PATHOLOGY OF THE HEART

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Suggested Reading:

McGavin & Zachary. Pathologic Basis of Veterinary Disease.
Chapter on Cardiovascular System (Ch 10 in the 6th edition)

Objectives:

- Reinforce understanding of normal cardiovascular function with particular emphasis on the chamber/valve relationship.
- Be able to identify and use the steps of the postmortem cardiac examination procedure to distinguish whether a heart is structurally normal or abnormal.
- Be able to classify a lesion in a cardiac abnormality.
- Understand and be able to describe the defining gross and histologic features of hypertrophic, dilated and restrictive cardiomyopathies.
- Understand the major infectious causes of myocarditis/myonecrosis in domestic veterinary species with particular reference to those of economic importance.
- Describe the pathologic changes in other organs/body cavities that occur as a sequela to left and right sided heart failure.

Gross evaluation of the heart for disease

Knowing normal is critical for being able to recognize abnormal. Distinguishing which part of the heart was responsible for the clinical signs observed often requires extensive investigation throughout the body away from the heart. Significant cardiac dysfunction changes the hemodynamics in other parts of the body (lungs/thorax and liver/abdomen). These lesions are used for determining which side of the heart had problems.

For example, right sided failure leads to increased caval pressures and therefore peripheral edema, ascites and liver congestion. Left sided failure leads to increased pressures in the pulmonary veins and associated vasculature leading to pulmonary edema. With biventricular failure both congestion and edema can be seen.

Note: Species differences do exist. In cats, left sided failure also produces pleural effusion likely as a result of pleural and bronchial veins draining into the left heart.

Myocardial diseases are covered individually in later pages.

Evaluation of the heart at necropsy:

1. *Position in the thoracic cavity and the lungs*

    a. Abnormal position: ectopia cordis (heart located outside of the chest), pericardial diaphragmatic hernia (communication between the pericardium and the abdominal cavity).

    b. Compression from growths or fluid elsewhere in the thoracic cavity: mediastinal mass, pyothorax etc.

2. *Pericardium: Parietal layer, pericardial fluid and visceral layer*

    a. Normal pericardium is composed of a layer of parietal mesothelium (covers the inner aspect of the pericardial sac) and a layer of visceral mesothelium (covers epicardium) supported by a thin layer of dense connective tissue. Grossly it appears smooth, white/gray and shiny. Histologically, mesothelial cells lie flat and can be difficult to tell that they are even there under normal conditions.

    b. An abnormal pericardium can look red and thickened from edema/hemorrhage and hyperemia. If there is some chronicity (>48-72 hours) to the injury, the mesothelial cells will proliferate, resulting in a shaggy or roughened appearance. There may also be fibrosis in chronic states that also thicken the tissue.

    c. There should be very little fluid in the pericardial sac (a few mls of clear, pale yellow to colorless, watery fluid). If the heart floats in the sac, that's too much fluid and therefore there is pericardial effusion. The fluid should be examined for turbidity and color. Some of it should also be saved for ancillary testing if an infectious disease is suspected. If the fluid happens to be blood, then reasons for bleeding into the pericardium need to be investigated. Causes include tears of the proximal great vessels, neoplasia (hemangiosarcoma), myocardial rupture and coagulopathies. ***Cardiac tamponade*** is the result of excessive filling of the pericardium with ***ANY*** fluid. This excessive fluid presence mostly affects the right ventricle during diastole (thinner weaker wall collapsing under external pressure and therefore inhibiting filling). Other causes for effusion include: inflammation (pericarditis) - esp. in cattle with traumatic reticulopericarditis "hardware disease": wire foreign body penetrates the rumen and the pericardium, myocardial disease, and neoplasia (mesothelioma). *If no underlying cause for a non-inflammatory effusion is detected, there is a syndrome of idiopathic pericardial effusion in dogs (I.e. diagnosis by exclusion)*.

    d. The epicardium should be smooth and the path of superficial coronary vessels and nerves should be visible. There should be some adipose tissue along the coronary grooves. The lack of this normal epicardial fat, especially in adult large animals in large animals should prompt a concern for negative energy balance – ***serous atrophy of fat*** (i.e. feeding issues, parasitism, poor housing in inclement weather etc).

3. In situ evaluation of all the great vessels: abnormalities of great vessels can often be suspected at this point just from an external exam.

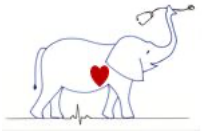
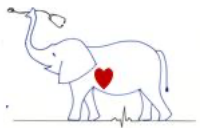
4. Removal of the respiratory tract and heart en bloc: this is important in that cardiac disease can often affect the lung and vice versa so we examine the lung and heart together. It also makes for tracing the pulmonary arteries a lot easier. While tracing the pulmonary arteries, we look for evidence of thrombosis and/or endoarteritis.

5. Evaluation of the cardiac chambers and valves is achieved by "following the flow" starting at the return of blood via the vena cava:

5. Continued:

With the heart now opened, examination of its internal and external features/lesions can occur.

a. Endothelium lines the chambers of the heart. Normally, the endothelial is very thin and almost invisible. Subendocardial tissue is composed of fibroblasts, nerves, collagen, veins and the conduction system. This can be glistening and white, especially in large animals.
b. **Endocardial thickening as a result of fibrosis** occurs in a number of pathological conditions including: 1) scarring secondary to turbid blood flow "jet lesions" and 2) restrictive cardiomyopathy 3) fibroelastosis.
c. Normal valvular structures and associated chordae tendinae. All four valves and myocardium are attached to the cardiac skeleton which is composed of fibrous tissue.
    - **Dysplasia**: The AV valves are the one most commonly affected. The valves may have either focal or diffuse thickened with fibrosis and abnormal, fibrotic and shortened chordae attachments. Some of the valve may be directly fused to the ventricular wall.
    - **Stenosis**: The lesions of stenosis often affect the pulmonary valve and less so the aortic valves. The stenosis may be directly in the valve or supra/subvalvular.
    - Ruptured chordae: see below. Ruptures lead to rapid valvular dysfunction and regurgitation culminating in acute congestive heart failure.
    - **Myxomatous valvular degeneration**: "endocardiosis". This is the most common valvular lesion in the dog and often an incidental finding in older dogs on post mortem on the mitral valve. Grossly, the free edges of the valves are thickened by 1-2mm smooth, shiny, opaque white nodules. Histologically, the valve stroma is expanded by myxomatous material. There may be concurrent chordae thickening and rupture (if rupture, then of course, this ceases to be an incidental finding!!!). In some small breed dogs, the changes are quite severe and occur very early in life with marked deformation of the valves and therefore valvular incompetency. There may be accompanying secondary atrial enlargement and endocardial fibrosis from turbulent flow.
    - **Valvular endocarditis:** This is distinguished from endocardiosis by the deposition of rough/ fibrinous, yellow to tan to red irregular, roughened deposits on the valves ("vegetations"). It is usually bacterial in origin and there are a large number of pathogens associated with this lesion. All species are affected (birds too!). Many of these bacteria have a tropism for infection (notably: Erysipelas rhusiopathiae) of the valve and the presence of an endocarditis warrants a search for a source of the bacteria (i.e. ulcerated skin, severe periodontal disease, abscess) that may produce a sustained bacteremia. Histologically, the vegetations are composed of fibrin, blood, inflammatory cells and colonies of bacteria. The bacteria are often enmeshed in fibrin and therefore accessing these organisms via antibiotics can be difficult! The inflammation can spread down the chordae resulting in rupture. The vegetations can also break off and embolize into the myocardium and lung.

6. Heart is weighed after the blood is removed from the chambers and the great vessels trimmed off. Comparative atrial and ventricular thicknesses as well as weights can also be obtained at this point.

Cardiac diseases typically result in cardiomegaly rather than microcardia. Normal heart weight in a dog should be less than 1% of body weight. Some dog breed (i.e. greyhound) have a higher normal heart:body weight ratio. If an animal is obese, then a heart weight in the high normal heart to body weight ratio range should be viewed with suspicion for cardiomegaly. In cats, there is less variation in body size, and so the absolute weight of the heart can be a useful indicator of disease. Cat hearts should weigh less than 18-20 grams.

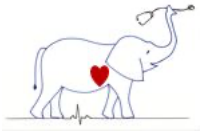
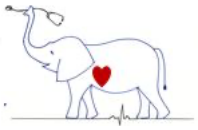
Brief review of normal cardiac structure and function

Cardiac myocytes contain 1-2 ***central*** nuclei. Cells are surrounded by connective tissue and rich capillary network. Sarcomeres are the contractile units, composed of overlapping actin and myosin fibers. The myosin fibers are anchored into the Z band via connexin, another protein. Myosin and actin are the chief contractile elements while tropomyosin and troponin are regulatory proteins. The myosin filaments have globular "heads" that contain myosin ATPase. Tropomyosin is present in between actin fibers and inhibits the interaction between myosin and actin. In contrast troponin sits at regular intervals along the actin strand. It has 3 subunits: TnI inhibits ATPase activity of the myosin heads and TnC binds calcium that regulates the contraction.

Specialized cell membrane (sarcolemma) structures: Intercalated disks can be seen on light microscopy and are composed of specialized proteins forming gap junctions between adjacent cardiac cells. The transverse tubular system is composed of invaginations of the sarcolemma creating increased surface area to contact the extracellular environment. This allows for ion transport that accompanies excitation and relaxation to occur quickly. The last membrane bound structures are the intracellular sarcoplasmic reticulum. These abut the T tubules at right angles and connect the T tubules with calcium stores in the terminal cisternae. Release of these stores is the necessary link from excitation to activation of the contractile mechanism.

Contraction: When calcium ions bind to TnC, it inhibits the activity of TnI and therefore allows interaction between myosin and actin. Contractile activity is generated through an ATP dependent reaction in the "flex" of the myosin heads on the actin filaments. Attachment and release cycles are accomplished though the cycling of ADP and binding of ATP. Given enough ATP, the process continues so long as there is enough calcium to inhibit the troponin-tropomyosin blockade. When the action potential ends, there is loss of calcium influx and calcium is pumped back into the sarcoplasmic reticulum. Tropomyosin then can inhibit the actin-myosin interaction.

Following the path of electrical impulse from generation to the myocardium: Contraction depends on organized propagation of electrical impulses along the conduction pathway. Action potential is created by ion fluxes through channels in the sarcolemma (those details are not in the scope of this lecture: see your cardiac physiology notes). There are three types of cardiac cells based on electrophysiology: pacemaker cells (SA node, AV node), rapid conducting fibers (Purkinje fibers) and ventricular/atrial muscle cells. Pacemaker cells are capable of self-initiated polarization in a rhythmic fashion. Atrial and ventricular cells can't do this on a normal basis but may do so if they are diseases. The SA node impulse is then spread to the surrounding atrial muscle through gap junctions and propagates the signal to

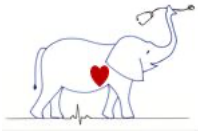
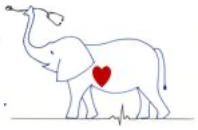



the AV node. Fibrous tissue surrounds the tricuspid and mitral valves so no electrical impulses can travel to the ventricle other than through the AV node. From the AV node, the action potential spreads to the bundles of His and Purkinje fibers to the ventricular muscle allowing for precise stimulation and contraction of the ventricles. ***Primary diseases of the conduction system are very poorly characterized histologically: in the few reports published, there is fibrosis and/or degeneration of the nodes and bundles. Most of the arrhythmias can often be attributed to underlying myocardial disease.***

Reaction of the heart to altered hemodynamics:

Increase preload: Increased blood volume causes an increased preload in the affected part of the circulatory system including the relevant cardiac ventricle. Acutely, there is stretching and dilation of the ventricle to accommodate the increased end diastolic volume but there is then increased pressure. If the preload persists, the ventricle responds via laying down sarcomeres in series (I.e. end to end, “eccentric hypertrophy”) to produce a large volume chamber and decreasing the pressure. There are limits to which the heart can do this before there is altered conduction, perfusion to the area and morphologic changes to valvular apposition and when that limit is reached, the result is congestive heart failure.

***Increased afterload*:** Where there is increased resistance to the ejection of blood, the heart has to generate increasing amounts of force to empty the ventricles. This leads to concentric hypertrophy with sarcomeres being laid down in parallel (i.e. side by side) and thus thickening the ventricular wall. Acquired disorders of increased afterload (e.g. hypertension) produces marked hypertrophy and there are corresponding increases in the perfusion distances from capillaries to the cells. The capillaries do not “grow” with the cells. Hypoxia can produce abnormal conduction and dysrhythmias. The hypertrophy is less severe in congenital cases of increased afterload (i.e. stenosis) since there is early capability of some cardiac hyperplasia and matching capillary growth.

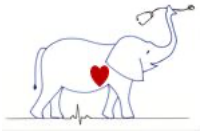
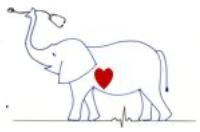



Myocardial Pathology

These lectures introduce myocardial pathology. The focus is on disease due to myocardial dysfunction, the underlying mechanisms (if known) and manifestations of these diseases.

1. *Growth Disturbances*
    a. Myocardial hypertrophy = increased muscle mass due to an increase in size of the myocytes.
        i. It is a compensatory response to increased workload or stimulation. It can be reversible if the stimulus is removed, for example cats with hyperthyroidism
        ii. In some situations, such as primary Idiopathic Hypertrophic Cardiomyopathy, it is not reversible.
        iii. There are 2 gross anatomic forms of hypertrophy (see earlier diagrams):
            a) Eccentric: enlarged ventricular chambers with normal or possibly thin ventricular walls, produced by lesions that increase blood volume load such as valvular insufficiency or septal defects.
            b) Concentric: small ventricular chambers with thick walls, produced by lesions that increase pressure load such as valvular stenosis, systemic hypertension or pulmonary disease
        iv. There are 3 stages of hypertrophy:
            a) Initiation
            b) Stable hyperfunction
            c) Dysfunction
    b. Right ventricular concentric hypertrophy – examples of disease associations
        i. Dirofilariasis can result in pulmonary hypertension
        ii. Pulmonic stenosis in dogs
        iii. Pulmonary hypertension in cattle due to hypoxia in high altitudes
        iv. Chronic alveolar emphysema in horses with “heaves”
    c. Left ventricular concentric hypertrophy – examples of disease associations
        i. Subaortic stenosis
        ii. Hyperthyroidism
        iii. Systemic hypertension
    d. Biventricular hypertrophy
        i. Can occur in Idiopathic Hypertrophic Cardiomyopathy
        ii. Some congenital anomalies
        iii. In the end stages of heart disease due to other causes

2. *Infiltration*
    a. Fatty infiltration: adipocytes in the myocardium, separating the cardiomyocytes.
        i. Usually in obese animals, not associated with dysfunction
        ii. Is also a microscopic feature of arrhythmogenic right ventricular cardiomyopathy (ARVC) in certain dog breeds (e.g. Boxers) that also have other microscopic cardiac lesions.
3. *Degeneration*
    a. Fatty degeneration: lipid droplets in the sarcoplasm that appear as clear vacuoles by light microscopy and special stains confirm the lipid. The heart may be pale pink to tan on gross exam. Occurs with severe anemia, copper deficiency and other systemic disorders.
    b. Hydropic degeneration: also vacuolated sarcoplasm but do not stain for lipid. Classically occurs with anthracyclines.

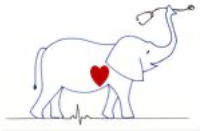
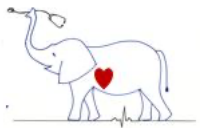
c. Lipofuscinosis: Yellow brown granules near the cardiomyocyte nuclei by light microscopy due to the accumulation of intralysosomal oxidized lipid residues. The heart may be brown or golden brown on gross exam. Typically, an age-related change but also occurs in starvation or hereditary in Ayrshire cattle.
d. Myofibrillar degeneration: Disruption of the sarcoplasm that results in loss of cross striations, and pale pink cytoplasm. Classically seen with furazolidone toxicity in birds and potassium deficiency in rats but is identified in many other toxicities or acute myocyte injury.

4. *Necrosis & Mineralization*
   a. Necrosis can result from many different types of injury: nutritional deficiency, toxin exposure, ischemia, metabolic disorders, physical injury and others. Some examples in veterinary species are: ionophore toxicity (horses), vitamin E-selenium imbalances in neonates/juveniles, anthracycline (doxorubicin) toxicity in dogs; gossypol toxicosis in pigs.
   b. Necrotic myocardium is:
      i. **Gross exam: Pale tan to white, sometimes gritty due to rapid dystrophic mineralization**
      ii. **Microscopic: Swollen hypereosinophilic fibers with shrunken nuclei and basophilic cytoplasmic granules**
      iii. **With chronicity, dead myofibrils are removed, myocytes may regenerate, and fibrosis can occur**
   c. Mineralization often occurs in conjunction with necrosis due to the calcium that is released from damaged sarcoplasmic reticulum. It is very prominent in some diseases such as hereditary calcinosis in mice, vitamin D toxicosis, and spontaneous in aged rats and guinea pigs.
   d. Mineralized myocardium is:
      i. Gross exam: gritty, white
      ii. Microscopic exam: basophilic and angular

5. *Cardiomyopathies*
   Multiple classifications exist. *This can be confusing.* It is important to recognize that regardless of the underlying cause, disease manifestation can be identical, resulting in any of the following either singularly or as combinations: myocardial hypertrophy, ventricular dilation, cellular degeneration and/or necrosis, reparative responses, fibrosis, and abnormal conductivity.

   Primary cardiomyopathies (Idiopathic). The underlying causes are <u>largely unknown or have poor understanding</u>. There 3 major types classified by the appearance of the heart:

   a. <u>Idiopathic Hypertrophic Cardiomyopathy (HCM)</u>:
      i. **HCM** is characterized by increased left ventricular +/- interventricular thickness (concentric hypertrophy). **It is most common in the <u>cat</u> but cases have been reported in dogs and cattle.**
      ii. Gross: Thick ventricle wall, small lumen. Weight is typically greater than 20g. When measuring a heart postmortem, make sure to remove all extraneous tissue (pericardium, great vessels, etc) to avoid falsely elevating the weight.
      iii. Microscopic: sometime no microscopic lesions, sometimes enlarged myocytes and fiber disarray
      iv. Pathophysiology: Myocytes "work harder" and enlarge. Hypertrophy reduces the compliance and diastolic function of the chamber thereby impairing ventricular filling. There may also be obstruction of

left ventricular outflow during systole because of anterior motion of a mitral valve leaflet from forces generated by the narrowed outflow tract by septal hypertrophy (the Venturi effect: best illustrated by the blowing in of your shower curtain when you turn on the shower, or if you're into vintage cars or lawnmowers, carburetors rely on this effect for fuel delivery @). Also, as a result of the valvular displacement, there is mitral regurgitation leading to enlarged atria. There may be blood stasis with atrial dilation and inappropriate activation of the endothelium leading to an atrial thrombosis. Portions of the thrombus can embolize, most commonly in the bifurcation of the abdominal aorta ("saddle thrombus").

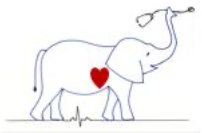
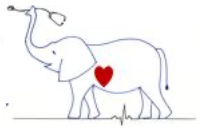
v. Associated genetic defect. Myosin binding protein C gene mutations have been associated with HCM.

b. <u>Idiopathic Dilated Cardiomyopathy (DCM)</u>:
   i. Ventricular and atrial dilation with ventricular hypertrophy (eccentric). **Dogs, cats, cattle and poultry (turkeys and broiler chickens) all have reported cases of DCM.** The hypertrophy may not be obvious in these cases as there is marked luminal dilation (weighing hearts is essential).
      a) A sub-category of DCM is the **arrhythmogenic right ventricular cardiomyopathy** that is associated with ventricular tachycardia most prominently in the Boxer dog. On histopathology, the right ventricle is infiltrated by various amounts of adipose and fibrous tissue.
   ii. Gross: Big, heavy, "flabby" heart
   iii. Microscopic: sometimes no microscopic lesions, sometimes attenuated/wavy fibers
   iv. Pathophysiology: In general, there is decreased contractility and subsequent declining stroke volume activates compensatory Frank Starling and neurohormonal mechanisms that cause myocytes to elongate. However, the compensatory mechanisms are not functional for the long-term and eventually myocyte degeneration develops resulting in volume overload and failure.

c. <u>Restrictive Cardiomyopathy (RCM)</u>:
   i. Primarily a disease of cats affecting the left ventricle. There is some evidence that RCM is preceded by an endocarditis, but the inciting cause is unknown.
   ii. Gross: thickened white left ventricular endocardium.
   iii. Microscopic: left ventricular endocardial and subendocardial fibrosis.
   iv. Pathophysiology: Endocardial/subendocardial fibrosis and/or infiltrates impair diastolic filling as the ventricle is more rigid than normal.

Secondary cardiomyopathies (due to known causes).

a. Heritable
   i. DCM
      a) In humans, mutations in several contractile protein genes and ion channel genes.
      b) X-linked muscular dystrophy resulting in DCM in dogs is associated with subendocardial and interstitial fibrosis.
   ii. HCM

c) Autosomal dominant in Maine Coon and American Shorthaired cats.
d) **Mutations in sarcomeric proteins have been implicated in the development of HCM**. Mutation in the myosin binding protein C3 has been identified in heritable HCM in cats. There are other mutations identified in humans including the myosin heavy chain gene and the troponin T gene. Given that mutated genes encode for proteins in the sarcomere complex there is impaired contractility. The cells therefore need to "work harder" resulting in cellular stress and compensatory hypertrophy. In addition, the blood supply may not keep pace with the cell growth leading to hypoxia. These factors ultimately lead to cellular degeneration and death followed by ineffectual reparative attempts.

b. Nutritional
    i. DCM: Taurine deficiency.
    ii. Myocardial necrosis due to deficiencies: selenium-vit E imbalances, potassium, copper, thiamine, magnesium.
c. Toxic
    i. Myocardial necrosis: cobalt, catecholamines, ionophores, vit D and calcinogenic plants, blister beetles, rapeseed oil, T-2 mycotoxin and many others.
d. Physical injury/Shock
    i. Myocardial necrosis: central nervous system lesions and trauma ("heart brain syndrome"), gastric dilation and volvulus, electrical defibrillation, hemorrhagic shock and others.
e. Endocrine disorders
    i. HCM: hyperthyroidism and others.
f. Infections – see below.
g. Neoplastic – see below.
h. Systemic hypertension in cats:
    i. HCM – spontaneous hypertension or associated with renal disease, hyperthyroidism, diabetes mellitus, primary aldosterism

In cardiomyopathies, haphazardly (i.e. not parallel) arranged myofibers are the hallmark of the disease although they are not always found.

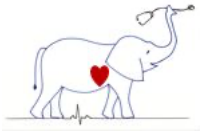
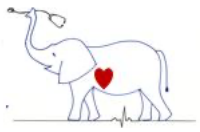
Myocarditis: selected examples of etiologic agents.

Myocarditis is inflammation of the myocardium. It can involve a range of different inflammatory cells. Each infectious agent often has a pattern of inflammatory cell types it attracts.

Autoimmune: In general, are poorly documented. A hypersensitivity reaction (eosinophilic myocarditis) in cattle to a plant toxin found in hairy vetch (*Vicia villosa*) is known.

Parasitic:

Sarcocystis spp Cysts: No immune reaction but there may be eosinophils with degenerating cysts. Multiple hosts.
Neospora caninum: myocarditis, myositis and encephalomyelitis. Dogs.
Toxoplasma gondii: myocarditis and/or systemic disease. Multiple hosts.
Larval tapeworms: *Taenia ovis, saginata, solium* and *Echinococcus granulosum*. Multiple hosts.
Trypanosoma cruzi (Chagas disease): pyogranulomatous myocarditis.

Bacterial and fungal: Generally are suppurative to necrotizing lesions. Any pyogenic bacterium has the potential More common ones include: *Actinobacillus equuli, Clostridium chauvoei* (can be necrotizing), *Aspergillus terreus* (German Shepherd dogs), *Histophilus somni, Streptococcus* spp.

Viral: Parvovirus and herpesvirus (canine herpesvirus-1) infection in puppies, equine herpes-1 in horses, foot and mouth disease—more necrotizing in young animals, West Nile virus in raptors, porcine circovirus/ porcine parvovirus, encephalomyocarditis virus (swine, laboratory rodents).

Plant toxins: cardiac glycosides containing plants are present across the world. Too numerous to mention here in detail but a good reference is Toxic Plants of North America.

Myocardial necrosis: selected examples of etiologic agents.

The following are agents that primarily cause myocardial death rather than myocardial inflammation with bystander necrosis (as above). But there is overlap. If the animal survives the necrotizing lesion, there is often an influx of immune cells responding to the injury. Thus, most necrotizing lesions have some component of inflammation as well.

Vitamin E/ Selenium responsive disease in pigs and ruminants: otherwise known as "mulberry heart" (Vit. E deficiency) in pigs (2-4 months of age mainly) from the myocardial hemorrhage. May also see degeneration of arterioles in multiple organs. The heart in "white muscle disease" in ruminants and horses occurs as a result of dystrophic mineralization of the myocardium.

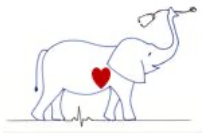
Ionophore and gossypol toxicosis: Ionophores (e.g. Monensin, coccidiostats) are often added to ruminant feeds to control coccidian parasites and promote growth. Mixing errors can result in toxic doses being added to feed. Horses are very sensitive to ionophore toxicosis and can present with peracute myocardial necrosis. Gossypol is found in cottonseed meal (another component in ruminant feed) and can be toxic in large quantities.

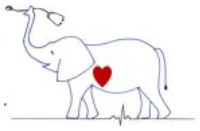
Doxorubicin toxicosis: This is an anthracycline chemotherapeutic agent and in dogs, can cause myocardial acute necrosis and chronic degeneration/necrosis via peroxidative injury and blockage of DNA, RNA, and protein synthesis.

Thrombo-embolic diseases: e.g. systemic inflammation, coagulopathies, vasculitis can result in cardiac necrosis. Arteriosclerosis is rarely severe enough in animals to cause myocardial infarction. There is a hyaline change in the myocardial vessels of older dogs that may be associated with infarcts of the papillary muscle and left ventricle. Grossly, arterial infarcts can appear white with well demarcated margins. The heart is a solid organ with little collateral vasculature so infarcts leave the tissue white from lack of blood supply.

Myocardial neoplasia:

Primary tumors of myocardial cells are very rare with infiltrating tumors from other systems more commonly found.





Hemangiosarcoma in dogs is one of the most common tumors most often found on the right auricular appendage although other locations have been reported in the heart. Histologically, the tumor is composed of bizarre spindle cells forming irregular vasculature.

Peripheral nerve sheath tumors in cattle can be seen on the epicardial surface and these are largely considered incidental findings. These are composed of whirling spindle cells with supporting fibrous stroma.

Rhabdomyomas or **muscular hamartomas** (malformations) can be seen as well delineated gray nodules in the muscle. These are rare but are most commonly found in the pig and have been reported in dogs, cattle and sheep.

B cell lymphoma associated with bovine leukosis virus infection in cattle. The heart can be massively affected with little myocardium remaining with few or no clinical signs of heart failure. Its usual site of origin is the right atrium. There may or may not be other visceral tumors as well.

Chemodectoma (aortic body tumors) are often found at the heart base and may be an incidental finding.

VASCULAR AND CARDIAC PATHOLOGY: REFERENCES

1. McGavin & Zachary. 2017. Pathologic Basis of Veterinary Disease. 6th ed. St. Louis, MO; Mosby Elsevier.

2. Maxie, M. Grant 2015. Pathology of Domestic Animals. 6th ed., vol 3. Edinburgh ; New York: Elsevier Saunders.

PATHOLOGY OF BLOOD VESSELS

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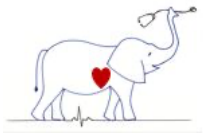
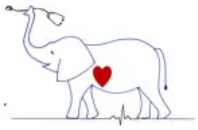
Suggested Reading:
McGavin & Zachary. Pathologic Basis of Veterinary Disease.
Chapter on Vascular Disorders and Thrombosis and Cardiovascular Disorders (Ch 2 and 10 in the 6th edition)

Objectives:

- Understand and describe how the vasculature responds to injury.
- Describe the different types of vascular pathologies at both a gross and histologic level
- Understand how the healing response may alter the normal structure and function of a vessel.
- Name at least 6 different specific veterinary diseases of the vasculature complete with cause (if relevant), tissue pathology and clinical sequelae?

A. Cardiovascular review:

1. Guiding principles: the vasculature is not simply just a conduit system.
    a. Cardiac output = arterial pressure/total peripheral resistance (cardiac output is inversely proportional to total peripheral resistance)
    b. Cardiac output and venous return are equal to one another under normal, non-stressful conditions. The factors that influence peripheral circulation (especially venous return) control cardiac output. The heart has a built-in system that pumps out whatever comes in (Frank Starling Law of the heart AND the stretch reactions/Bainbridge reflex—increases heart rate triggered when the myocardium is stretched).
    c. Local blood flow is tuned to the needs of local tissue metabolism
    d. Vessel compliance = change in volume/change in pressure.
        - The vasculature can adjust the compliance via smooth muscle contraction in physiologic circumstances.
        - Compliance is altered in vascular disease. The ability of the vessel wall to respond to changes can be profoundly affected.

2. Normal structure of arterial and venous wall
   a. Artery
      - Intima: endothelial cells and the subintima. Normal endothelial barrier is impermeable to large molecules, anti-inflammatory, resists leukocyte adhesion, promotes vasodilation and resists thrombosis.

      - Media:
         - Composed of elastin fibers (inner/outer elastic laminae), smooth muscle and extracellular matrix.
         - Enables the contractile and elastic properties of the vessel.
         - The elastic component is more apparent in larger arteries (aorta, pulmonary artery) and functions to stretch during systole and recoil during diastole.
         - Arterioles have more prominent muscle content which constricts or relaxes (compliance) to regulate blood flow. Muscle cells respond (constrict/relax) to circulating substances as well as those produced by nerve terminals and endothelial cells.
         - The myocytes can also produce extracellular matrix and inflammatory mediators.

      - Adventitia: nerves, lymphatics, blood vessels (vasa vasorum)

   b. Vein: similar to arteries <u>EXCEPT</u>: subendothelial layer is thin, thinner muscular media with intermixed elastic fibers. Veins typically lack intrinsic vasomotor activity meaning than the flow of blood is dependent on external compression of the skeletal muscle and one-way valves.

B. Reactions patterns of the vasculature

1. ***Intimal thickening***: smooth muscle proliferation with matrix deposition that thickens the intima. When there is any type of injury to the vessel (break to the endothelium), there is recruitment of smooth muscle cells into the intima where they divide and produce ECM. They have a different, non-contractile phenotype when compared to the medial smooth muscle cells. The injured endothelium (as well as platelets and macrophages) is partially responsible for elaborating signals that promote this migration and proliferation. With normalization of the endothelial layer, these smooth muscle cells return to their normal non proliferative state but the intimal thickening remains. The thickening can also be a part of aging changes.

2. ***Altered thrombotic surfaces****:* Certain stimuli lead to a normal endothelial activation with maintenance of antithrombotic properties and appropriate smooth muscle tone. Detrimental stimuli (e.g. viral / bacterial infections, hypertension) or excessive physiologic stimuli (persistent hypoxia/ acidosis, cytokines) can lead to endothelial dysfunction. Dysfunction can manifest as pro-thrombogenic surface and/or abnormal signaling to the underlying smooth muscle cells (altered vasoreactivity). Some changes are immediate and do not require protein synthesis (endothelial reaction under the influence of histamine) while others take a longer time to manifest.

3. ***Altered vascular reactivity and medial proliferation*** (also see above on endothelial cells): Smooth muscle cells are capable of proliferation as well as the production of extracellular matrix, growth factors and cytokines. They function to dilate and constrict vessels when subject to physiologic or pathologic stimuli.

4. ***Arteriosclerosis*:** this is a *general* reaction pattern with endothelial damage that results in a loss of elasticity and wall thickening. (Note: "**atherosclerosis**" [see below] is a specific type of arteriosclerosis). In arteriosclerosis, vessels can become thickened due to multiple causes including responses to hypertension, calcification and/or atherosclerotic plaques. Arteriosclerosis is common in veterinary medicine. The causes of arteriosclerosis are largely unknown but altered hemodynamics is hypothesized to contribute. Arteriosclerotic thickenings are white and may appear grossly as a wrinkling on the intimal surface.
    a. In response to hypertension, the vessels can have an increased amount of extracellular matrix deposition stimulated in part by protein leakage across a damaged endothelial wall "hyaline arteriosclerosis").
    b. Under some conditions of persistent hypercalcemia, inflammation or old age, arteries may calcify ("medial sclerosis").

5. **Atherosclerosis**: common in people but is relatively uncommon in domestic animals.
    a. Certain species such as rabbits, chickens, non-human primates and pigs are more susceptible to developing atherosclerosis than dogs, cats, cattle, rats and goats.
    b. The disease affects large elastic (aorta) and medium muscular (i.e. coronary, femoral) arteries. The hallmark of atherosclerosis is raised intimal "plaques" composed of foamy cells believed to be of smooth muscle origin, monocytes/macrophages and accumulations of lipid that protrude into the lumen. Grossly, these plaques are yellow raised areas with an irregular surface that bulge into the lumen.
    c. This disease is now seen as a chronic inflammatory condition with a healing response (see above on intimal thickening). Plaques often mineralize.
    d. **In brief, the pathogenesis involves chronic endothelial injury→accumulation of lipid in the vessel wall → monocyte adhesion and migration into the intima (foam cells) → platelet adhesion → induction of smooth muscle recruitment, proliferation and deposition of ECM -→ lipid accumulation in muscle and macrophages.**
    e. The surfaces of the plaques are highly thrombogenic and can induce thrombosis leading to downstream ischemia. The pressure to the underlying media can weaken the structure of the vessel and lead to pathologic dilation and rupture.

6. ***Aneurysms***
    a. Focal abnormal dilation of the vessel wall

    b. Can be inherited/congenital or acquired (see above, atherosclerosis): The various specific causes of aneurysms usually end up altering the vessel wall in three general ways:

        i. Defective connective tissue to begin with (most of the inherited conditions, usually involves connective tissue gene mutations, (e.g. Marfan syndrome)
        ii. Increased collagen destruction/decreased synthesis (proteases in inflammatory conditions including vasculitis and atherosclerosis) and
        iii. Loss of smooth muscle and/or synthesis of non-elastic ECM such as glycosaminoglycans ("cystic medial degeneration")

    c. A false aneurysm is where the vessel bulge is created by a hematoma (focal) forming in the wall (between tunica media and adventitia) usually as a result of

extravasation from the lumen and a dissecting lesion is when the blood enters the wall and dissects the layer longitudinally.

C. Specific vascular conditions in the veterinary species

1. ***Vasculitis*** is defined as the presence of inflammation (within the blood vessel) causing vessel wall damage demonstrated by the presence of perivascular/ vascular fibrin deposition, necrosis of endothelial and stromal cells and/or collagen degeneration. The consequences of vasculitis include thrombosis and hemorrhage with downstream ischemia. *The presence of perivascular inflammatory cells is **NOT** sufficient for the diagnosis of vasculitis as the vessel is not the target of the inflammation!* There are many causes of vasculitis, some of which are known and others that are poorly understood. A few are highlighted below that are considered to be very important either because they are relatively common OR they are considered reportable diseases.

a. Viral mediated

- Feline infectious peritonitis (mutated coronavirus)
- Equine arteritis virus (arterivirus)
- African horse sickness (orbivirus)
- African swine fever (asfivirus)
- Hog cholera/ classical swine fever (pestivirus)

b. **Autoimmune origin**: polyarteritis nodosa (PN) and hypersensitivity vasculitides. PN is a descriptive term applied a group of sporadically occurring lesions with similar appearance. The classic picture is one of necrosis and inflammation of small to medium sized arteries in a segmental pattern. Lesions may occur with no clinical signs. Hypersensitivity reactions can involve small caliber vessels such as arterioles and venules and capillaries and can involve reactions to drugs, bacterial proteins as well as tumor antigens.

c. Bacterial/ rickettsial agents:

- Rocky Mountain Fever (Rickettsia rickettsia)
- Heartwater (Ehrlichia ruminantium)
- Hepatic abscesses in cattle: these often involve the adjacent vena cava leading to phlebitis and thrombosis. This can then lead to pulmonary thromboembolism, pulmonary abscesses or venous/arterial aneurysms that rupture and cause massive hemorrhage and death.

d. Fungal:

- Mycotic ruminitis (often Mucor spp.) and guttural pouch mycosis (often Aspergillus spp): in both these cases, there is fungal induced necrosis of the arterial wall with resultant hemorrhage and/ or thrombus formation with subsequent ischemia to the tissue.

e. Parasitic:

- *Strongylus vulgaris*: large strongyle of the horse. Infective 3rd stage larvae ingested → penetrate intestinal submucosa → molt to 4th stage → penetrate arteriolar intima (day 7) and migrate to the cranial mesenteric artery (day 11-21) → molt to 5th stage and return to the gut mucosa and develop into adults in 6-8 weeks. Prepatent period is therefore 6-7 months. Most horses have some evidence of infection but the advent of ivermectin and azoles have largely reduced the more severe cases. Lesions range from irregular intimal tracks in the mesenteric artery to occlusive, aneurysmal-like lesions. The wall

becomes thickened from inflammation and reparative efforts but can also be thinned to dilated from weakening of the wall. The lesions are commonly located in the cranial mesenteric artery and the ileocecal artery. The migration pattern seldom crosses into the aorta. The tracks are composed of necrosis, fibrin and inflammatory cells (eosinophils and others) and are covered by endothelium and replaced by smooth muscle cells and ECM over time.

- Trematode infections: *schistosomiasis*. A variety of trematodes cause thrombophlebitis (inflammation of the vein) in a variety of species and include organisms from the group *Schistosoma* spp and *Heterobilharzia* spp. They are typically snail borne infections and result in the male and female worm infecting the hepatic, pulmonary and intestinal blood vessels.
- *Dirofilaria immitis*: heartworm disease will be covered in this course in detail by other instructors but for our purposes in this section, heartworm is a pulmonary vascular disease and causes intimal proliferation. The reaction is to immature and adult worms and starts as an endoarteritis with eosinophils. Over time, the inflammatory cell population subsides and is replaced by intimal proliferation in attempts to fortify the endothelial surface and engulf the worm. Caval syndrome is seen in dogs with a large number of worms that fill the right atrium and vena cava which decreases venous return.

2. **Arteriosclerosis:**

a. *Systemic hypertension*: can be as cause (retention of sodium and water leading to volume overload) or effect (via decreased renal perfusion and activation of the renin-angiotensin system) of renal disease in dog and cats. Often the process is self-perpetuating as increased pressures lead to medial hypertrophy and hyalinization (*see section above on arteriosclerosis*) which lead to decreased perfusion and therefore more hypertension. Hypertension is also seen in other disease states such as pheochromocytoma, diabetes mellitus and hyperthyroidism (among others). In addition to the renal vasculature, hypertension also affects the retinal vessel degeneration: this can result in retinal degeneration, hemorrhage and detachment.

b. *Pulmonary hypertension (PH):* can be the cause or result of pulmonary arterial disease. Cattle and pigs are prone to developing hypertensive heart failure at high altitudes (~2500m and above) but individual reactions vary. The hypoxia induces a pulmonary arterial constriction and hypertrophy that leads to hypertension. PH is also seen in some cardiac diseases such as atrial or septal defects that can produce left to right shunting. Other causes of PH include medial proliferation secondary to an arteritis (*see below on inflammation of vessels*).

c. *Mineralization:* occurs as dystrophic or metastatic mineralization **(Review and know the difference in these two processes).** Examples of diseases associated with mineralization are vitamin D toxicity which leads to mineralization of vessels and soft tissue in conjunction with hypercalcemia. Sources of poisoning include certain plants, feed mixing errors and certain topical medications. Other chronic inflammatory processes such as Johne's disease in cattle (*Mycobacterium paratuberculosis*) can also produce vessel mineralization.

d. *Uremia:* In uremic animals, there is endothelial damage leading to the fibrin leakage in to the media and collagen degeneration within thickening of the wall. There may also be calcification as well from hypercalcemia/hyperphosphatemia.

3. **Aneurysmal conditions**: These are poorly defined but often happen secondary to inflammation or hemodynamic changes in the veterinary species. There are certainly a large number of inherited diseases of extracellular matrix (ECM) that are primary causes of changes such as Marfan syndrome (fibrillin defect). Copper deficiency in swine can produce degenerative changes in the aorta as copper is a component of the lysyl oxidase which is responsible for cross linking collagen and elastin.

4. **Miscellaneous syndromes**

a. Cystic rete ovarii in cats, ovarian varicosities in horses, uterine artery rupture in horses: These are all degenerative conditions of the reproductive vasculature that may result in infertility and/or hemoabdomen.

b. Aortic rupture in horses: uncommon but is thought to be secondary to increased aortic pressure. Possible underlying degeneration in the vessel of unknown origin. Hemorrhage may be in the pericardium, myocardium where conduction disturbances may arise or free in the thoracic cavity.

c. Telangiectasia in the liver of cats and cattle: these are multifocal, small dilations of the hepatic sinusoids that are of little clinical significance. They present as blood filled plaques on the subcapsular surface.

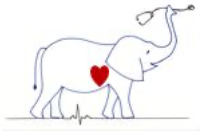
5. **Neoplastic conditions**

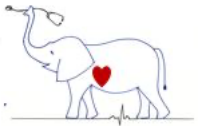
a. Endothelial cell tumors
- Hemangiomas/ hamartomas: These are benign, proliferative conditions of endothelial cells typically in the dermis and subcutis and present as a red to pink nodule or plaque with or without ulceration. Complete excision is curative. In the horse, they may look like granulation tissue. There are a variety of different morphologic variations for these tumors but no prognostic significance is known.
- Hemangiosarcoma: These are often extremely aggressive, malignant tumors of endothelium. They come in two different forms: cutaneous/peripheral soft tissue OR visceral. The cutaneous form is thought to be less aggressive than the visceral form. Common sites for the visceral form include: right auricle, spleen, liver, kidney, and retroperitoneum. Widespread metastasis to the lung, body cavities and brain is common. Clinical signs can be attributed to coagulation dysregulation from blood flowing/clotting in neoplastic vessels and/or hemoabdomen/hemothorax/hemopericardium.

b. Vascular wall tumors: these include benign and low-grade malignancies that are derived from either the smooth muscle of the wall (leiomyoangioma/ angiosarcoma) or from other supporting cells (pericytes—hemangiopericytoma).

6. **Malformation conditions of the vasculature**

a. Malformations of the great vessels are covered elsewhere. However, 2 conditions here bear mentioning:
   i. *AV fistulas* are small abnormal connections between arteries and veins that bypass the capillary bed. They can be of congenital origin but can also result from trauma or inflammation.
   ii. *Portosystemic shunts*. Abnormal placement of a vessel connecting the portal and system circulation.





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