes
- Infiltration
    - Fatty infiltration → adipocytes in myocardium → separate cardiomyocytes
        - Obese animals, not associated with dysfunction
        - Microscopic feature of arrhythmogenic right ventricular cardiomyopathy in certain dog breeds (e.g. Boxers)
- Degeneration
    - Fatty degeneration
        - Lipid droplets in the sarcoplasm
        - Light microscopy → clear vacuoles, special stains to confirm the lipid
        - Gross exam: heart may be pale pink to tan
        - Occurs with severe anemia, copper deficiency, other systemic disorders
    - Hydropic degeneration
        - Vacuolated sarcoplasm, do not stain for lipid
        - Classically occurs with anthracyclines

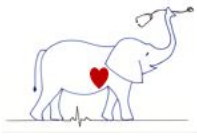
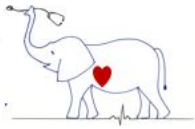
- Lipofuscinosis
  - Accumulation of intralysosomal oxidized lipid residues
  - Light microscopy → yellow brown granules near the cardiomyocyte nuclei
  - Gross exam: heart may be brown or golden brown
  - Age-related change
  - Can occur in starvation or hereditary in Ayrshire cattle
- Myofibrillar degeneration
  - Disruption of sarcoplasm → loss of cross striations and pale pink cytoplasm
  - Classically seen with furazolidone toxicity in birds
  - Potassium deficiency in rats
  - Acute myocyte injury and many other toxicities

- Necrosis & Mineralization
  - Necrosis → result from many types of injury
    - Nutritional deficiency, toxin exposure, ischemia, metabolic disorder, physical injury, etc.
    - Examples: ionophore toxicity (equine), vitamin E-selenium imbalance (neonates/ juveniles), anthracycline toxicity (dogs), gossypol toxicosis (pigs)
  - Necrotic myocardium
    - Gross exam: pale tan to white, sometimes gritty (rapid dystrophic mineralization)
    - Microscopic: Swollen hypereosinophilic fibers with shrunken nuclei and basophilic cytoplasmic granules
    - With chronicity, dead myofibrils are removed, myocytes may regenerate, and fibrosis can occur
  - Mineralization → often occurs in conjunction with necrosis → calcium released from damaged sarcoplasmic reticulum
    - Prominent in hereditary calcinosis (mice), vitamin D toxicosis, spontaneous in aged rats and guinea pigs
  - Mineralized myocardium
    - Gross exam: gritty, white
    - Microscopic exam: basophilic, angular
- Cardiomyopathies
  - Primary cardiomyopathies (Idiopathic) → underlying causes are largely unknown
    - Idiopathic Hypertrophic Cardiomyopathy (HCM)
      - Increased left ventricular +/- interventricular thickness (concentric hypertrophy), **most common in cats**
      - Gross: thick ventricle wall, small lumen. Weight > 20g
      - Microscopic: none to enlarged myocytes and fiber disarray
      - Pathophysiology: myocytes work harder and enlarge → hypertrophy reduces the compliance and diastolic function → impairs ventricular filling.
        Obstruction of left ventricular outflow during systole can be seen → forces generated by the narrowed outflow tract by septal hypertrophy → anterior motion of mitral valve leaflet
        Valvular displacement → mitral regurgitation → enlarge atria → blood stasis + inappropriate activation of endothelium → atrial thrombosis
      - Associated genetic defect → myosin binding protein C gene mutation

- Idiopathic Dilated Cardiomyopathy (DCM)
    - Ventricular and atrial dilation with ventricular hypertrophy (eccentric). **Dogs, cats, cattle, poultry.** Hypertrophy may not be obvious
    - Subcategory: **arrhythmogenic right ventricular cardiomyopathy**
        - Associated with ventricular tachycardia, most prominently in Boxer dogs
        - Histopathology: right ventricle infiltrated by adipose and fibrous tissue
    - Gross: big, heavy, flabby heart
    - Microscopic: sometimes attenuated/wavy fibers
    - Pathophysiology: decreased contractility and declining stroke volume → compensatory Frank Starling and neurohormonal mechanisms → myocytes elongate
      Long-term → compensatory mechanism not functional → myocyte degeneration → volume overload and failure
- Restrictive Cardiomyopathy (RCM)
    - Primarily in cats, affecting left ventricle. Some evidence that RCM is preceded by endocarditis, but inciting cause is unknown
    - Gross: thickened white left ventricular endocardium
    - Microscopic: left ventricular endocardial and subendocardial fibrosis
    - Pathophysiology: endocardial/subendocardial fibrosis + infiltrates → impair diastolic filling (ventricle more rigid than normal)

- Secondary cardiomyopathies (known causes)
    - Heritable
        - DCM
            - Human: mutation in several contractile protein and ion channel genes
            - X-linked muscular dystrophy (Dogs), associated with subendocardial and interstitial fibrosis
        - HCM
            - Autosomal dominant in Maine Coon and American Shorthaired cats
            - Mutations in sarcomeric proteins → mutation in the myosin binding protein C has been identified in heritable HCM in cats
    - Nutritional
        - DCM: taurine deficiency
        - Myocardial necrosis (due to deficiency): selenium-vit E imbalance, potassium, copper, thiamine, magnesium
    - Toxic
        - Myocardial necrosis: cobalt, catecholamines, ionophores, vit D and calcinogenic plants, blister beetles, rapeseed oil, T-2 mycotoxin
    - Physical injury/Shock
        - Myocardial necrosis: CNS lesions and trauma, GDV, electrical defibrillation, hemorrhagic shock
        - Endocrine disorders → HCM: hyperthyroidism
    - Infections
    - Neoplastic

- Systemic hypertension in cats → HCM: spontaneous hypertension, renal disease, hyperthyroidism, diabetes mellitus, primary aldosterism

Myocarditis → Inflammation of the myocardium, involve in a range of different inflammatory cells

Selected examples of etiologic agents

- Autoimmune: poorly documented, a hypersensitivity reaction (eosinophilic myocarditis) in cattle to plant toxin is known
- Parasitic:
  - Sarcocytis spp Cysts: no immune reaction but may see eosinophils with degenerating cysts, multiple hosts
  - Neospora caninum (dogs): myocarditis, myositis and encephalomyelitis
  - Toxoplasma gondii (multiple hosts): myocarditis, systemic disease
  - Larval tapeworms (multiple hosts): Taenia ovis, saginata, solium, and Echinococcus granulosum
  - Trypanosom cruzi: Chagas disease, pyogranulomatous myocarditis
- Bacterial and fungal
  - Generally → suppurative to necrotizing lesions
  - Any pyogenic bacterium, more common ones include: Actinobacillus equuli, Clostridium chauvoei, Aspergillus terreus, Histophilus somni, Streptococcus spp.
- Viral
  - Parvovirus and herpesvirus (puppies)
  - Equine Herpesvirus – 1
  - Foot and mouth disease → more necrotizing in young animals
  - West Nile (raptors)
  - Porcine circovirus/porcine parvovirus
  - Encephalomyocarditis virus (swine, lab rodents)
- Plant toxins: cardiac glycosides

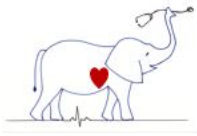
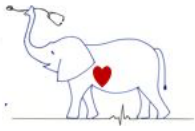
Myocardial necrosis

Selected examples of etiologic agents

- Vitamin E/Selenium responsive disease (pigs and ruminants)
  - "mulberry heart" in pigs (2-4 months of age mainly)
  - May see degeneration of arterioles in multiple organs
  - "white muscle disease" in ruminants and horses → result of dystrophic mineralization of the myocardium
- Ionophore and gossypol toxicosis
  - Ionophore in ruminant feed → control coccidian parasites and promote growth
    - Mixing error → toxic doses added to feed
    - Horses are very sensitive → peracute myocardial necrosis
    - Gossypol → found in cottonseed meal, can be toxic in large quantities
- Doxorubicin toxicosis
  - Anthracycline chemotherapeutic agent
  - In dogs, can cause myocardial acute necrosis and chronic degeneration/necrosis via peroxidative injury and blockage of DNA, RNA, and protein synthesis
- Thromboembolic diseases
  - Systemic inflammation, coagulopathies, vasculitis can result in cardiac necrosis
  - Arteriosclerosis → rarely severe enough in animals to cause myocardial infarction

Myocardial neoplasia

- Primary tumors of myocardial cells → very rare
- Infiltrating tumors from other systems more commonly found
  - Hemangiosarcoma in dogs

        - One of the most common tumors
        - Often found on the right auricular appendage
        - Histologically: tumor composed of bizarre spindle cells → irregular vasculature
    - Peripheral nerve sheath tumors in cattle
        - Epicardial surface
        - Most considered incidental findings
        - Whirling spindle cells with supporting fibrous stroma
    - Rhabdomyomas or muscular hamartomas
        - Rare
        - Most commonly found in pigs, have been reported in dogs, cattle, sheep
    - B cell lymphoma
        - Bovine leukosis virus in cattle
        - Heart can be massively affected → little myocardium remaining with few or no clinical signs of heart failure
        - Usual site → right atrium
    - Chemodectoma (aortic body tumors)
        - Heart base most often
        - May be an incidental finding

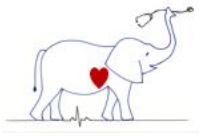
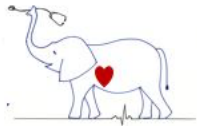
Pathology of Blood Vessels

Normal Vasculature Composition:

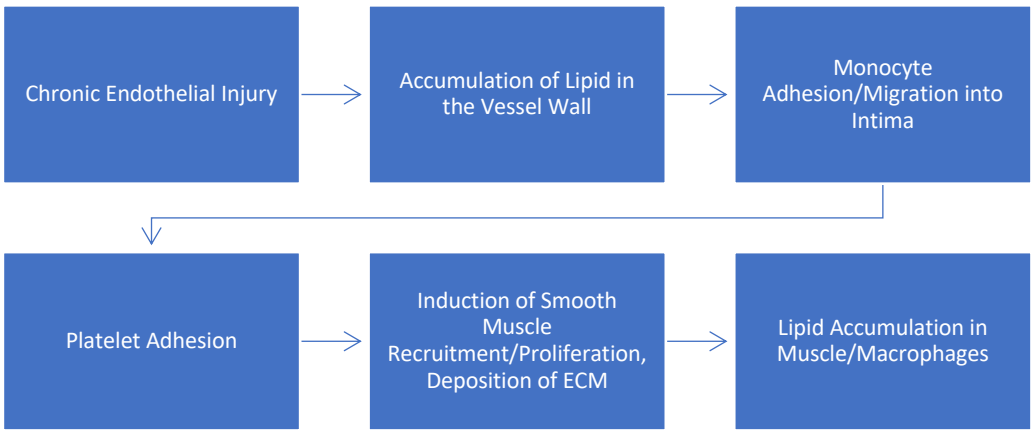
- Arteries
    - Intima: includes endothelial cells and the subintima
        - Normally impermeable to large molecules
        - Anti-inflammatory
        - Resists leukocyte adhesion and thrombosis, promotes vasodilation
    - Media: composed of elastin fibers, smooth muscle, and extracellular matrix
        - Enables the contractile and elastic properties of the vessel
            - Aorta/pulmonary artery: allows for stretch during systole and recoil during diastole
            - Arterioles: more prominent muscle content allows for constriction/relaxation to regulate blood flow in response to circulating substances
        - Can also produce extracellular matrix and inflammatory mediators
    - Adventitia: contains nerves, lymphatics, blood vessels
- Veins are very similar to arteries EXCEPT:
    - Thinner subendothelial layer and muscular media
    - Typically lack intrinsic vasomotor activity → blood flow is dependent on external compression of the skeletal muscle and one-way valves

Vasculature Reactions

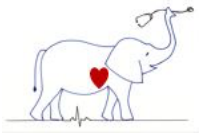
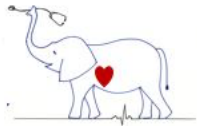
- ***Intimal Thickening***: non-contractile smooth muscle cells are recruited via endothelial signals into the intima, where they divide and produce ECM
    - Usually a response to vessel injury or aging
    - Even with normalization of the endothelial layer **intimal thickening remains**

- ***Altered Thrombotic Surfaces***:
    - Physiologic: normal endothelial activation with maintenance of antithrombotic properties and appropriate smooth muscle tone
    - Pathologic: endothelial dysfunction as a result of detrimental stimuli (e.g. viral/bacterial infections, hypertension) or excessive physiologic stimuli (persistent hypoxia/acidosis, cytokines)
        - Results in pro-thrombogenic surface and/or abnormal signaling to the underlying smooth muscle cells (altered vasoreactivity)
- ***Altered vascular reactivity and medial proliferation***: smooth muscle can dilate or constrict vessels in response to physiologic/pathologic stimuli
- ***Arteriosclerosis*****:** a common general reaction pattern to endothelial damage that results in a loss of elasticity and wall thickening
    - Thickenings are grossly white and intimal surface may appear wrinkled
    - Result of multiple causes (hypertension, calcification, plaques, etc) related to altered hemodynamics
        - **Hypertension:** causes increased extracellular matrix deposition in vessels due to protein leakage across damaged endothelia ("hyaline arteriosclerosis")
        - **Persistent Hypercalcemia/Inflammation/Aging**: may cause arterial calcification ("medial sclerosis")
- ***Atherosclerosis***: a type of arteriosclerosis that is uncommon in domestic animals (may occur in rabbits, chickens, parrots, non-human primates, and pigs)
    - Regarded as a healing response to a chronic inflammatory condition that affects large elastic (aorta) and medium muscular (i.e. coronary, femoral) arteries
    - Hallmark is yellow, irregular, and raised intimal "plaques" that protrude into the lumen and are often mineralized
        - Composed of foamy cells of likely smooth muscle origin, monocytes/macrophages, and accumulations of lipid
        - Plaques surfaces are highly thrombogenic and can cause ischemia
        - Pressure to the underlying media can weaken the vessel and cause pathologic dilation/rupture
    - Pathogenesis:



- ***Aneurysms***: inherited/congenital or acquired focal abnormal dilation of the vessel wall
    - Usually the result of vessel alternation in three ways:
        1. Congenital defects to connective tissue (e.g. Marfan syndrome)

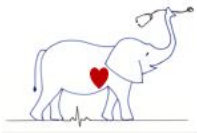
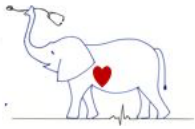



2. Increased collagen destruction/decreased collagen synthesis (e.g. protease activity in inflammatory conditions)
3. Loss of smooth muscle and/or synthesis of non-elastic ECM (e.g. "cystic medial degeneration")

- **False aneurysm:** a vessel bulge created by an extravasated focal hematoma forming in the wall between the tunica media and adventitia

Vascular Conditions in Veterinary Species

- ***Vasculitis***: inflammation within the blood vessel, causing vessel wall damage
  - Hallmarks: perivascular/vascular fibrin deposition, endothelial and stromal cell necrosis, and/or collagen degeneration
    - **NOTE:** perivascular inflammatory cell presence is **NOT** sufficient to diagnose vasculitis!
  - Can cause thrombosis and hemorrhage with downstream ischemia
  - Some important causes of vasculitis include:
    - **Viral Disease** (ex. FIP, equine arteritis virus, African horse sickness, African swine fever, hog cholera/classical swine fever)
    - **Autoimmune Disease** (ex. polyarteritis nodosa, hypersensitivity vasculitides)
    - **Bacterial/Rickettsial Agents** (ex. Rocky Mountain fever, heartwater, hepatic abscesses in cattle)
    - **Fungal Disease:** (ex. mycotic ruminitis, guttural pouch mycosis)
    - **Parasitic:** (ex. *Strongylus vulgaris*, schistosomiasis, *Dirofilaria immitis*)
- ***Arteriosclerosis*:**
  - *Systemic hypertension*: can be a cause or effect of renal disease, or related to pheochromocytoma, diabetes mellitus, or hyperthyroidism (among others)
    - Self-perpetuating (increased pressures lead to medial hypertrophy/hyalinization → decreased perfusion → more hypertension)
    - Can also result in retinal degeneration, hemorrhage and detachment
  - *Pulmonary hypertension (PH):* can be a cause or result of pulmonary arterial disease, or related to cardiac diseases (ex. left to right shunting) or medial proliferation secondary to arteritis
    - Hypoxia → pulmonary arterial constriction/hypertrophy → hypertension
    - Cattle and pigs can develop hypertensive heart failure at high altitudes
  - *Mineralization:* dystrophic or metastatic types (ex. vitamin D toxicity, Johne's disease in cattle, hypercalcemia)
  - *Uremia:* endothelial damage causes fibrin leakage into the media and collagen degeneration within the wall
    - Calcification may also occur from hypercalcemia/hyperphosphatemia
- ***Aneurysmal conditions***: often secondary to inflammation or hemodynamic changes (ex. Marfan syndrome, Copper deficiency in swine)
- ***Miscellaneous syndromes***
  - *Cystic rete ovarii in cats, ovarian varicosities in horses, uterine artery rupture in horses*: degenerative conditions of the reproductive vasculature that may result in infertility and/or hemoabdomen
  - *Aortic rupture in horses*: uncommon but thought to be secondary to increased aortic pressure; hemorrhage can occur in the pericardium, myocardium or thoracic cavity
  - *Telangiectasia in the liver of cats/cattle*: multifocal, small dilations of the hepatic sinusoids that present as blood filled plaques on the subcapsular surface

- ***Neoplastic conditions***
    - Endothelial cell tumors
        - ◊ Hemangiomas/hamartomas: benign, proliferative conditions of endothelial cells often in the dermis/subcutis
            - Present as a red-pink nodule or plaque with or without ulceration (may look like granulation tissue in horses)
            - Complete excision is curative
        - ◊ Hemangiosarcoma: often very aggressive, malignant endothelial tumors
            - Cutaneous/peripheral soft tissue: less aggressive than visceral form
            - Visceral: commonly seen in right auricle, spleen, liver, kidney, and retroperitoneum with widespread metastasis to the lung, body cavities and brain
                - ♦ Clinical signs related to coagulation dysregulation from blood flowing/clotting in neoplastic vessels and/or hemoabdomen/hemothorax/hemopericardium
    - Vascular wall tumors: benign/low-grade malignancies derived from smooth muscle of the wall (leiomyoangioma/angiosarcoma) or from supporting cells (hemangiopericytoma)
- ***Malformation conditions of the vasculature***
    - ◊ *AV fistulas*: small abnormal connections between arteries and veins that bypass the capillary bed; can be the result of congenital factors, trauma or inflammation
    - ◊ *Portosystemic shunts*: abnormal placement of a vessel connecting the portal and system circulation